Abstract Publication
More than 4,300 abstracts are published in this supplement. Abstracts are arranged by the abstract type**, then by presentation date*, and then by chronological publication number. Abstracts with a “PUB” number will not be presented at the ASN Annual Meeting.

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

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

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

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

Abstract Reference Format
To cite abstracts in this publication, please use the following format: Author Names: Abstract Title [Abstract]. J Am Soc Nephrol 24, 2013: Page(s).


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

Abstract Disclaimer and Copyright
The Abstract Issue of JASN® contains proprietary information belonging to the American Society of Nephrology (ASN). It is published as a service for the personal, noncommercial, and informational use only of its members and Kidney Week participants. Any commercial use is strictly prohibited. ASN’s program materials and publications facilitate scientific discourse for educational purposes. ASN accepts no responsibility for any products, presentations, opinions, statements, or positions expressed, and inclusion of such material within Kidney Week and other ASN publications, or online postings does not constitute an endorsement by ASN.
The Association between Single Nucleotide Polymorphisms in the FAS Pathway with Acute Kidney Injury
Christine W. Hsu,1 Paramita Mukherjee,1 Bryan R. Kestenaub1, Jonathan Himmelfarb,1 Mark M. Wrulc1
1Div of Nephrology, University of Washington, Seattle, WA; 2ARDSNet Investigators, Div of Pulmonary & Critical Care Medicine, Univ of Washington, Seattle, WA.

Background: Inflammation and apoptosis of renal tubular cells may be central to the pathophysiology of acute kidney injury (AKI). The Fas/Fas ligand pathway is a key initiator of both inflammation and apoptosis. Fas is a transmembrane protein in the tumor necrosis factor family that can induce inflammation and apoptosis upon binding Fas ligand.

Methods: We performed a retrospective cohort study of 401 patients who provided consent for genotyping while enrolled in the NHBLI ARDSNet Fluid and Catheter Trial (FACTT) from 2000-2005. We genotyped 376 single nucleotide polymorphisms (SNPs) on 45 genes of the Fas/Fas ligand pathway, and then used logistic regression, assuming an additive genetic model to identify associations between SNPs in Fas pathway genes and the development of AKI by day 2 after enrollment in FACTT. We classified levels of AKI using the Acute Kidney Injury Network (AKIN) criteria. In the primary analysis, we compared patients with AKI (AKIN stage 1 and above) to those without AKI (AKIN stage 0). In a sensitivity analysis, we compared patients with severe AKI (AKIN stage 2 and 3) to those without AKI (AKIN stage 0). Analyses were performed separately by race (Caucasian vs. African-American).

Results: In our Caucasian patients, we identified two associations between two SNPs and the incidence of AKI. For rs1050851 and rs2233417, both are found within the gene for nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (NFKBIA). For rs1050851 and rs2233417, the odds ratios (ORs) were 2.34 (95% confidence interval (CI)=1.86-2.94; p=1.84x10-5) and 2.46 (CI=1.61-3.76; p=1.81x10-5) for each minor allele, respectively. The associations were stronger still for AKIN stage 2-3 (severe AKI), with ORs 4.00 (CI=2.10-7.62; p=1.05x10-5) and 4.03 (CI=2.09-7.77; p=1.88x10-5) for each minor allele, respectively.

Conclusions: In critically ill Caucasian patients with AKI, the presence of minor alleles in two SNPs in NFKBIA was strongly associated with the development of AKI.

Funding: NIDDK Support

TH-OR001

The Temporal Trend in Dialysis-Requires Acute Kidney Injury in the U.S.
Raymond K. Hsu, Charles E. McCulloch, Chi-Yuan Hsu, Univ of California, San Francisco.

Background: The U.S. population incidence of dialysis-requiring acute kidney injury (AKI-D) has increased rapidly, but reasons for this temporal trend are incompletely understood.

Methods: We analyzed data from the 2006-2010 Nationwide Inpatient Sample, a nationally representative sample of hospitalizations, and identified cases of AKI-D using validated ICD9 codes. To explore potential reasons for the temporal trend in risk of AKI-D among hospitalized patients, we identified the top 15 diagnoses and the top 15 procedures most strongly associated with AKI-D. We then used multivariate logistic regression to examine the degree to which accounting for the 15 diagnoses or for the 15 procedures attenuated observed temporal trends in AKI-D.

Results: From 2006-2010, the odds of developing AKI-D among hospitalized patients in the U.S. increased by 9% per year (unadjusted OR 1.09, 95% CI 1.07-1.11). After adding sex, age, race, and the 15 top medical diagnoses as covariates, the temporal trend was significantly increased, (OR 1.20 (CI=1.16-1.23); p<10-5) for each minor allele.

Conclusions: The increasing rates of AKI-D observed in the U.S. appear to correlate with higher burden of acute and chronic conditions (such as infectious and cardiovascular disease) among hospitalized patients but not with increases in surgeries and procedures.

Funding: NIDDK Support

TH-OR002

Explaining the Temporal Trend in Dialysis-Requires Acute Kidney Injury
Raymond K. Hsu, Charles E. McCulloch, Chi-Yuan Hsu, Univ of California, San Francisco.

Background: In the prospective audit, most referrals had AKI3 (76.7%), an average of 4 AKI risk factors and ~70% occurring pre-admission. Length of stay was significantly increased, from a hospital average of 5 days, to 14d for AKI3. AKI3 post-admission increased length of stay further to 22d (AKI3). Overall in-hospital mortality of those referred was around 15%. e-alerts from Aug 2012-Apr 2013 recorded 50-60 cases of AKI per month, 50% occurring pre-admission. Overall mortality was 32.3%, usually due to hypotension and/or sepsis. Analysis of AKI1-3 showed up to 500 cases/month, the majority being AKI1.

Methods: Prospective data on all renal referrals over a six month period was collected, reviewing source of referral, AKI stage, if the AKI occurred pre- or post-admission and potential causes, length of stay and 90-day mortality. An e-alert was also added to our pathology system, generating AKI1-3 flags for all cases, this was strongly associated following the KDIGO AKI definition. Monthly reports were run and data analysed by AKI stage, location and clinical speciality.

Results: The prospective audit, most referrals had AKI3 (76.7%), an average of 4 AKI risk factors and ~70% occurring pre-admission. Length of stay was significantly increased, from a hospital average of 5 days, to 14d for AKI3. AKI3 post-admission increased length of stay further to 22d (AKI3). Overall in-hospital mortality of those referred was around 15%. e-alerts from Aug 2012-Apr 2013 recorded 50-60 cases of AKI per month, 50% occurring pre-admission. Overall mortality was 32.3%, usually due to hypotension and/or sepsis. Analysis of AKI1-3 showed up to 500 cases/month, the majority being AKI1.

Conclusions: AKI increases hospital length of stay and overall morbidity is high. The use of e-alerts increased awareness of the prevalence of AKI in our hospital. We can now target areas where AKI occurs most frequently, using local guidelines and our AKI outreach nurses to increase awareness of AKI amongst junior medical and nursing staff. The impact of these interventions will need to be re-audited but as reported elsewhere (e.g. Selby et al in Derby, UK), they can be effective at reducing mortality and cost.

Funding: Government Support - Non-U.S.

TH-OR005

Acute Kidney Injury prior to End-Stage Renal Disease Predicts Poor Dialysis Outcomes
Timmy C. Lee,1 Anthony Leonard,1 Pratik Parikh,3 Charahus V. Thakar,1,2 1Internal Medicine, Univ of Cincinnati, Cincinnati, OH; 2Medicine, Univ of Alabama at Birmingham, Birmingham, AL; 3Biomedical, Industrial and Human Factors Engineering, Wright State Univ, Dayton, OH.

Background: Previous studies have not evaluated the role of pre-end stage renal disease (ESRD) acute kidney injury (AKI) on major clinical outcomes at or after hemodialysis (HD) initiation.

Methods: We evaluated 47,327 adult incident hemodialysis patients (age ≥18) from the United States Renal Data System (USRDS) who initiated HD from January 1, 2008 to December 31, 2008 and had pre-ESRD Medicare claims during the two calendar years prior to initiating HD. Using administrative records, pre-ESRD AKI was assessed as a risk factor for two separate outcomes: type of vascular access [catheter versus arteriovenous (AV) access] at HD initiation and one-year mortality after HD. Both unadjusted risks, and risks adjusted (by logistic regression) for demographic and comorbidity factors were calculated. Results: Mean age at HD initiation was 72 years, 54% were male, 70% were white, and mean BMI was 29. 18% of patients initiated hemodialysis with an AV access (14% with AV fistula) and 82% with a catheter/otherers. 32% of patients died within 12 months of HD initiation. 53% of total patients had an AKI event, during inpatient stay in the pre-ESRD period. Patients with pre-ESRD AKI event were more likely to initiate HD with catheter compared to those without pre-ESRD AKI event (87% vs 74%; p=0.0001) and less likely with an AVF (8% vs 20%; p<0.0001); the adjusted risk of starting HD with a catheter was higher in pre-ESRD AKI group (odds ratio (OR) = 2.2, 95% confidence interval (CI)) = (2.1, 2.3)). After adjusting for access type, pre-ESRD AKI was associated with higher risk of 1-year mortality in HD (OR = 1.6, 95% CI = (1.5, 1.6)).

Conclusions: AKI events prior to ESRD predict higher rates of catheter use in HD patients, and higher one year mortality when adjusted for access type. Preventing AKI and improving processes of care after AKI may improve dialysis outcomes. Biological and process-of-care relationships between these events need further analyses.

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

1A
TH-OR006

De Novo Acute Kidney Injury and Subsequent Chronic Kidney Disease: Analysis of a National Sample of Veterans

Michael Heung,1 Diane Steffick,1 Tanushree Banerjee,2 Neil R. Powe,2 Meda E. Pavkov,1 Desmond Williams,1 Vahahn B. Shahnian.1 1Univ of Michigan, Ann Arbor; 2Univ of California San Francisco; 1Centers for Disease Control and Prevention, Atlanta, GA.

Background: Acute kidney injury (AKI) is a risk factor for chronic kidney disease (CKD). We compared the odds of developing CKD within 1 year of discharge in patients with & without in-hospital AKI and also stratified by AKI type.

Methods: Patients with 1+ outpatient visit in 2005 and 1+ hospitalizations of >1 day with 2+ inpatient serum creatinine (SCr) tests in 2005-8 were selected from a 5% sample of national Veterans Affairs data. Baseline was the SCr closest to 1 week before admission but <1 year; if not available, then a SCr <7 days before admission or the national Veterans Affairs data. Baseline was the SCr closest to 1 week before admission but with CKD. We compared the odds of developing CKD within 1 year of discharge in patients that hospitalization.

Outcomes

1 year of discharge were excluded. CKD by 1 year was defined as: ICD9 codes, dialysis, transplant, or eGFR closest to 1 year <60. AKI was defined as a 0.3 mg/dL increase in SCr from baseline to peak. Subgroups of AKI were: pre-renal (SCr decrease within 2 days of peak), recovery-renal (peak inpatient eGFR <60) or non-recovered AKI (eGFR <60). Logistic models estimated the association of AKI with CKD within 1 yr, after adjusting for age, race, sex, diabetes, and hypertension.

Results: Of the 13,563 patients in the sample, 1,937 (14.3%) had CKD by 1 year; 26.3% of those with AKI & 11.5% without AKI. Those with AKI had 2.5 times the odds of having CKD as those without. All AKI subgroups had elevated odds of CKD compared with those without.

Conclusions: De novo AKI is a strong risk factor for CKD. This relation persisted for AKI patients with rapid resolution of kidney function, suggestive of pre-renal AKI, for patients who develop Acute Kidney Injury (AKI) in the community. We have reviewed outcomes

TH-OR007

Community-Acquired Acute Kidney Injury: Hospital Admissions and Outcomes

Adil Hazara, Sunil Bhandari. Hull and East Yorkshire Hospitals NHS Trust, United Kingdom.

Background: Hospital-based emergency services are often the first point of contact for patients who develop Acute Kidney Injury (AKI) in the community. We have reviewed patterns of AKI presentation and their relationship with length of hospital stay, re-admissions and mortality.

Methods: Admissions with AKI were identified using a computerized algorithm developed in accordance with Acute Kidney Injury Network (AKIN) criteria. Baseline, admission, peak and final SCr values were reviewed retrospectively along with data relating to patient demographics, reasons for admission and outcomes.

Results: 172 patients were identified to have AKI in one month (1.8% of all hospital attendances). Mean age: 72 (range 19–100) years; Males: 76 (44%). Of these, 99 (58%), 50 (29%) and 23 (13%) patients had stage 1, 2 and 3 AKI respectively.

Conclusions: Survivors of AKI episodes had 1.21 higher adjusted odds for 30-day hospital readmission (95% CI 1.08, 1.36), which persisted at 60 (OR 1.15; 95% CI 1.03, 1.29) and 90 (OR 1.13; 95% CI 1.02, 1.25) days. AKI was associated with higher odds for 30-day hospital readmission in patients originally hospitalized on medical services (OR 1.29; 95% CI 1.14, 1.46), younger patients (OR 1.34; 95% CI 1.26, 1.49), those with fewer comorbidities (OR 1.34; 95% CI 1.16, 1.56), and higher baseline eGFR (OR 1.20; 95% CI 1.04, 1.39).

Conclusions: Survivors of hospital-acquired AKI experience a higher risk of early hospital readmission. Transitions of care services may be warranted for such patients to prevent readmissions and reduce healthcare costs.
TH-OR099


Background: AKI is associated with mortality in neonatal and pediatric critically ill populations, but the true incidence, risk factors and outcomes in VLBW are yet fully known.

Objective: To determine incidence, risk factors and outcome of development of AKI in first two weeks of life in VLBW Infants.

Methods: Between Feb 2012 to Feb 2013, 91 VLBW Infants (birth weight <1200 gm or gestational age <31 weeks) were prospectively followed. Serum creatinine (SCr) values collected on days 1,2,3,4, and 14; and combined with clinically measured Scr were used to determine AKI status according to KDIGO. Stage 1 AKI was defined as Scr ≥0.3 mg/dl or ≥150-200% from lowest previous value. Stage 2: Scr ≥300-300% from previous value and Stage 3 AKI: Scr > 2.5 mg/dl or Scr> 300% from previous value. Bronchopulmonary dysplasia (BPD) was defined if an infant was oxygen dependent at 28 days. Those who were alive at 36 weeks post-conception or discharged home were deemed survivors.

Results: Cumulative incidence of AKI over first two weeks of life was (27/87) 31%. Differences in infant and maternal demographics and co-morbidities and outcomes between AKI and No AKI showed that female, white race, lower gestational age, lower 5 minute Apgar and UAC were risk factors for AKI (p value <0.05), while pre-eclampsia was inversely associated with AKI (p value <0.001). AKI group had higher BPD, trend towards longer hospital stay, and lower survival.

Conclusions: AKI is common in VLBW infants. Development of AKI in first two weeks of life can result in higher incidence of BPD and lower survival.

TH-OR010


Background: This year, World Kidney Day (WKD, March 14, 2013) focused on raising awareness of the short- and long-term consequences of AKI.

Methods: To estimate the extent of in-hospital and outpatient nephrology effort devoted to the care of patients with AKI, we conducted an internet-based survey of all (~4907) US-based ASN physician members, on WKD.

Results: We received survey responses from 598 nephrologists (12% response rate). 49% worked in a teaching hospital with a median of 398 beds. Nephrologists were asked about patients seen on WKD. Respondents saw a median (25th, 75th percentile) of 12 (5, 18) patients in the hospital compared to 8 (5, 12) patients seen in clinic. A median of 4 (1, 6) patients seen in the hospital had pre-existing ESRD while 5 (2, 8) patients had AKI (p=0.002). In total, most patients seen in the hospital had AKI, comprising 46% (n=1500) of the sample, followed by ESRD (38%; n=1235). Among patients seen in the hospital for AKI, a median of 2 (1, 3) were critically ill, and 1 (0, 2) required renal replacement therapy (RRT). The delivered dose of intermittent hemodialysis was measured in only 17% Among patients seen in clinic, a median of 1 (0, 1) patient was seen for follow-up of in-hospital AKI; 55% reported that in the prior year, <10% of patients seen in clinic were for follow-up of in-hospital AKI.

Conclusions: AKI is the most common in-hospital diagnosis seen by US nephrologists. Patients with AKI are often critically ill and receive RRT. However, the delivered dose of intermittent hemodialysis is infrequently measured, and survivors of in-hospital AKI do not constitute a large patient cohort for future clinical encounters, and might be lost to nephrology follow-up. These findings call for continued efforts to promote excellence in the delivery of RRT to patients with AKI, and reliable transition of care services following hospital discharge from an AKI episode.

Funding: Private Foundation Support

TH-OR011


Background: Acute kidney injury (AKI) results in microvascular damage that stays lead to fibrosis. The Id1 and 3 proteins promote angiogenesis during development and tumor growth by functioning as dominant negative regulators of HHLH transcription factors. The goal of this study was to determine if Id proteins regulate microvascular repair and if increased Id1 expression in mice on microvascular repair following ischemia-reperfusion injury (IRI) was examined using Id1−/−, Id1RFP+/+ (Id1/3 KO) and Tek(Tie2)−/−R1A, TRE-lacz/TRE Id1 (TRE Id1) mice with dioxycyline inducible endothelial Id1 and β-galactosidase expression.

Results: Id1 and 3 were co-localized in endothelial cells in adult kidneys and protein levels were increased at day 3 following IRI. In comparison with WT littermates, Id1/3 KO mice had decreased baseline capillary density and pericyte coverage and increased tubular damage following IRI but no fibrosis. TRE Id1 mice had no capillary rarefaction and no pericyte loss at all capillaries. Following IRI, X-gal positive interstitial cells were located in areas of collagen deposition in dioxycyline treated TRE Id1/ TRE-lacz mice while positive cells from dioxycyline treated single transgenic TRE-lacz mice were confined to capillary lumens. TRE Id1 mice had increased proliferation of Id1+/PGDFβR+ positive interstitial cells and medullary collagen deposition. These differences were associated with increased Angiopoietin 1 (Ang1) and decreased Ang2 expression in TRE Id1 mice. Examination of gene expression in microvascular cells isolated from WT, Id1/3 KO and TRE Id1 mice showed increased Ang1 and cSmA in Id1 overexpressing cells and decreased markers in cells from Id1/3 KO mice.

Conclusions: Transgenic endothelial Id1 expression resulted in reduced capillary rarefaction and increased perivascular fibroblast proliferation and matrix deposition following IRI. Id1 expression was increased in microvascular cells in areas of fibrosis and was associated with increased Ang1 levels, suggesting a role in abnormal microvascular remodeling following injury.

TH-OR012

Differennted Kidney Epithelial Cells Repair Injured Proximal Tubule without Evidence for Intratubular Progenitors Tetsuro Kusaba, Matthew A. Lalli, Akio Kobayashi, Benjamin D. Humphreys. Renal Div, Brigham and Women's Hospital, Boston, MA.

Objective: To determine incidence, risk factors and outcome of development of AKI in very low birth weight infants (VLBW) and if medications used for chronic lung disease (CLD) impaired repair.

Methods: Between Feb 2012 to Feb 2013, 91 VLBW Infants (birth weight <1200 gm or gestational age <31 weeks) were prospectively followed. Serum creatinine (SCr) values collected on days 1,2,3,4, and 14; and combined with clinically measured Scr were used to determine AKI status according to KDIGO. Stage 1 AKI was defined as Scr ≥0.3 mg/dl or ≥150-200% from lowest previous value. Stage 2: Scr ≥300-300% from previous value and Stage 3 AKI: Scr > 2.5 mg/dl or Scr> 300% from previous value. Bronchopulmonary dysplasia (BPD) was defined if an infant was oxygen dependent at 28 days. Those who were alive at 36 weeks post-conception or discharged home were deemed survivors.

Results: Cumulative incidence of AKI over first two weeks of life was (27/87) 31%. Differences in infant and maternal demographics and co-morbidities and outcomes between AKI and No AKI showed that female, white race, lower gestational age, lower 5 minute Apgar and UAC were risk factors for AKI (p value <0.05), while pre-eclampsia was inversely associated with AKI (p value <0.001). AKI group had higher BPD, trend towards longer hospital stay, and lower survival.

Conclusions: AKI is common in VLBW infants. Development of AKI in first two weeks of life can result in higher incidence of BPD and lower survival.

TH-OR013

Exploring the Origin and Limitation of Kidney Regeneration Motoko Yanagita,1 Tomomi Endo,1 Tomohiko Okuda,1 Jin Nakamura,1 Misako Asada,2 Masayuki Takase,3 Ryo Yamada,1 Sato Yuki,1 Koji Takaori,1 Akio Oyuchi,4 Taku Iguchi,5 Eri Muso.1 1Nephrology, Kyoto Univ, Japan; 2Nephrology, Kitano Hospital, Osaka, Japan.

Background: Recent epidemiological data indicates that acute kidney injury (AKI) increases the risk for chronic kidney disease (CKD), however the molecular mechanism remains unknown.

Methods: To answer these questions, we generated new transgenic mouse strain (NDRG1); mice in which more than 90% of mature proximal tubule cells are labeled by Cre-ER2 and driven by PGDFβR. These mice were labeled at p=0.01. Single labeled proximal tubule cells not only expressed injury (KIM-1) and proliferation (Ki67) markers but also transiently expressed vimentin and Pax-2 markers thought to identify intratubular epithelial progenitors in other species. This finding was recapitulated by ex vivo proximal tubule culture. After complete labeling of proximal tubule followed by injury and repair, there was no dilution of the fate marker despite substantial proliferation, strongly arguing against an undifferentiated intratubular progenitor. When single proximal tubular cells were labeled at e14.5, clone size expanded by P14, suggesting a mechanism of tubule as epithelial organ.

Results: During this study, we observed AKI followed by repair showed that the bulk of labeled cells proliferate after injury with increased clonal expansion after severe compared to moderate injury. For example, clone size-frequency analysis before and after injury revealed that the fraction of clones 5 cells or larger increased from 0 before injury to 24.1 +/- 8.5% after injury,avg +/- SE, p<0.001. Single labeled proximal tubule cells not only expressed injury (KIM-1) and proliferation (Ki67) markers but also transiently expressed vimentin and Pax-2 markers thought to identify intratubular epithelial progenitors in other species. This finding was recapitulated by ex vivo proximal tubule culture. After complete labeling of proximal tubule followed by injury and repair, there was no dilution of the fate marker despite substantial proliferation, strongly arguing against an undifferentiated intratubular progenitor. When single proximal tubular cells were labeled at e14.5, clone size expanded by P14, suggesting a mechanism of tubule as epithelial organ.

Conclusions: These findings provide no evidence for a scattered intratubular progenitor population in mouse proximal tubule epithelia but indicate that fully differentiated epithelia re-express apparent progenitor markers during injury-induced dedifferentiation and repair.

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

Oral Abstract/Thursday
TH-OR014
KIM-1-Mediated Phagocytosis Induces Autophagy and MHC Antigen Presentation in Epithelial Cells

Craig R. Brooks,1 Hui Chen,2 Joel M. Henderson,1 Takaharu Ichimura,3 Joseph V. Bonventre.1

TH-OR015
KIM-1 Interacts with Gα12 and Suppresses Its Activity to Mediate Efferocytosis

Ola Zivad Ismail, Xizhong Zhang, Lakshman Gunatnam. Western Univ, London, Canada.

TH-OR016
Elucidating the Mechanisms of Therapeutic Augmentation of Kidney Repair after Acute Kidney Injury

Lauren Brilli,1 Takuto Chiba,1 Nataliya Skrypnyk,2 Lee McDermott,3 Mark P. De Caestecker,4,5 Neil A. Hukriede.1

Developmental Biology, Univ of Pittsburgh, Pittsburgh, PA; 2Pharmaceutical Sciences, Univ of Pittsburgh, Pittsburgh, PA; 3Cell and Developmental Biology, Vanderbilt Univ Medical Center, Nashville, TN; 4Medicine, Vanderbilt Univ Medical Center, Nashville, TN.

TH-OR017
Retinoic Acid Signaling Promotes Epithelial Cell Repair after Acute Kidney Injury

Takuto Chiba,1 Lauren Brilli,2 Nataliya Skrypnyk,2 Neil A. Hukriede.1

Mark P. De Caestecker.1 Medicine, Vanderbilt Univ, Nashville, TN; 2Developmental Biology, Univ of Pittsburgh, Pittsburgh, PA.

TH-OR018
Rationalizing RA Signaling in Kidney Regeneration: Lessons from Larvae and Mouse

Lauren Brilli,1 Takuto Chiba,3 Nataliya Skrypnyk,1 Neil A. Hukriede.1

Mark P. De Caestecker.1 Medicine, Vanderbilt Univ, Nashville, TN; 3Cell and Developmental Biology, Vanderbilt Univ Medical Center, Nashville, TN.

TH-OR019
Extracellular Adenosine Controls the Kidney Microenvironment and Regulates Acute and Chronic Kidney Injury

Li Li,1 Liping Huang,1 Hong Ye,1 Diane L. Rosin,2 Mark D. Okusa.1

Div of Nephrology, CIBR, Univ of Virginia, Charlottesville, VA; 2Dept of Pharmacology, Univ of Virginia, Charlottesville, VA.

TH-OR020
AKI Repair: The Nexus of Tubules, Inflammation, and Vasculature

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

This abstract represents presenting author/disclosure.
Results: Acute kidney injury (AKI) after IR was the same in CD73<sup>fl</sup>/fl and WT (B6) mice (plasma creatinine, P<0.05). Because discrete tissue localization of CD73 may be important in regulating the adenosine microenvironment, we deleted CD73 on proximal tubule cells by generating PEPPCK-Cre/CD73<sup>fl</sup>/fl mice and these mice had higher P<sub>C</sub> than P<sub>PEPPCK-Cre</sub> controls (P<0.05) after IRI. Interestingly, conditional knockout of CD73 on CD11c<sup>+</sup> dendritic cells (DCs) (CD11c-Cre/CD73<sup>fl</sup>/fl) also resulted in more kidney inflammation compared with CD11c<sup>+</sup>Cx3cr1<sup>GFP</sup> mice following IRI (P<0.05). These studies indicate that the expression of CD73 on hematopoietic and kidney epithelial cells is important for AKI.

Locally produced adenosine may activate its receptors. Our previous studies using CD11c<sup>+</sup>Cx3cr1<sup>GFP</sup> A2aR<sup>-/-</sup> mice showed that activation of adenosine 2A receptors (A2aR) on DCs has a critical role in suppressing the immune response in kidney IRI. In this study we further investigated the downstream effects of CD73 in chronic kidney injury, we examined and demonstrated that CD11c<sup>+</sup>Cx3cr1<sup>GFP</sup> A2aR<sup>-/-</sup> mice also have more kidney fibrosis with higher P<sub>C</sub> (P<0.01; as revealed by contralateral nephrectomy on day 14) compared with CD11c-Cx3cr1<sup>GFP</sup> mice 15 d after unilateral IRI.

Conclusions: Our studies reveal that hematopoietic and renal CD73 promote the production of adenosine that is important for AKI, and activation of A2aRs on DCs attenuates or halts initiation/progression of CKD following ischemia/reperfusion injury (IRI) and tried to verify their roles in the development of renal recovery phase following ischemia.

**TH-OR021**

Impact of Phosphorus-Based Food Additives on Bone and Mineral Metabolism in Healthy Volunteers

**Orlando M. Gutierrez, 1 George R. Beck, 2 UAB; 1Emory.**

**Background:** Phosphorus-based food additives substantially increase phosphorus intake in westernized diets. Few studies examined the impact of these additives on bone and mineral metabolism in humans.

**Methods:** 10 healthy volunteers participated in the study. Subjects needed to be 19-45 years old. Exclusion criteria included kidney disease, BMI ≥30 kg/m², or intake of medications known to affect phosphorus metabolism. After a two-week run-in period during which baseline biochemical data were obtained, subjects were fed standardized diets prepared by the metabolic kitchen over the following 2 weeks. During the 1st week, they were fed a diet designed to provide ~2,000 kcal and 900 mg of phosphorus (P<sub>D</sub>) per day using foods known to be free of Pi additives. During the 2nd week, they consumed a diet containing the same food items as the low-additive diet only the foods contained Pi additives. Blood and urine specimens were collected at regular intervals throughout the intervention period.

**Results:** The mean age of subjects was 32.8±8 years old, 30% were male, and 70% were female. The measured Pi content of the high-additive diet was ~617 mg higher than the low-additive diet, and the measured sodium content was ~1.3 grams higher; there were no other differences in the measured content of the two diets. There were no statistically significant changes in serum Pi, calcium, PTH, CTX, or P1NP during the dietary intervention period. FGF23 concentrations declined after one week of the low-additive diet, then significantly increased after 1 week of the high-additive diet (Figure).

**Conclusions:** One week of eating a diet rich in Pi additives significantly increased FGF23 and osteopontin concentrations, and significantly decreased sclerostin concentrations in healthy volunteers.

**Funding:** NIDDK Support

**TH-OR020**

The Role of M2 Macrophage in the Progression of Chronic Kidney Disease following Acute Kidney Injury

**Myung-Gyu Kim, Sang-Kyung Jo, Won-Yong Cho, Hyoung-Kyu Kim.**

**Dept of Internal Medicine, Korea Univ Anam Hospital, Seoul, Republic of Korea.**

**Background:** Acute kidney injury (AKI) is frequently accompanied by maladaptive repair and renal fibrogenesis, however, the molecular mechanisms that mediate progression from acute kidney injury to chronic kidney disease remain poorly understood.

**Methods:** Here we examined the role of epidermal growth factor receptor (EGFR) in this process using waved-2 (Wa-2) mice, which have reduced EGFR activity, and their wild type (WT) littermates after renal ischemia.

**Results:** Renal EGFR phosphorylation was induced within 2 days after ischemia, increased further at time, and remained elevated at 28 days in WT mice, but this was diminished in Wa-2 mice. At the early stage of post-ischemia (2 days), Wa-2 mice developed more severe PCr compared with WT littermates after renal ischemia.

**Conclusions:** Thus, blockade of EGFR holds a novel therapeutic potential for attenuating or halting initiation/progression of CKD following ischemia/reperfusion injury.

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

**TH-OR022**

Fibroblast Growth Factor 23 Rises Early in Acute Kidney Injury after Cardiac Surgery and Predicts Adverse Outcomes

**David E. Leaf, 1 Marta Christov, 2 Harald Jüppner, 3 Myles S. Wolf, 2 Sushrut S. Waikar, 1 Brigham and Women’s Hospital; 2Massachusetts General Hospital; 3Univ of Miami Miller School of Medicine.**

**Background:** FGF23 levels increase as CKD progresses and are strongly associated with increased mortality in both CKD and ESRD. The kinetics and prognostic value of FGF23 among patients with acute kidney injury (AKI), however, have not been well characterized. We hypothesized that FGF23 rises early in AKI and is associated with the composite outcome of hospital mortality or need for renal replacement therapy (death/RRT).

**Methods:** We performed a nested case-control study of 100 participants with and without AKI after cardiac surgery (N=50 in each group). Controls were matched based on age and eGFR. Plasma FGF23 and creatinine levels were measured at four timepoints: pre-op, end of cardiopulmonary bypass, and postoperative days 1 and 3. Logistic regression was used to assess the association between FGF23 area under the curve (AUC), calculated by the trapezoid method, and death/RRT among AKI cases. Secondary outcomes included post-op sepsis and post-op vasoressor requirement beyond 24 hours.

**Conclusions:** Although known to be important in facilitating recovery, M2 macrophages are thought to be main culprit in the development of renal fibrosis following IRI.
**TH-OR024**

No Decrease in Albuminuria with Cholecalciferol in a Randomized Placebo Controlled Trial in Older Patients with Heart Failure  
Amanda Gomez,1 Brian Schmotzer,1 Lavinia A. Negrea,1 Rebecca S. Boxer.2  
1Nephrology and Hypertension, Univ Hospitals Case Medical Center, Cleveland, OH;  
2Cardiovascular Medicine, Univ Hospitals Case Medical Center, Cleveland, OH;  
1Center for Clinical Investigation, Case Western Reserve Univ, Cleveland, OH.

**Background:** Proteinuria is an established risk factor for cardiovascular morbidity and mortality and adverse renal outcomes. Both microalbuminuria and macroalbuminuria are prevalent in heart failure. The mainstay for treatment of proteinuria is inhibition of the renin-angiotensin system. In vitro and animal studies have shown vitamin D to have a suppressive role on RAS. Activated vitamin D has been shown to reduce albuminuria in patients with type 2 diabetes and with chronic kidney disease. Oral cholecalciferol has also been shown to reduce albuminuria in type 2 diabetic nephropathy. The study objective is to determine the effect of oral cholecalciferol (D3) on urine albumin creatinine ratio (ACR) in an older adults with heart failure.

**Methods:** Single center, double blind, randomized placebo-controlled trial among 64 patients with heart failure greater than 50 years of age and low or low normal 25OH vitamin D were randomly assigned to receive 6 months of weekly treatment of 50,000 units of oral cholecalciferol (D3) (n=31) or placebo (n=33), both groups received calcium citrate 800mg daily. We measured change in ACR between 0 and 6 months.

**Results:** Treatment with 50,000 units of cholecalciferol resulted in an increase in serum 25OH vitamin D of 42±16 ng/mL and was unchanged in the placebo group (0±7 ng/mL) from baseline to 6 months. ACR levels were not associated with Vitamin D level at baseline (r=0.08, p=0.56). The treatment group did not demonstrate a reduction in urine ACR relative to the placebo group (p=0.18) from baseline to 6 months (treatment group change -6±52 mg/gm, placebo group change -3±32 mg/gm). There was also no difference in reduction in ACR between diabetics and non-diabetics (p=0.54).

**Conclusions:** 6 months of treatment with 50,000 units of weekly cholecalciferol did not result in reduction in albumin creatinine ratio in older patients with heart failure.

**TH-OR025**

Fasting Status, Serum Phosphorus, and Mortality: Results from NHANES III  
Alex Chang, M. Grams.  
Nephrology, Johns Hopkins Univ.

**Background:** Most but not all studies have found associations between elevated serum phosphorus levels and mortality; negative studies tend to use single random measurements. Since serum phosphorus levels may be affected by dietary phosphorus intake, we hypothesized that fasting status modifies the association between serum phosphorus and mortality.

**Methods:** The interaction between fasting status (≥12 hours without food or drink other than water), serum phosphorus levels and mortality; negative studies tend to use single random measurements. Since serum phosphorus levels may be affected by dietary phosphorus intake, we hypothesized that fasting status modifies the association between serum phosphorus and mortality.

**Results:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly correlated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** FGF23 levels were significantly higher among cases than controls (figure1). Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.

**Conclusions:** Among cases, FGF23 levels rose early in the course of AKI, becoming significantly elevated (11.3-fold) by the second timepoint (end of cardiopulmonary bypass). FGF23 AUC was significantly associated with death/RRT [OR 1.82, 95% CI 1.10-3.00, p=0.02] and Pi (r = 0.34, both p < 0.001). These changes were similar in patients on or off dialysis.
Cardiac FGF23 Expression Is Associated with Left Ventricular Hypertrophy in Pediatric Patients with Chronic Kidney Disease

Maren Leifheit-Nestler,1 Kathrin Flasbart,1 Robert Grosse Siemens,1 Dagmar-Christian Fischer,1 Michael Klintisch,1 Jan U. Becker,1 Tomas Seemann,1 Christoph Aufricht,1 Dieter Hafner1
1Dept of Pediatric Nephrology, Hannover Medical School, Hannover, Germany; 2Dept of Pediatrics, Univ Hospital Rostock; Rostock, Germany; 3Institute for Forensic Medicine, Hannover Medical School, Hannover, Germany; 4Div of Pediatric Nephrology, Univ Children’s Hospital Motol, Prague, Czech Republic; 5Div of Pediatric Nephrology, Univ Children’s Hospital Vienna, Vienna, Austria.

Background: Left ventricular hypertrophy (LVH) is an important cause of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD). Experimental and clinical studies demonstrated an association between elevated serum levels of fibroblast growth factor 23 (FGF23) and LVH in CKD.

Methods: We conducted a retrospective study in 19 deceased pediatric patients with end-stage renal disease (age 11±8y) and 23 age- and sex-matched healthy controls. Myocardial autopsy samples of the left ventricle (LV) were evaluated by immunohistochemistry and qPCR with respect to FGF23 expression, and signaling involved in calcineurin-NFAT associated pathway of hypertrophy. Expression of brain natriuretic peptide (BNP) served as a marker of LVH.

Results: FGF23 was expressed in all samples to the same extent. Cardiac FGF23 protein expression tended to be enhanced in samples of CKD patients compared to controls. Cardiac FGF23 mRNA was 3-fold increased in LV of CKD patients versus controls (p<0.05), and associated with the duration of CKD (r=0.636, p<0.05). Cardiac BNP mRNA levels were enhanced in samples of CKD patients compared to controls, and associated with cardiac FGF23 gene expression (r=0.982, p<0.05). In line with a causative role of FGF23 in LVH, calcineurin mRNA expression was 19-fold higher in hypertrophic heart tissue compared to healthy tissue.

Conclusions: FGF23 expression as well as the FGF23-dependent calcineurin pathway is upregulated in heart tissue samples of pediatric CKD patients and significantly associated with duration of CKD and marker of LVH.
TH-OR030

Reduced VEGFA Expression in Bone Marrow Cells Is Associated with Altered Bone Formation in CKD

Neal X. Chen,1 Kalisha O'Neill,1 Matthew R. Allen,2 Christopher Newman,3 Vincent H. Gattone,4 Sharon M. Moe.5
1Indiana University School of Medicine, Indpls, IN; 2YAMC.

Background: Over suppression of osteoblastic bone formation is considered an adverse effect of aggressive management of elevated PTH in CKD-MBD. Osteoblasts, critical in bone formation, derive from bone marrow mesenchymal stem cells (MSC), a process in part regulated by vascular endothelial growth factor (VEGFA). Therefore, an alternative hypothesis is that CKD leads to impaired bone formation due to reduced VEGFA that is over suppressed by the setting of high PTH.

Methods: To test this hypothesis, we analyzed bone marrow cells (BMC) from CKD (Cy/+ rats) for expression of VEGFA and transcription factors of MSC differentiation pathways and determined the relationship to histomorphometry indices of bone turnover (BFR), mineralization (BS/BS) and bone volume (BV/TV). Normal BMCs were compared to CKD rats (CKD; high PTH and high BFR), CKD treated with calcimimetic (CKD-Ca; low PTH and low BFR), and CKD treated with zoledronic acid, known to have runx2 expression to levels similar to Zol treatment, a known VEGFA inhibitor.

Results: The expression of VEGFA was reduced in BMC from CKD vs NL animals, and further reduced by both Ca and Zol (p < 0.04). In contrast, there was no difference in the VEGF-receptor expression between the groups. In CKD BMC VEGFA expression was correlated with BFR, MS/BS, and BV (r = 0.80, 0.65 and 0.85, respectively, all p < 0.01). VEGFA is known to increase the differentiation towards osteoblast (RUNX2) rather than adipocyte lineage (PPARy). The expression of these factors was strongly correlated with VEGFA expression, and the RUNX2 expression was equivalent in CKD animals compared to NL, but decreased in both CKD-Ca and CKD-Zol(p< 0.001). Similar results were obtained with PPARy but CKD was slightly lower than NL.

Conclusions: We conclude that CKD is associated with decreased VEGFA expression in BMC. These results suggest that in untreated CKD animals, the elevated PTH could overcome the low VEGFA and increase RUNX2 and BFR. In contrast, the induction of low BFR and suppression of PTH with Ca is associated with reduced VEGFA and RUNX2 expression to levels similar to Zol treatment, a known VEGFA inhibitor.

Funding: Other NIH Support - NIAMS, Veterans Affairs Support

TH-OR031

LPA-LPA_1 Signaling Drives Renal Fibrosis by Inducing Fibroblast Accumulation through MRTF-SRF-Dependent Epithelial CTGF Expression

Norihiko Sakai,1 Takashi Wada,2 Andrew M. Tager.1 1Div of Rheumatology, Massachusetts General Hospital, Boston, MA; 2Div of Pulmonary and Critical Care Unit, Massachusetts General Hospital, Boston, MA.

Background: Renal fibrosis is a common pathway of progressive renal diseases and results in renal failure. But the mechanisms driving this pathway remain to be fully identified. We previously implicated the lipid mediator lysophosphatidic acid (LPA) and one of its receptors, LPA_1, in lung and skin fibrosis. Recently, we have demonstrated that LPA and LPA_1 drive fibroblast fibrosis by inducing connective tissue growth factor fibroblast accumulation. LPA signaling through LPA_1, on peritoneal mesothelial cells drives CTGF production in these cells by activating myocardin-related transcription factor (MRTF)-serum response factor (SRF)-dependant transcription. We therefore examined the role of this LPA-LPA_1-MRTF-SRF-CTGF pathway in renal fibrosis induced by unilateral ureteric obstruction (UUD).

Methods: Type I pro-collagen promoter-driven green fluorescent protein (GFP) mice were crossed with LPA_1-deficient mice (LPA, KO-GFP) or wild-type mice (WT-GFP). Results: UUO-induced increases in renal hydroxyproline content were significantly attenuated in LPA_1-KO compared with WT-GFP animals. Renal accumulation of a-smooth muscle actin myofibroblasts and GFP fibroblasts was also significantly reduced in LPA, KO-GFP mice. Renal CTGF expression was mainly detected in renal epithelial cells, and the levels of renal CTGF expression were suppressed in LPA, KO-GFP compared with those in WT-GFP mice. We also found that LPA directly induced CTGF expression dependent on an LPA-MRTF-SRF axis in mouse primary renal epithelial cells. Finally, supernatants of renal epithelial cells stimulated with LPA were found to contain CTGF protein, and to enhance fibroblast proliferation.

Conclusions: Our results suggest that LPA and LPA_1 drive renal fibrosis by inducing fibroblast accumulation through epithelial CTGF production, by activating MRTF-SRF-dependent transcription in epithelial cells.

TH-OR032

A Cationic-Independent Mannose 6-Phosphate Receptor Inhibitor (PXS64) Ameliorates Kidney Fibrosis Independent of Smad, AKT and ERK Signaling Pathways

Jie Zhang, May Yu Wong, Muh Geot Wong, Carol A. Pollock, Sonia Saad. 1Kolling Institute of Medical Research, Univ of Sydney, St. Leonards, NSW, Australia.

Background: Agents which completely inhibit transforming growth factor-β (TGFβ) have limited clinical use due to unwanted side effects. The cationic-independent mannose 6-phosphate receptor (C-1-MPR) is a multifunctional protein which inhibits the activation of TGFβ without completely inhibiting TGFβ. We have previously shown that PXS25, has anti-fibrotic properties in human proximal tubular cells (HK-2) but is limited by its bioavailability. We aim to determine the role of PXS64, a pro-drug of PXS-25, in renal fibrosis and in HK-2 cells.

Methods: A 7 day unilateral ureteric obstruction (UUO) model was examined in 6-8 week old male C57BL/6 mice (20-25g, n=5) in the following groups: (i) Sham operated; (ii) UUO control; (iii) PXS64 (10mg/kg, by daily intraperitoneal injection) and (iv) Telmisartan (3mg/kg, in drinking water). Semiquantitative morphometric analyses of glomerulosclerosis and tubulointerstitial fibrosis were performed. Kidney tissue was analysed for fibrotic and inflammatory markers. HK-2 cells were exposed to TGFβ1 (1ng/ml) with or without PXS64 (10 μM/L) for 24 hours. The mRNA expression of Collagen IV (COLIV) and Fibronectin (FN) was assessed by real time PCR.

Results: The mRNA expression of COLIV and FN in kidney tissue was lower in animal treated with PXS64 as compared to the vehicle control (PBS) (p<0.05). The mRNA expression of TGFβ1 and MCP1 were suppressed by PXS64 and Telmisartan (p<0.05, both) compared to the vehicle. Tissue treated with PXS64 had lower tubulointerstitial fibrosis score, FN and ColIV protein expression. In the in vitro study, PXS-64 inhibits TGFβ1-induced mRNA regulation and protein expression of COLIV and FN compared to controls (p < 0.05) but did not inhibit TGFβ1-induced Smad2/3, AKT and ERK signaling.

Conclusions: PXS64 is as effective as Telmisartan as an antifibrotic agent in kidney fibrosis. PXS64 attenuates TGFβ1-induced matrix regulation independent of Smad2/3, AKT and ERK1/2 signaling pathways.

TH-OR033

MicroRNA Regulation of the Cell Cycle in Aristolochic Acid Nephropathy

Robert H. Jenkins,1 Donald Fraser,1 Luke C. Davies,2 Philip R. Taylor,2 Timothy Bowen.3 1Institute of Molecular and Experimental Medicine, Cardiff Univ, Cardiff, Wales, United Kingdom; 2Department of Infection, Immunity and Biochemistry, Cardiff Univ, Cardiff, Wales, United Kingdom.

Background: Aristolochic acid nephropathy (AAN) is characterised by progressive tubulointerstitial nephritis culminating in end stage renal failure. A recent study causally links epithelial cell G2/M cell cycle arrest to fibrosis, following acute ischaemic, aristolochic acid (AA), and obstructive injuries (Yang L et al. Nat Med 2010; 16(5) 535). We have previously characterised miRNA expression in response to AA, including the induction of cell cycle associated microRNAs, miR-192, -194, -450a, and -542-3p. The purpose of this study was to investigate the mechanism of miRNA regulation of cell cycle arrest in AAN.

Methods: An in vitro study in proximal tubule epithelial cells in a model of AAN, using stable-expression cell lines, TaqMan RT-qPCR, Flow Cytometry, Western Blots, and immunofluorescence.

Results: AA induced profound G2/M arrest in proximal tubular cells via p53-mediated downstream inactivation of the maturation promoting complex CDK1/Cyclin-B1. This was associated with the formation of RNA stress granules, termed processing-bodies, indicative of G2/M arrest and translational repression. The mechanism of G 2/M arrest was due to miR-192 up-regulation, in miR-192 reconstituted G/M arrest and translational repression. The mechanism of G/M arrest was due to miR-192 repression of the E3 ubiquitin ligase MDM2, a negative regulator of p53. The subsequent induction of p53 transcriptionally induced p21 and the growth arrest and DNA damage 45 (GADD45) proteins, which phosphorylated, inactivated and disassociated the maturation promoting complex CDK1/Cyclin-B1.

Conclusions: These data define a mechanism by which miRNAs control cell cycle arrest in epithelial cells in a model of AAN. This is of mechanistic importance in the recently described pro-fibrotic G/M arrest seen following a range of acute renal injuries.

TH-OR034

Nrp3 Regulates Apoptosis in Renal Tubular Epithelial Cells

Nekoda Vilaysane, Daniel A. Muruve.

1Institute of Molecular and Experimental Medicine, Cardiff Univ, Cardiff, Wales, United Kingdom.

Background: Tubular cell apoptosis contributes to the pathogenesis of progressive chronic kidney disease (CKD). Caspases play an important role in this process that result in tubular atrophy, tubulointerstitial inflammation and fibrosis. Previous work from our lab showed reduced apoptosis in the renal epithelium of Nrp3−/− mice undergoing unilateral ureteral obstruction when compared to wild-type controls. The mechanism behind this distinction in Nrp3−/− renal cells is unknown but does not appear to be simply due to classical Nrp3 inflammation mediated by the adaptor protein ASC and caspase-1 which mediates the maturation of pro-inflammatory cytokines such as IL-1β.

Methods: Apoptotic responses were analyzed in primary mouse tubular epithelial cells from wild type and Nrp3−/− mice.

Results: Mouse tubular epithelial cells (mTECs) were found to express Nrp3 and ASC proteins, however active caspase-1 subunits and IL-1β were undetectable suggesting.
Inflamasome-independent roles for Nlrp3 and ASC in these cells. Primary Nlrp3−/− mTECs displayed reduced caspase-8, -3, and -7 activation and reduced poly-ADP ribose polymerase (PARP) cleavage after incubation with extracellular ligands, TNFα and Fas ligand. The reduction in apoptosis in Nlrp3−/− cells occurred independent of ASC since apoptotic responses in these cells were comparable to wild type mTECs. Differences in cell death between Nlrp3 deficient and wild-type mTECs appear to be independent of death inducing signaling (DISC) formation, mitochondrial NO and NF-κB pro-survival signaling. Likewise, tumor necrosis factor receptor 1 (TNFR1) protein levels remained similar between both cell types. Consistent with these findings, overexpression of NLRP3 in HeLa cells increased levels of active caspase-8 over GFP controls. Initial experiments have localized NLRP3 to mitochondria in renal tubular epithelial cells suggesting that NLRP3 may modulate cell death by sensing or regulating mitochondrial function.

Conclusions: Taken together, these results support an inflammasome-independent role for Nlrp3 in renal cell death, which in addition to its roles in cytokine maturation and inflammation, identify this protein as a potential therapeutic target in progressive CKD.

Funding: Government Support - Non-U.S.

TH-OR035

Fibroblast αv Integrins Are Key Mediators of Renal Fibrosis – Potential Novel Targets for Anti-Fibrosis Therapy

Yongen Chang,1,3 Deon Sheppard,1

1Medicine/Div of Nephrology, Univ of California San Francisco, San Francisco, CA; 2Medicine/Div of Pulmonary and Critical Care, Univ of California San Francisco, San Francisco, CA.

Background: Renal fibrosis is the common pathway of chronic kidney disease. So far, its molecular mechanism is not entirely clear. While epithelial αv integrins, i.e. αvβ6, were identified as key pro-fibrotic factors through activation of transforming growth factor β (TGFβ) signaling, αvβ3 integrins are still poorly understood.

Methods: Platelet-derived growth factor receptor β (PDGFRβ) is highly expressed in activated pericytes, a main source of fibroblasts. Using a PDGFRβ promoter driven Cre system, we deleted αv integrins specifically in activated pericytes in mice while turning on TdTomato reporter fluorescence in these cells. We then performed unilateral ureteral obstruction (UUO) surgery to induce interstitial fibrosis in these mice. We identified TdTomato positive wild type or αv null renal fibroblasts using fluorescence-activated cell sorting. For TGFβ activation assays, isolated fibroblasts were co-cultured with mink lung epithelial cells expressing firefly luciferase downstream of a TGFβ response element (HRE-Luc) and Nip3 were increased in ctgf-null MEF under normal oxygen conditions.

Conclusions: These results indicate that systemic deletion of CTGF, but not podocyte-specific inhibition of CTGF, can reduce proteinuria and macrofage infiltration to ameliorate glomerular injury in anti-GBM nephritis.

Funding: Other NIH Support - T32 Training Grant from September 2012-September 2013, Private Foundation Support

TH-OR036

Impact of Connective Tissue Growth Factor (CCN2) on Hypoxia Inducible Factor-1α (HIF-1α) Responsiveness

Leighton R. James,1,3 Catherine Le.1,3

1Dept of Medicine, Nephrology Div, Univ of Florida, Jacksonville, FL; 2Cell and Molecular Biology, Colorado State Univ, Fort Collins, CO; 3Dept of Medicine, UT-Southwestern Medical Center, Dallas, TX.

Background: CTGF is implicated in the pathogenesis of diverse fibrotic conditions. Hypoxia adaptation to hypoxia, vasodilation, glucose disposal and intermediary metabolism. However, the interaction between CTGF and Hif-1α is contradictory. Hypoxia may induce CTGF via hif-1α in lungs, but inhibit CTGF expression in proximal tubular epithelial cells (protective effect of hypoxic preconditioning), while in some conditions CTGF regulate HIF1 stability. Recently, we have observed that ctgf expression may influence blood pressure in a mouse model. The objective of the current study was to examine effect of ctgf gene dose on Hif-1α expression and downstream Hif-1α targets.

Methods: CTGF knockout and CTGF gene-duplicated mice, as well as, mouse embryonic fibroblasts (MEFs) derived from these lines, were studied. Expression analysis was also performed with Mouse Array Chip (Illumina). Expression of constructs containing Hif-1α responsive elements (HRE-Luc) and pro-angiogenic Nip3 promoter and Endothelin-1 (Etn-1) promoter levels were assessed. Blood pressure was assessed using automated tail-cuff method.

Results: Disruption of ctgf gene enhances MEF growth. Expression array analysis revealed that relative to wildtype, there was increased expression of HIF-1α-responsive genes including angiotensin II type 1 receptor, fifty percent reduction in Etn-1 and, concurrently enhanced expression of Hif-1α antagonistic factors necln and claudin 1. Expression of HRE-Luc and Nip3 were increased in ctgf-null MEF under normal oxygen conditions. Nip3 promoter mutation abrogated expression in wildtype MEF, but marginally influenced expression in ctgf-null MEFs. Etn-1 protein was reduced in ctgf-null MEF and, in parallel with elevated blood pressure in mice, enhanced CTGF expression accentuated Et-1 levels.

Conclusions: Variation in ctgf expression impacts Hif-1α and potentially influences normal physiologic processes as well as cellular responses to perturbation and injury.

Funding: NIDDK Support, Private Foundation Support

TH-OR037

Systemic Deletion of CTGF Ameliorates Anti-Glomerular Basement Membrane Nephritis with Reduction of Macrophage Infiltration Numbers

Hidde Yokota,1,2 Mari Nakama,1,2 Masamichi Miki,1,2 Yuko Nakamura,1,2 Hiroko Ishii,3 Kenichi Koga,3 Keita P. Mori,4 Takahide Kuwabara,4 Hirotaka Imamura,4 Akira Ishii,3 Kenichi Koga,1 Keita P. Mori,1 Akira Ishii,3 Kenichi Koga,1 Kenichi Koga,1 Kenichi Koga,1 Kenichi Koga,1

1Dept of Medicine and Clinical Science, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 2Dept of Internal Medicine, Tokai Univ School of Medicine, Kanagawa, Japan.

Background: Connective tissue growth factor (CTGF/CCN2) regulates signaling of other growth factors and promotes fibrosis. Although we previously showed that drug-inducible systemic CTGF knockout mice attenuated anti-glomerular basement membrane (anti-GBM) nephritis, the molecular mechanism how systemic deletion of CTGF ameliorated nephritis was unclear. To address these questions, we generate podocyte-specific CTGF knockout (pod-CTGF cKO) mice and drug-inducible systemic CTGF knockout (Rosa-CTGF cKO) mice.

Methods: CTGF floxed mice were crossed with RosaCreER2 mice, which ubiquitously express a tamoxifen-inducible Cre recombinase, to generate Rosa-CTGF cKO mice. Nephrin-Cre mice were used to create pod-CTGF cKO mice. We evoked anti-GBM nephritis and investigated the progression of glomerular injury including macrophage infiltration for 28 days.

Results: Rosa-CTGF cKO mice and pod-CTGF cKO mice showed normal renal appearance and no proteinuria without nephritis. After induction of anti-GBM nephritis, cortex proteinuria and glomerular injury were developed in control mice. Pod-CTGF-cKO mice showed similar renal injury and proteinuria. In contrast, Rosa-CTGF cKO mice exhibited reduced proteinuria by half at day 7 with ameliorated histological changes. The number of MAC2-positive cells in glomeruli was reduced in Rosa-CTGF cKO mice but not in Pod-CTGF cKO mice. Glomerular numbers of TNF-α and F4/80 were upregulated in control mice, and these increments were significantly reduced in Rosa-CTGF cKO mice, but not in Pod-CTGF cKO mice.

Conclusions: These results indicate that systemic deletion of CTGF, but not podocyte-specific inhibition of CTGF, can reduce proteinuria and macrophage infiltration to ameliorate glomerular injury in anti-GBM nephritis.

Funding: TH-OR038

Molecular Mechanism for Asymmetric Dimethylarginine Dysregulation in Patients with Chronic Kidney Disease

Crystal A. Gadebeck,1,2 Subhasish Bose,1 Wenjun Ju,2 Louis G. D’alecy,2 Kalyani Perumal,3 Zeenat Yousuf Bhat,4 Matthias Kretzler,2,3 Temple Univ; 1Univ of Michigan, 2John H. Stroger Hospital, 3Wayne State Univ, 4Michigan O’Brien Renal Center (P30).

Background: Endothelial dysfunction is implicated in accelerated atherosclerosis in patients with chronic kidney disease (CKD). Plasma asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of nitric oxide synthesis, is linked to cardiovascular morbidity and mortality and reaches high levels in CKD. ADMA is generated by protein methyltransferase 1 (PRMT1) and metabolized by dimethylarginine dimethylaminohydrolase (DDAH). This study was designed to characterize intra-renal molecular markers of ADMA metabolism in patients that have been implicated in experimental studies.

Methods: Renal biopsy tissue stored in the Michigan O’Brien Renal Center biobank from 29 consented individuals underwent gene expression analysis using Affymetrix microarrays. Gene expression levels were examined using the DDAH and PRMT1 signal intensity that may contribute to CVD burden in CKD. These findings support animal model data demonstrating up-regulation of PRMT1 and down-regulation of DDAH1 associated with oxidative stress in CKD.

Funding: NIDDK Support
Uremic Cardiomyopathy Is Associated with Glutathione Peroxidase 3 Deficiency

**Background:** Glutathione peroxidase 3 (GPX3) is synthesized primarily in the kidney. Patients with chronic kidney disease (CKD) have deficient levels of circulating GPX3. This may lead to a form of cardiomyopathy due to the accumulation of reactive oxygen species that exacerbate inflammatory signaling in the myocardium.

**Methods:** 9 patients with CKD, had serum collected, were followed prospectively, and monitored for cardiac endpoints. Proteomic analysis was performed by LC-tandem mass spectrometry. GPX3 +/- and wild type mice underwent 5/6 nephrectomy followed by echocardiography 4 weeks and 8 weeks after injury.

**Results:** We identified several circulating proteins of interest based on plasma proteomic analysis of patients with CKD and cardiac endpoints.

**Conclusion:** This was evident by the dramatic worsening of cardiac function after subtotal nephrectomy in GPX3 +/- animals. GPX3 deficiency is also associated with increased frequency of cardiac events in patients with CKD and may offer a targeted therapy for renal-induced cardiomyopathy.

**Funding:** NIDDD Support

**TH-OR040**

**Activation of Aryl Hydrocarbon Receptor Mediates Suppression of Hypoxia Inducible Factor-Dependent Erythropoietin Expression by Indoxyl Sulfate**

**Background:** Uremic toxins are considered to have a role in renal anemia which is caused by inadequate renal erythropoietin (EPO) production. Indoxyl sulfate (IS), a representative uremic toxin, has been reported to suppress the activation of hypoxia inducible factor (HIF) and subsequent EPO production. In this study, we investigated the inhibitory effect of IS. Similar to IS, TCDD also significantly inhibited the HIF activation at 20 μM or more.

**Results:** IS significantly inhibited cobalt chloride-induced elevation of EPO expression at 100 μM or more. PhS slightly inhibited the EPO expression at relatively higher concentration (1.5 mM), whereas PCS (up to 1.5 mM) had no effect. IS also significantly inhibited the HIF activation at 20 μM or more, while PCS had no inhibitory effect. Inactivation of HIF by either CH-223191 or the specific siRNA completely abolished the inhibitory effect of IS. Similar to IS, TCDD also significantly inhibited the HIF activation.

**Conclusion:** In this study we investigate if proteins encoded by the intrarenal CKD transcript panel as a proof of principle study. We have employed a gene expression profiling study in renal biopsies of the European Renal cDNA Bank (ERCB) and identified a set of 68 intrarenal transcripts that was able to predict degree of CKD in ERCB training (r=0.84) and test cohorts (r=0.53), as well as in 42 patients of the Michigan O’Brien Renal Center CAP-PROBE cohort.

**Funding:** NIDDD Support

**TH-OR041**

**Impact of Genetic TNFR1 Modulation on Diabetic Nephropathy Course in a Murine Model of Diabetic Nephropathy**

**Background:** Circulating TNFR1 was identified as a strong predictor of diabetic nephropathy (DN) progression in the Joslin Kidney Study. Aim of this work was to evaluate whether TNFR1 contributes to the injury of the diabetic kidney. We tested our hypothesis in a murine model of DN in which hyperglycemia was chemically induced with streptozotocin (STZ) and TNFR1 expression was genetically modulated.

**Methods:** Tnfrsf1atm1Imx knockout (TNFR1-/-), TNFR1 transgenic (TNFR1tg) and control WT (WT) mice all in the C57BL/6 background (n=8 per group of 8 weeks of age) were used in our study. We confirmed their TNFR1 genotype with RT-PCR and their protein expression with ELISA. Repeated measurements of glycemia and albumin excretion rate (AER) were performed over a 12 week period following STZ injection.

**Results:** Serum TNFR1 levels were undetectable in TNFR1tg mice, 140±81 ng/ml in TNFR1-/- mice and 0.89±0.16 ng/ml in WT mice. Albuminuria course over time was significantly different among the 3 groups of mice, AER values were lower in TNFR1-/- and higher in TNFR1tg compared to the control group, respectively (p=0.007, significance obtained with mixed effect model). Survival of TNFR1tg mice was significantly reduced compared to the other groups (deaths: TNFR1tg: 5/9, vs. TNFR1-/-: 2/6, WT: 2/8).

**Conclusion:** We demonstrated that the modulation of TNFR1 expression impacts albuminuria course in an experimental model of murine DN. Our data suggest that TNFR1 may play a causative role in DN progression and warrants its consideration for therapeutic applications.

**Funding:** NIDDD Support

**TH-OR042**

**Tissue Transcriptome-Driven Approach Facilitates Discovery of Non-Invasive Biomarkers for Chronic Kidney Disease**

**Background:** Defining intra-renal molecular mechanism associated with CKD is critical for identification of therapeutic targets and molecular marker definition. We have employed a gene expression profiling study in renal biopsies of the European Renal cDNA Bank (ERCB) and identified a set of 68 intrarenal transcripts that was able to predict degree of CKD in ERCB training (r=0.84) and test cohorts (r=0.53), as well as in 42 patients of the Michigan O’Brien Renal Center CAP-PROBE cohort.

**Methods:** In this study we investigate if proteins encoded by the intrarenal CKD associated transcripts can be discovered in urine, if urinary proteins correlate with intrarenal transcript level and if they maintain their association with eGFR. Epidermal growth factor (EGF) was selected from the transcript panel as a proof of principle study.

**Results:** Intrarenal EGF mRNA correlates with eGFR in the ERCB test cohort (r=0.66) and C-PROBE cohort (r=0.42). In C-PROBE, matching urine samples at time of biopsy (n=34) were evaluated for EGF and demonstrated a significant correlation with intrarenal EGF mRNA (r=0.7, p=0.001). Urinary EGF retained its correlation with eGFR in 93 C-PROBE patients irrespective of underlying disease type, stage, age, gender or race (r=0.82, p<0.0001). Robustness of the EGF-eGFR association in proteinic patients was demonstrated in 213 patients from the Nephrotic Syndrome Study Network (NEPTUNE) (r=0.83, p<0.0001, urine protein level ranges from 0.01 to 66.8 g/g creatinine).

**Funding:** NIDDK Support
Conclusions: In conclusion, intrarenal transcripts with strong associations to eGFR can be used to define urine protein markers for non-invasive stratification of CKD patients according to progression toward end-stage renal failure. Funding: NIDDK Support, Pharmaceutical Company Support - F. Hoffmann-La Roche Ltd

TH-OR043

In Vitro Human Renal Primary Cells for Studies of Mineral Ion Homeostasis Rebecca M. Waday, 1 Lydia E. Searchfield, 1 Sally A. Price, 2 Daniella Riccardi, 1 1Cardiff Univ, United Kingdom; 2AstraZeneca, United Kingdom.

Background: FGF23, PTH and Vitamin D play important roles in mineral ion homeostasis. The complex interactions between these hormones are difficult to investigate in vivo. We have characterised a human primary renal cell model in an attempt to specifically dissect out the role the kidney plays within the FGF23, PTH and Vitamin D axis.

Methods: Primary renal cells were isolated from ethically-consented kidney cortical tissue from patients undergoing nephrectomy. Cell monolayers were cultured on transwells without passaging and characterised in terms of viability (proliferation/apoptosis), morphology (electron microscopy) and expression of proximal and distal markers, N- and E-cadherin, respectively. Expression of NaPiIIa (type 2a Na+-Pi cotransporter), NCx1 (Na+-Ca2+ exchanger), PMCA1 (plasma membrane Ca2+ ATPase), FGF11-4 and Klotho were determined by immunohistochemistry (on kidney sections) and western blotting (of kidney lysate) and then confirmed in isolated cells. Functional readouts included Pi-dependent NaPiIIa upregulation, ERK activation, 1-hydroxylase activity and Pi-induced mineralisation.

Results: Cell proliferation rates were high and apoptosis rates low throughout culture. Dual N- and E-cadherin immunostaining revealed that primary cultures consisted of 70% proximal and 30% distal cells after 3 days. When cultured on transwells, NaPiIIa expression was present up to day 8 and NCX1, PMCA1, FGF11-4 and Klotho proteins up to day 15. Proximal tubule brush border membranes were visible by electron microscopy at day 5. NaPiIIa expression was upregulated following 24h exposure to Pi-free medium. FGF23 treatment induced ERK activation, which could be blocked by inhibiting MEK. MEK inhibition also increased Pi-dependent mineralisation.

Conclusions: Primary human kidney cells retain the morphological and functional properties of kidney cells in vivo and express key proteins involved in mineral ion homeostasis. These observations suggest great potential for this preparation as a model for investigating the interplay between FGF23, PTH and Vitamin D in mineral ion homeostasis, and for understanding how mineral ion dysregulation occurs in chronic kidney disease.

TH-OR044

Urinary Proteomics: The Development of a Diagnostic Biomarker Panel for Pre-Eclampsia Kate Bramham, 1 Hiten Mistry, 1 Marta Hentschke, 1 Steven Lynham, 1 Malcolm Ward, 2 Lucilla Poston, 1 Lucy C. Chappell. 1 1Div of Women’s Health, King’s College London, London, United Kingdom; 2Centre of Excellence for Mass Spectrometry, King’s College London, London, United Kingdom.

Background: Early detection/diagnosis of pre-eclampsia allows appropriate monitoring and targeting of therapeutic strategies. Urinary proteomics is a rapidly developing field that allows detection and identification of individual proteins. Our hypothesis is that a distinctive pre-eclampsia urinary protein profile can be identified.

Methods: A proteome profile for time-of-disease urine samples from twelve pre-eclamptic and twelve gestation-matched controls was established using a validated workflow, involving selective immunodetection, 1D SDS-PAGE gel fractionation, in-gel digestion of gel sections, LC/MS/MS analysis, spectral analysis and selection of candidate proteins for Selective Reaction Monitoring (SRM) verification and quantification.

Results: 981 proteins were identified using minimal stringency in Scaffold, and 8 proteins showed 5-fold changes between cases and controls. Subsequent SRM area-under-peak analysis revealed 7 proteins which were present in significantly higher levels in pre-eclamptic urine samples than controls and 1 protein was significantly lower in pre-eclamptic samples. An example of spectral peaks are shown in Figure 1.

For protection of intellectual property protein identities are omitted.

Conclusions: A urinary proteomic signature can be identified in the urine of women with pre-eclampsia samples. Validation of this differential proteomic profile using a larger number of samples, including women with CKD and superimposed pre-eclampsia, chronic and gestational hypertension is currently underway. The use of a diagnostic urinary biomarker will be invaluable in low socioeconomic countries where facilities for blood taking and processing are limited.

TH-OR045

P-Cresol (PC) and P-Cresyl Sulfate (PCS) Stimulate Chemoattractant Protein-1 ( MCP-1) Expression in Human Vascular Smooth Muscle Cells (VSMC) Rayana Ariane Pereira Maciel, 1 Lisenny Campoli Tono Rempel, 1 Alessandra Becker Finco, 1 Wesley M. Souza, 1 Roberto Pecoits-Filho, 1 Andréa Marques Stinghen, 1 Bruna Bosquetti, 1 1Universidade Federal do Paraná, Curitiba, Brazil; 2Pontificia Universidade Catolica do Parana, Curitiba, Brazil.

Background: Uremic toxins such as PC and its conjugate PCS are responsible for many of the uremia clinical consequences, such as atherosclerosis in CKD patients. In this study we investigate the in vitro role of PC and PCS in MCP-1 expression via transcription factor NF-κB p65 in VSMC.

Methods: PCS was synthesized by PC sulfatation. VSMC were extracted by enzymatic digestion of umbilical cord vein and characterized by immunofluorescence against α-actin antibodies. The VSMC were treated with PC and PCS in a kinetics of 0 and 3 h in the normal (PC 0.60 and PCS1 2.87 mg/L), minimum (PC20 2.10 and PCS2 15.6 mg/L) and maximum uremic concentrations (PC40 7.40 and PCS3 74.20 mg/L). Cell viability was assessed by MITT. MCP-1 expression was investigated by ELISA in cells supernatant after toxins treatment in the presence or absence of NF-κB p65 inhibitor.

Results: No significant difference was observed in cell viability after toxins treatment for all concentrations tested. After 3h there was a significant increase in MCP-1 expression in cells treated with PC2 (150.16 pg/mL, P<0.001), PC3 (144.28 pg/mL, P<0.05), PCS1 (145.24 pg/mL, P<0.005), PCS2 (150.13 pg/mL, P<0.001) and PCS3 (160.8 pg/mL, P<0.001), compared with control cells (37.31 pg/mL). When VSMC were treated with NF-κB p65 inhibitor, we observed after 3h a pronounced decrease in MCP-1 levels, especially to PC2 (150.16 pg/mL vs 56±10 pg/mL, P<0.001) and PC3 and PCS1 vs 50±18 pg/mL, P<0.001, but not with the inhibitor was adding with PCS.

Conclusions: VSMC are involved in atherosclerosis lesion formation and cytokines production such as MCP-1, which contributes to the inflammatory response initiation and propagation to lipid. Our results suggest for the first time that PC mediates MCP-1 production in VSMC, probably through NF-κB p65 pathway, although we hypothesize that PCS acts through a different subunit pathway since NF-κB p65 inhibitor was not able to inhibit MCP-1 production.

Funding: Government Support - Non-U.S.

TH-OR046

Targeting the CRBN/DBD1/Cul4A E3 Ubiquitin Ligase Prevents Kidney Fibrosis Yuan yuan Shi, 1 Yan Lin, 1 William E. Mitch, 1 Zhaoying Hu, 1 1Nephrology Div, Second Hospital of Shanxi Medical Univ, Taiyuan, Shanxi, China; 2Nephrology Div, Baylor College of Medicine, Houston, TX.

Background: Cereblon (CRBN) interacts with damaged DNA binding protein 1 (DBD1) and Culin 4A (Cul4A), forming an E3 ubiquitin ligase complex, the first step toward degradation by proteasomes (UPS). CRBN is the critical element that recognizes substrate proteins leading to their conjugation with ubiquitin and ultimately, UPS degradation. Notably, the CRBN/DBD1/Cul4A is activated by inflammation, in stress response and it can influence cell growth. Since CRBN is stimulated by inflammation, etc. we investigated whether blocking CRBN would ameliorate the progression of kidney fibrosis. The mechanisms of fibrosis are pertinent because the degree of fibrosis is closely associated with progression of chronic kidney disease (CKD). Unfortunately, there are few therapies that effectively block or suppress kidney fibrosis. We investigated whether blocking CRBN would ameliorate the progression of kidney fibrosis.

Methods: In mice with genomic or pharmacological inhibition of CRBN, we evaluated inflammatory mediators and the degree of kidney fibrosis following unilateral ureteral obstruction (UUO).

Results: At 7 days after UUO in wild type mice, there was increased expression of collagen, fibronectin and SMAa, as demonstrated by many investigators. Mice with CRBN knockout exhibited reduced expression of collagen I (60%), fibronectin (>80%) and SMAa (>90%). Importantly, there was also suppression of the tubulointerstitial fibrosis caused by UUO. Inhibition of CRBN suppressed TGFb1 mRNA expression as well as phosphorylation of Smad3. In cultured kidney fibroblasts and wild-type UUO mice, we found that thalidomide, a CRBN inhibitor, suppressed ubiquitin conjugation to SmoN, this results in an increase in Smad3 and inhibition of TGFb1 expression. These responses eda fibrosis in the kidney despite UUO.

Conclusions: The ubiquitin E3 ligase of the CRBN/DBD1/Cul4A E3 complex regulates the kidney expression of TGFb1 and ultimately, fibrosis. We have identified a molecular basis for an anti-fibrotic effect of blocking CRBN and this could become a treatment strategy for the fibrosis that damages the kidney in CKD.

Funding: NIDDK Support

TH-OR047

Resistance Exercise Prevents Muscle Wasting in Mice with Chronic Kidney Disease by Increasing microRNA-23 Cong Zhang, 1 Li Hu, 1 Janet D. Klein, 1 Russ Price, 1 Xiaonan H. Wang. 1 1Renal Medicine, Emory Univ, Atlanta, GA; 2Renal Medicine, Atlanta VAMC, Decatur, GA.

Background: There are 23 individual microRNAs that are significantly changed in muscle of chronic kidney disease (CKD) mice (Wang et al, JASN 2010). We previously showed that exercise improves muscle protein synthesis and prevents accelerated protein degradation in muscle of CKD mice (Wang et al, Kid 2009). This study identifies In silico

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
analysis and other reports suggested that microRNA-23 (miR-23) targets several proteins associated with muscle atrophy. In this study, we evaluated whether exercise increases the level of miR-23 in CKD mice.

Methods: CKD was induced in 20-25-g mice by 5/6 nephrectomy. Muscle overloading, produced by removing the gastrocnemius and soleus muscles from both hindlimbs of control and CKD mice, was used as an exercise model.

Results: Since atrophy, MuRF-1, Y1 and PTEN are putative targets of miR-23, and each of them can impact muscle wasting, we verified whether miR-23 changes the expression of each target using 3'UTR-luciferase reporter assays. Overexpression of miR-23 in cultured muscle cells inhibits the reporter gene activities of atrogin-1 and MuRF-1, suggesting that miR-23 attenuates the expression of its predicted targets. Exercise significantly increased the level of miR-23 in muscle of CKD mice vs. unexercised CKD mice. Consistent with the response, exercise decreased PTEN protein and increased Akt phosphorylation (2.3-fold, P < 0.001) which would limit muscle atrophy. Exercise increased MyoD, myogenin and eMyHC, myogenic proteins that are linked to YY1 transcription factor in CKD mice. Finally, miRNAs for the muscle-specific E3 ubiquitin ligases, atrogin-1, and MuRF-1, were attenuated by exercise in CKD mice. Other muscle-specific miRs (i.e., miR-1, miR-133b and miR-206) were unchanged by exercise in muscle of CKD mice, indicating specificity of the miR-23 response.

Conclusions: Resistance exercise can prevent CKD-induced muscle loss by increasing miR-23. This leads to a suppression of multiple atrophy-related target proteins that may contribute to the muscle-sparing effects of exercise in CKD.

Funding: NIDDK, Support, Other NIH Support - NIH AR060268 (XHW); DK095610 (SRP), Veterans Affairs Support

TH-OR048
GFR Decline as an Endpoint for Clinical Trials in CKD – A Meta-Analysis of Treatment Effects from Randomized Trials: Report of an NKF-FDA Workshop

Lesley Inker, Hiddo Jan Lambers Heerspink, Hasi Mondal, Josep Coresh, Tom Greene, Andrew S. Levey, Tufts Medical Center; Johns Hopkins Univ; Univ of Utah; Univ Medical Center Groningen

Background: The FDA accepts doubling of serum creatinine (Scr) (halving of GFR), as a surrogate endpoint for kidney failure in trials of CKD progression. Substantial time is often required to reach this endpoint. Lesser declines in GFR could reduce the length of trials, increasing feasibility of RCTs. The NKF and FDA sponsored a workshop to examine data supporting alternative definitions of GFR decline as endpoints in RCT’s.

Methods: Using a pooled dataset of 12821 patients from 43 CKD studies, we compared the treatment effect using established endpoints (EE) of dialysis, GFR<15 or 2XScr over the entire trial period to the alternative endpoints (AE) of a decline in GFR of 20, 30 or 40% at the end of the entire trial or 12, 18 and 24 months. Cox analyses were performed within study, followed by random effects analyses summarizing results across studies of same intervention.

Results: The table compares percent differences in hazard ratios for the treatment effect on AE’s compared to the EE.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>All 24 months</th>
<th>18 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA50</td>
<td>40%</td>
<td>10%</td>
<td>30%</td>
</tr>
<tr>
<td>RA50+CBX</td>
<td>50%</td>
<td>15%</td>
<td>35%</td>
</tr>
<tr>
<td>SB</td>
<td>2.5</td>
<td>0.5</td>
<td>5.0</td>
</tr>
<tr>
<td>LPE</td>
<td>5.0</td>
<td>10.0</td>
<td>6.0</td>
</tr>
<tr>
<td>G</td>
<td>24-25</td>
<td>49-50</td>
<td>61-65</td>
</tr>
</tbody>
</table>

Higher values indicate greater HR for the AE (less strong treatment effect) than HR of the EE. Pooled results may not apply to each studies. Solid shading: differences in HR due to the short duration. Scr based AE should not be used to evaluate interventions that effect nonScr determinants of Scr.

Funding: Private Foundation Support

TH-OR049
GFR Decline as an Alternative Endpoint for Kidney Failure – Meta-Analysis of CKD Prognosis Consortium Cohorts: A Report from an NKF-FDA Workshop

Josep Coresh, Kunihiro Matushita, Yingying Sang, Shoshana Ballew, Lawrence J. Appel, Jamie Alton Green, Gunnar H. Heine, Lesley Inker, Arcef Ishani, Angharad Marks, Tanvir Chowdhury Turin, Kunitoshi Iseki, Andrew S. Levey. CKD Prognosis Consortium

Background: The NKF and FDA convened a workshop to evaluate the evidence for GFR smaller than doubling (2x) of serum creatinine as a alternative endpoint to kidney failure in studies of CKD progression.

Methods: We evaluated the change in eGFR smaller than doubling (2x) of serum creatinine as an alternative endpoint to kidney failure in studies of CKD progression.

Conclusions: Declines in eGFR, smaller than doubling of serum creatinine, are strongly and consistently associated with the risk of ESRD adjusted for the baseline eGFR and covariates supporting alternative endpoints for CKD progression.

Funding: Private Foundation Support

TH-OR050
Serum Level of Soluble (Pro)renin Receptor Is Modulated in Chronic Kidney Disease (CKD) and a Novel Valuable Biomarker for Progression of CKD: A Longitudinal Follow-Up Study

Kazu Hamada, Yoshiko Shimamura, Koji Ogata, Kosuke Inoue, Yoshinori Taniguchi, Taro Horino, Kenji Yuasa, Yoshio Terada

Methods: A total of 374 patients with CKD were enrolled. Serum creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), hemoglobin (Hb), and the urine protein/Cr ratio were also measured. Similarly, clinical parameters were also evaluated using serum and urine sample collected after 1 year (n = 204).

Results: Serum (P)RR levels were positively associated with serum Cr, BUN, UA, and the urine protein/Cr ratio were also measured. Similarly, clinical parameters were also evaluated using serum and urine sample collected after 1 year (n = 204).

Conclusions: Levels of soluble (P)RR correlated with the stage of CKD, and had a positive correlation with the decline rate of eGFR. Our findings suggest that soluble (P)RR may be involved in renal injury and influence progression of CKD and become a novel valuable biomarker to predict the prognosis of kidney diseases.

TH-OR051
Elevated NT-proBNP and Kidney Function Decline

Meevun Park, Eric Vittinghoff, Michael Shlipak, Mary Whooley, Nisha Bansal

Background: Venous congestion may be an important contributor to kidney function decline even in patients without clinical heart failure (HF). N-terminal pro-brain natriuretic peptide (NT-proBNP) is released from cardiac myocytes in response to pressure or volume overload. We evaluated associations of NT-proBNP with longitudinal changes in kidney function among patients with stable coronary heart disease and without clinical HF.

Methods: Participants in the Heart and Soul Study had NT-proBNP measured from baseline serum samples. We excluded individuals with baseline HF and categorized NT-proBNP into tertiles, comparing the highest (≥396 pg/mL) to the lowest (<72 pg/mL) quartile. We evaluated associations of NT-proBNP with longitudinal changes in estimated
glomerular filtration rate (eGFR), defined as a percent loss per year and as rapid eGFR loss (>3% eGFR loss per year). We adjusted for cardiovascular disease risk factors, echocardiography measures, and baseline kidney function.

**Results:** Among 810 participants without HF, mean age was 67 (SD 11); 82% were male; 60% were white. Median NT-proBNP was 150 pg/mL (IQR 67-377). Mean eGFR was 72 (SD 21) ml/min/1.73m². After multivariable adjustment, the highest quartile of NT-proBNP was associated with a 1.7% (0.5-3) faster loss in eGFR per year (p=0.007) compared with the lowest quartile. Participants in the highest quartile also had >5 times the odds of rapid eGFR loss compared with those in the lowest quartile (Table); findings were similar when restricted to participants with eGFR>60 ml/min/1.73m² at baseline (N=550).

**Conclusions:** NT-proBNP is strongly associated with accelerated kidney function loss in individuals without HF, suggesting that venous congestion may be an important contributor to adverse kidney outcomes.

**Funding:** NIDDK Support

**TH-OR052**

**Changes in Mortality Rates among Patients with End-Stage Renal Disease (ESRD) and Changes in Incident Rates of ESRD before and after the Great East Japan Earthquake and Tsunami 2011**

Masaki Ohnawaya, Hygiene and Preventive Medicine, Iwate Medical Univ, Iwate, Japan.

**Background:** The Great East Japan Earthquake and Tsunami (March 11th 2011) caused significant damage to people in Iwate Prefecture (North-east area in Japan). Patients with end-stage renal disease (ESRD) are thought to be vulnerable for disasters and prolonged sedentary lifestyle during evacuation may contribute to worsening diabetic and hypertensive status of the refugees living in shelters. It is hypothesized that mortality rates in patients with ESRD increased and incident rates of ESRD increased in disaster area.

**Methods:** The Iwate ESRD registry program based on inventory survey was initiated in 2010 and this program has been continued to the present. We obtained data from the database of Iwate ESRD registry program from Iwate Medical Association. We counted total annual number of deaths in ESRD patients and total annual number of incident ESRD in Iwate Prefecture across the sea coast area (Tsunami disaster area) and inland region, respectively, in 2010 and 2011 (disaster year).

**Results:** The results are shown in the table. There were 4 ESRD patients who were missing and feared dead after Tsunami disaster in sea coast area.

**Conclusions:** Mortality rates in patients with ESRD did not increase after The Great East Japan Earthquake and Tsunami. Incident rates of ESRD increased in Tsunami disaster area after the disaster.

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

**TH-OR053**

**Association of Body Mass Index with Progression of Kidney Disease in Patients with Non-Dialysis Dependent CKD**

Jun Ling Lu,1 Kamyar Kalantar-Zadeh,2 Jennie Z. Ma,3 Leigh Darryl Quarles,3 Csaba P. Kovesdy.1,4

**Methods:** We examined the association of BMI with CKD progression in a national cohort of 453,946 US veterans with estimated glomerular filtration rate (eGFR) ≤60ml/min/1.73m². CKD progression was defined as the incidence of the composite of doubling of serum creatinine or End Stage Renal Disease (ESRD), and as the risk of slopes of eGFR <−4 ml/min/1.73m²/year. Associations were examined in crude (Model 1) and in multivariable adjusted Cox models and logistic regression models. Adjustments were made for age (Model 2), race (Model 3), comorbidities and medications (Model 4), and baseline estimated GFR (Model 5).

**Results:** The mean age (Standard Deviation [SD]) was 73.9(9.3) years, 9.1% were African American, and the mean estimated GFR (SD) was 47.8 (9.9) ml/min/1.73m². 4876 patients died (mortality rate: 73.9/1000 Patient-Year [95% confidence interval (CI):73.5-74.3]). BMI showed U-shaped association with both the incidence of the composite renal end point (Figure 1), and the risk of steeper slopes (Figure 2). Patients with BMI 25-30 kg/m² had the best outcomes.

**Conclusions:** The association of BMI with kidney disease is complex, with both relatively low and high BMI showing increased risk of progressive CKD. Overweight patients with CKD appear to have the best renal outcomes.

**Funding:** NIDDK Support, Veterans Affairs Support

**TH-OR054**

**Percutaneous Coronary Intervention versus Optimal Medical Therapy for Stable Angina in Late-Stage Chronic Kidney Disease: A Decision Analysis**

Ernest I. Mandel,1 Matthew R. Reynolds,2 David M. Charytan.1

**Background:** Performing percutaneous coronary interventions (PCI) in the setting of stable symptomatic angina is often delayed in late-stage chronic kidney disease until necessitated by a more acute indication or until dialysis has been initiated. Whether immediate PCI or deferral of PCI in favor of optimal medical management (MM) improves quality of life or survival is uncertain.

**Methods:** Quality-adjusted life-years (QALYs) following PCI vs. MM in late-stage CKD and stable symptomatic angina were compared in a decision analysis. A Markov model was created to capture the possible disease states taking into account successful relief of symptomatic angina from the chosen intervention, dialysis-dependence as a result of CKD progression or contrast-induced nephropathy (CIN) from PCI, and procedural morbidity and mortality. Utilities and transition probabilities were derived from previous studies, literature review, and USRDS data. The Markov model was run in 3-month cycles for a total of three years of follow-up. Probabilistic sensitivity analyses on the likelihood of dialysis-dependent CIN and other transition probabilities were conducted using Monte Carlo simulation with 10,000 trials.

**Results:** The PCI strategy yielded a mean (SD) of 1.44 (0.04) QALYs over three years of follow-up while the MM strategy yielded a mean of 1.40 (0.04) QALYs (p=0.0001). The difference (95% CI) in QALYS between the two strategies was 0.038 (0.037 to 0.039).

**Conclusions:** A strategy of PCI for relief of stable symptomatic angina yielded higher expected QALYS than MM. The probability of CIN at which the advanced CKD patient would be indifferent between MM and PCI, or over which would prefer MM, was 0.42.

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

**TH-OR055**

**Monogenic Forms of Nephrotic Syndrome Occur in Diverse Genes across the Lifespan in North American Subjects**

Matthew G. Sampson,1,2 Edgar Otto,1,2 Trotsoy,1,2 Crystal A. Gadegbeku,1,2 Matthias Kretzler.1,2

**Background:** The frequency of causal mutations in children and adults with nephrotic syndrome in North America nephrology practices is unknown. This is in part because genetic and phenotypic heterogeneity of NS, and cost, precludes sequencing all known NS genes in all affected patients. To address this, we sequenced 21 monogenic NS genes in 103 unselected NS subjects from two prospective, multi-center glomerular disease cohorts.

**Methods:** NEPTUNE (n=67) enrolls at time of initial clinical biopsy and CPROBE (n=36) enrolls incident and prevalent patients. Recruitment is not based on age, suspicion of genetic NS, or steroid resistance. Subjects had either minimal change disease or FSGS or biopsy. All exons of 21 NS-associated genes were analyzed by microfluidic PCR paired with Next-Gen sequencing. After mapping and comparison to the Exome Variant Server, variants with minor allele frequency <1% and (NP_0552229VQ variant) were validated by Sanger sequencing. Variants deemed causal were based on previous reports of pathogenicity, <0.3% frequency or absence in control populations, and cross species conservation.

**Results:** We identified 15 NS-associated genes in 26 (25%) NS subjects. In NEPTUNE and CPROBE combined, 32 (31%) NS subjects had a causative genetic variant. In 26 (25%) NS subjects, 15 NS-associated genes were identified in at least one subject. The frequency of causal mutations was highest in children with NS (44%, 13/29), intermediate in preadolescents (24%, 8/34), and lower in adults (18%, 2/11).

**Conclusions:** We identified a diverse spectrum of causative genetic mutations in NS across the lifespan in North America. This suggests that genetic testing may be considered in all NS patients, regardless of age.
Results: 8/103 (8%) of NS subjects had a probable monogenic cause (5/8; > age 21; 0/8 with family history of NS). Variants were found in NPHP2 (3), ACTN4, CD2AP, LMX1B, MYO1E, and WFS1 in 11 affected members of seven families. We included a person in their 60s with compound heterozygosity of MYO1E, their 40s with an LMX1B variant, and a teen with a CD2AP variant. The five adult-onset subjects had variants in five different genes.

Conclusions: High-throughput sequencing reveals a diverse set of genetic forms of NS in 8% of this phenotypically varied cohort. This suggests that in sporadically affected subjects, targeting only subsets of bases based on age or other characteristics may result in missing genetic causes of NS. Discovery of additional monogenic NS genes will increase the prevalence of monogenic forms of NS. More frequent, or functional non-coding, NR-associated risk variants may explain a portion of the remaining heritability.

Funding: NIDDK Support

TH-OR056

MIR-17-92 Is Required for Nephrogenesis and Renal Function

April Marrone,1 Sheldon Bastacky,2 Donna Beer Stolz,3 Andrew J. Bodnar,1 Jacqueline Ho.1

1Inserm U983, Necker Hospital, Paris, France; 2Dept of Pediatrics, School of Medicine, Univ of Pittsburgh, Pittsburgh, PA; 3Dept of Cell Biology, Univ of Pittsburgh, Pittsburgh, PA

Background: MicroRNAs (miRNAs) are small non-coding RNAs that act as novel regulators of gene expression through the repression of their target mRNAs. Although deletion of miRNAs in nephron progenitors demonstrates a critical role for miRNAs in progenitor survival, the specific miRNAs responsible have not been identified. Deletions in the MIR17HG cluster (miR-17~92 in mice) represent the first miRNA mutations to be associated with a developmental defect in humans, leading to Feingold syndrome. While MIR17HG is expressed in the developing kidney, and a subset of patients with Feingold syndrome have renal anomalies, it remains unclear to what extent MIR17HG contributes to renal development and function.

Methods: To define the role of miR-17~92, we generated a conditional deletion of miR-17~92 in nephron progenitors and their derivatives in mice, resulting in renal hypoplasia. The nephron progenitor population is preserved; however, there are decreased developing nephrons. Cell division analyses throughout embryogenesis suggests that progenitors and their progeny divide less in the absence of miR-17~92, providing a possible mechanism causing low nephron endowment. Postnatally, the mice develop signs of renal disease by six weeks with albuminuria, and then focal podocyte foot process effacement and glomerulosclerosis at three months.

Conclusions: Taken together, these data support the first report for a single miRNA cluster in renal development, specifically in the regulation of nephron development, with subsequent consequences for renal function in adult mice.

Funding: NIDDK Support

TH-OR057

A Novel Variant of the Mitochondrial Heavy Strand Promoter Causes Renal Disease and Reduced Oxygen Consumption

Thomas Michael Connor,1 Daniel P. Gale,1 Phillippa J. Carling,2 Gavin Hudson,2 Patrick F. Chinnery,2 Patrick H. Maxwell.1 1UCL Centre for Nephropathy, Univ College London, London, United Kingdom; 2Institute of Genetic Medicine, Univ of Newcastle, Newcastle, United Kingdom

Background: In the past few years, mitochondrial dysfunction has become a focus of research in human disease. Disorders of mitochondrial DNA (mtDNA) are an important cause of genetic disease and produce highly variable clinical features. There is a renal phenotype associated with a number of complex mitochondrial disorders, and evidence of accelerated frequency of single nucleotide polymorphisms and deletions in end-stage renal disease. To date, the majority of pathogenic mutations have involved coding regions of the mitochondrial genome. We investigated a large Caucasian pedigree that included 17 individuals affected with adult-onset renal disease in the maternal line. There were no extra-renal signs in any of the affected individuals.

Methods: DNA was genotyped using the Illumina 300K chip. The mitochondrial gene sequencing was performed using Big Dye Terminator cycle sequencing and compared with the reference sequence. Primary dermal fibroblasts were cultured from four affected individuals and three healthy controls. Cybrids were created by fusion with 143B rho zero cells. Mitochondrial respiration was measured using the Seahorse XF bioanalyzer.

Results: Linkage analysis demonstrated extra-chromosomal inheritance in this family. Mitochondrial sequencing showed the presence of a novel polymorphism located within the heavy strand promoter 1 (HSPI) and expressed at homoplasmic levels. Primary fibroblasts showed a reduction in the ratio of transcripts from the HSPI and a reduced rate of oxygen consumption. These findings were confirmed in cybrids, which showed an even greater reduction in HSPI transcription and mitochondrial protein synthesis.

Conclusions: This is the first description of familial nephropathy due to a mutation in the mitochondrial heavy strand promoter. Reduced promoter function results in decreased transcription, and causes reduced oxygen consumption with a compensatory increase in glycolysis. These findings confirm the importance of mitochondrial function in renal disease.

Funding: Government Support - Non-U.S.

TH-OR058

Mutation Analysis in 30 Mouse Model Candidate Genes in 790 Humans with Isolated CAKUT

Stefan Kohl,1 Gabriel C. Dworschak,2 Alina Hilger,2 Pawaree Saisawat,2 Elijah O. Kehinde,3 Heiko M. Reutter,2 Velibor Tasic,2 Friedhelm Hildebrandt,3 1Dept of Nephrology, Children’s Hospital, Boston; 2Dept of Pediatrics, Univ of Michigan, Ann Arbor; 3Medical Faculty, Univ of Belgrade, Belgrade, Serbia; 4Institute of Human Genetics, Univ of Bonn, Bonn, Germany; 5Institute of Pediatric Nephrology, Children’s Hospital, Skopje, Macedonia, The Former Yugoslav Republic of; 6Howard Hughes Medical Institute, Chevy Chase.

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) account for ~50% of the ESRD cases in children. In order to identify single-gene causes of CAKUT, we performed exon resequencing in 790 children (690 families) with non-syndromic CAKUT examining 30 genes that (i) cause renal agenesis in mice and (ii) previously have not been implicated in pathogenesis of human CAKUT.

Methods: The coding sequences of 30 genes were re-sequenced using a high-throughput mutation analysis by array-based PCR (Fluidigm®) and next-generation sequencing (1).

Conclusions: Our results indicate that in genes known to cause Fraser syndrome if truncating alleles are present, hypomorphic mutations cause isolated CAKUT. In 690 families with CAKUT we could molecularly “solve” ~2.5% with recessive hypomorphic mutations in FRAS1, FREM2, and GRIP1. Furthermore, we identified 3 genes that cause CAKUT in mice mutations in 3 families, thereby making them candidates for mutation analysis in future studies.

Funding: Government Support - Non-U.S.
TH-OR060
Copy-Number Variation in Children with a Solitary Functioning Kidney – The KIMONO-GENE Study Rik Westland,1,2,3 Brittany J. Perry,1 Miguel VERBITSKY,1 Michiel Schreuder,2 Petra Jg Zwijnenburg,1 Ali G. Gharavi,1 Joanna Van Wijk,1 Simone Sanna-Ccherchi,1 1Div of Nephrology, Columbia Univ, New York City, NY; 2Dept of Pediatric Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; 3Dept of Clinical Genetics, VU Univ Medical Center, Amsterdam, Netherlands.

Background: Rare genic copy-number variations (CNVs) have been associated with congenital renal malformations. We investigated the role of rare CNVs in children with a solitary functioning kidney derived from the KIMONO study.

Methods: Genome-wide genotyping for CNV analysis was performed with the Illumina OmniExpress platform (730k markers). PennCNV was used to determine the CNV calls using generalized genotyping methods. To identify rare pathogenic CNVs, we compared data to 23,362 controls. Criteria for pathogenic CNVs were: 1) CNV-size ≥100kb, 2) confidence score ≥30 and 3) frequency of <1:5,000 in controls.

Results: 64 children with a solitary functioning kidney were included. Clinical phenotypes were renal hypodysplasia (48%), unilateral renal agenesis (30%), vesicoureteric reflux (14%) and obstructive nephropathy (8%). A total of 99 large, high-quality CNVs were identified (mean 1.55 per case), of which 58 (59%) were duplications and 41 (41%) were deletions. Median CNV-size was 173kb (IQR 133–250kb). CNVs overlapping significantly with known genomic disorders were identified in 6 (9%) patients (e.g. 3p29 microdeletion syndrome, 16p13.11 duplication and 16p12.1 distal deletion). Furthermore, 6 (9%) children were found to carry CNVs that were larger than 250kb, disrupting coding segments and adjacent regulatory DNA.

Conclusions: In silico analysis and functional assays consisting of DNA binding and transactivation studies were performed. Immunohistochemistry to evaluate the impact of dysregulated PAHX on expression of a target, WT1, was done.

Results: Six and seven heterozygous non-synonymous private variants were found in the familial FSGS and CAFKU cohort, respectively. There was an enrichment of rare variants in the patient groups compared to controls (p<0.05). In the CAFKU group, most variants localized to outside of this region. As predicted, the PAHX2 variant impaired DNA binding and transactivation activity while the PAHX2 stop variant resulted in enhanced repressor activity without affecting DNA binding. Immunohistochemical staining revealed reduced WT1 expression in both sclerosed and non-sclerosed glomeruli.

Conclusions: PAHX2 mutations lead to FSGS and CAFKU. Functional studies suggest that mutations lead to haploinsufficiency or dominant negative effects. Dysregulation of PAHX2 targets expressed in the podocyte such as WT1 may lead to FSGS by dysruption of this cell critical for filtration.

Funding: Other NIH Support - DK54931 to Dr. Martin Pollak.; NHLBI/NHGRI Exome Project grant R01HL094963

TH-OR062
Mutations in PAX2 Cause Adult-Onset Familial Focal and Segmental Glomerulosclerosis Moumita Baruah,1 Emilia Stellacci,2 Lorenzo Stella,2 Astrid Weis,1 Giulio Genovese,3 Valentina Muto,2 Hakan R. Toka,1 Victoria Charoongratana,1 Martin R. Pollak,1 1Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; 2Div of Nephrology, Columbia Univ, New York City, NY; 3Dept of Pediatric Nephrology, VU Univ Medical Center, Amsterdam, Netherlands.

Background: FSGS is a histologically defined kidney injury characterized by sclerosis of some but not all glomeruli. Mutations in the transcription factor gene, PAX2, have been shown to cause congenital abnormalities of the kidney and urinary tract (CANTK) as part of an autosomal dominant condition named papillonoidal syndrome. We show that PAX2 mutations lead to FSGS and demonstrate the mechanisms of disease.

Methods: Exome sequencing in a family with adult-onset FSGS revealed a suspicious PAX2 variant. PAX2 was sequenced in 175 FSGS families and 85 CAFKU individuals. In silico analysis and functional assays consisting of DNA binding and transactivation studies were performed. Immunohistochemistry to evaluate the impact of dysregulated PAX2 on expression of a target, WT1, was done.

Results: Six and seven heterozygous non-synonymous private variants were found in the familial FSGS and CAFKU cohort, respectively. There was an enrichment of rare variants in the patient groups compared to controls (p<0.05). In the CAFKU group, most variants localized to outside of this region. As predicted, the PAX2 variant impaired DNA binding and transactivation activity while the PAX2 stop variant resulted in enhanced repressor activity without affecting DNA binding. Immunohistochemical staining revealed reduced WT1 expression in both sclerosed and non-sclerosed glomeruli.

Conclusions: PAX2 mutations lead to FSGS and CAFKU. Functional studies suggest that mutations lead to haploinsufficiency or dominant negative effects. Dysregulation of PAX2 targets expressed in the podocyte such as WT1 may lead to FSGS by dysruption of this cell critical for filtration.

Funding: Other NIH Support - DK54931 to Dr. Martin Pollak.; NHLBI/NHGRI Exome Project grant R01HL094963

TH-OR061
A Novel Mutation Specific Cause of Fanconi Syndrome and Nephrocalcinosis in HNF4A Alexander J. Hamilton,1,2 Coralie Bingham,2 Sian Ellard,1 Andrew Hattersley,1 1Univ of Exeter Medical School, Exeter, Devon, United Kingdom; 2Renal Unit, Royal Devon and Exeter Hospital, Exeter, Devon, United Kingdom.

Background: We have identified 5 individuals from 3 families with an HNF4A R67W mutation that co-segregates with Fanconi syndrome and nephrocalcinosis. HNF4A mutations cause maturity onset diabetes of the young (MODY), but are not among the 8 genes known to cause proximal tubulopathy. We aimed to describe this new phenotype and establish if this was a generalised or mutation specific effect by comparison with a cohort of patients with other HNF4A mutations.

Methods: We measured fasted urines in the R76W group and in 20 patients with other HNF4A mutations. Renal ultrasounds were performed in 15 patients. Results were compared using the independent samples median test or Z scores.

Results:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>R76W (n=5)</th>
<th>Other HNF4A (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary α1-microglobulin mg/l, median</td>
<td>92 (60)</td>
<td>60 (48)</td>
</tr>
<tr>
<td>Urinary β2-microglobulin mg/l, median</td>
<td>60.4</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Urinary retinol binding protein mg/l, median</td>
<td>28.0</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Urinary glucose mmol/l, median</td>
<td>122</td>
<td>127 (0)</td>
</tr>
<tr>
<td>Urinary α2-microglobulin mg/l, median</td>
<td>10.5</td>
<td>60.0</td>
</tr>
<tr>
<td>Serum magnesium mmol/l, median</td>
<td>0.71</td>
<td>0.75</td>
</tr>
<tr>
<td>Serum calcium mmol/l, median</td>
<td>2.13</td>
<td>2.16</td>
</tr>
<tr>
<td>Serum creatinine mg/dl, median</td>
<td>1.35</td>
<td>1.35</td>
</tr>
<tr>
<td>Serum urate umol/L, median</td>
<td>268.0</td>
<td>352.0</td>
</tr>
<tr>
<td>Urinary a41-actin, mean ± SD</td>
<td>2.33 ± 0.16</td>
<td>1.92 ± 0.18</td>
</tr>
</tbody>
</table>

Conclusions: Patients with the HNF4A R67W mutation have a novel and specific phenotype of proximal tubulopathy and nephrocalcinosis characterised by aminoaciduria, massive low molecular weight proteinuria and glycosuria. These features were not seen in 20 patients with other HNF4A mutations. In silico modelling suggests that the R76 residue is involved in DNA binding to promoters and we hypothesize that the mutation may affect target specificity. This is the first description of a mutation specific effect in the MODY genes, hitherto not known to be related to renal tubular dysfunction or renal tract calcification.

Funding: Government Support - Non-U.S.

TH-OR063
IQCJ Podocytopathy Causes Primary Renal Failure and De Novo Membranous Nephropathy Post Transplantation Rachael Lennom,1 Edward A. McKenzie,1 Sarah B. Daly,1 Helen Mary Stuart,1 Jill Clayton-Smith,1 Shelly Harris,1 Lorna J. McWilliam,1 Colin Short,2 Laurence R. Solomon,3 Ian D. Pettitt,1 Ron Korstanje,4 Mario Schiffer,4 Paul E. Brenchley,1 1Univ of Manchester, United Kingdom; 2Central Manchester NHS Trust, United Kingdom; 3Lancashire Teaching Hospitals, Preston, United Kingdom; 4Univ of Oxford, Oxford, United Kingdom; 5Jackson Labs, Bar Harbor; 6Univ Medical School, Hannover, Germany.

Background: We describe a novel podocytopathy causing primary renal failure in two siblings identified following “de novo” membranous nephropathy (MN) in their allografts.

Methods: A consanguineous family where parents and two children suffered CKD was investigated genetically following the post transplant development of the novo MN in both siblings resulting in allograft loss within two years. Autosyotigraphy mapping identified a novel gene deletion of 129kb, near IQ Domain-Containing Protein J (IQCJ) on chr 3. Exome sequencing excluded known podocytopathies. Native kidney biopsy of an affected sibling showed a podocytopathy and excluded MN. In vitro and in vivo experimental systems were used to investigate the biological function of IQCJ.

Results: Parents were heterozygous and affected siblings homozygous for the gene deletion. Both affected cases became seropositive for anti-IQCJ antibodies detected by ELISA post transplantation. Immunostaining of normal kidney for IQCJ showed podocyte specific staining. In cultured normal podocytes, mRNA transcript for IQCJ was detected by PCR and immunostaining with anti-IQCJ located the antigen in transport vesicles with a distribution from perinuclear to cell membrane showing colocalisation with known transport proteins. Transient knock down of IQCJ mRNA in zebrilla caused edema consistent with a glomerular phenotype.

Conclusions: Alloimmunization following transplantation can reveal abnormal gene/protein expression causing the primary renal disease e.g. Alports Disease. Such a mechanism may explain two different renal phenotypes (in native and allograft kidney) occurring in this family and caused by a single podocyte gene, IQCJ. This gene may play a wider role in primary glomerulopathies and as a target for “de novo” MN post transplantation.

Funding: Private Foundation Support
TH-OR064

Mutations in DGKE Cause a Novel Form of Recessive Atypical Hemolytic-Uremic Syndrome without Complement Activation

Mathieu Lemarié,1,2 Veronique Frenoulle-Bacchi,1 Franz Schaefer,3 Murim Choi,1,4 Jack Tang,1 Mogile Le Quintrec,1 Fadi Fakhouri,1 Sophie Taque,1 Francois Nobili,1 Weizhen Ji,1,2 John Overton,1 Shrikant M. Mane,1 Gudrun Nürnberg,1 Denis Morin,1 Véronique Baudouin,1 Brigitte Llanas,1 Eva Simkova,1 Peter Nuernberg,1 Gilbert W. Mocek1,2 John Hwa,1 Chantal Loirat,1 Richard P. Lifton1,2,4,5,6,7

1Yale Univ; 2Howard Hughes Medical Institute; 3Hôpital Européen Georges-Pompidou; 4Centre de Recherche des Cordeliers; 5Heidelberg Univ; 6Yale Center for Mendelian Genomics; 7CHU Nantes; 8CHU Besançon; 9Univ of Cologne; 10CHU Montpellier; 11Hôpital Universitaire Robert-Debré; 12CHU Bordeaux; 13Dubai Hospital; 14ATLAS Bioids GmbH.

Background: Atypical Hemolytic-uremic syndrome (aHUS) is caused by pathological complement activation due to hereditary or acquired factors. Renal outcomes have improved since complement pathway inhibitors were introduced. Half of aHUS patients remain unexplained.

Methods: We performed exome sequencing on samples from two unrelated families each with 2 affected children. Bioinformatics analysis yielded a list of variants shared by each sibling set: gene(s) present in both lists were sequenced to identify disease-causing mutations.

Results: We identified a novel recessive damaging and missense mutations in DGKE (dicylglycerol kinase ε): mutations co-segregated with disease in 13 subjects from 9 unrelated kindreds. All patients presented before age 1, none had overt complement abnormalities, many developed chronic kidney disease with age, transplantation was uneventful in 3, and one had a HUS relapse while on eculizumab. DGKE protein is found in glomerular endothelium, podocytes, and platelets. DGKE terminates signaling by directly degrading its substrate dicylglycerol, a potent activator of protein kinase C.

Conclusions: We infer that loss of DGKE function causes a novel form of renal thrombotic microangiopathy that does not require complement activation. The limited benefits of eculizumab for patients with DGKE nephropathy may lead to revision of aHUS treatment guidelines.

Funding: Other NIH Support - US National Institutes of Health (NIH) grants U54 HG006504 01 (Yale Center for Mendelian Genomics), P30 DK079310 05 (Yale O'Brien Center for Kidney Research) and UL1TR001420 07 (Yale Center for Translational Research).

TH-OR065

Differential Role of IL-6 Classical and Trans-Signaling in Crescentic Nephritis

Yoshikuni Nagayama,1 Gerald S. Braun,1 Claudia R.C. van Klinken,2 Ursula Kautz,2 Andreas Hennig,1 Timm Schild,1 Jennifer R. Holdsworth,1 Shahn A. Summers,1 Oliver M. Steinmetz.2 Centre for Inflammatory Diseases, Monash Medical Centre, Melbourne, Australia; 3Med. Klinik, Univ of Hamburg, Germany; 4Biochemistry, Univ of Kiel, Germany.

Background: The pleiotropic cytokine IL-6 critically required for Th17 immunity, is elevated in patients with ANCA vasculitis. IL-6 signaling occurs via the classic pathway using membrane bound IL-6 receptor (mIL-6R) and the trans-pathway via soluble IL-6 receptor (sIL-6R). Anti-IL-6R therapy has recently been established as treatment for rheumatoid arthritis while the role in renal disease remains unclear.

Methods: We induced autoimmune anti-myeloperoxidase (MPO) glomerulonephritis (AIAmPOGN) by immunising C57BL/6 mice with murine MPO. Renal injury was triggered after 14 days by administration of a sub-nephritogenic dose of nephrotoxic serum. Effects of IL-6 inhibition administered during the induction phase (days -1 and 7) or during the effector phase (day 14) of injury were assessed using antibodies targeting IL-6, mIL-6R (classical and trans pathway), or sIL-6R (trans pathway only).

Results: mIL-6R blockade during the induction phase attenuated humoral and cellular autoimmunity. Anti-MPO IgG levels as well as spleen sizes and proliferative activity were significantly reduced. In line, MPO-stimulated splenocyte IL-17A and IFNγ production was impaired in anti mIL-6R treated mice. Importantly, renal injury was also attenuated in terms of histological damage and albuminuria. To clarify the role of IL-6 as effector cytokine, we also studied IL-6 pathway blockade in the effector phase of AIAmPOGN. However, neither systemic autoimmunity nor renal injury was altered by effector phase blockade of either IL-6, mIL-6R or sIL-6R.

Conclusions: IL-6 critically controls the development of cellular and humoral autoimmunity in ANCA associated glomerulonephritis but does not seem to play a major role as effector cytokine. Early mIL-6R blockade significantly attenuated glomerulonephritis and therefore offers exciting therapeutic potential for ANCA vasculitis.

Funding: Government Support - Non-U.S.

TH-OR066

Inhibition of IL-6 Receptor Attenuates Autoimmunity and Glomerulonephritis in Experimental ANCA Vasculitis

Sharon Lee Ford,1,2,3 Bente Marie Møller,1,4,5,6,7 Mathilde Vinge Møller,1,2,3,7,8,9,10 Mathilde K. Böttiger,1,2,3,7,8,9,10 Christian Franz,3,4 Christian Melbye,1,2,3,4,5,6,7,8,9,10 Mathilde Olesen,1,2,3,4,5,6,7,8,9,10 Christian Lehmann,1,2,3,4,5,6,7,8,9,10 Christian Kjaer-Eriksen,1,2,3,4,5,6,7,8,9,10 Anne Katrin Dettmar,1 Isabell Kopka,2 Christoph Licht,2 Markus J. Kemper,1 Peter F. Zippel,1 Jun Oh,1 Univ Hamburg-Eppendorf, Hamburg, Germany; 2Hans-Knöll-Institut, Jena, Germany; 3The Hospital for Sick Children, Toronto, Canada.

Background: The activation of the complement system plays an important role in various kidney diseases. The majority of the circulating complement components are produced in the liver. But in the last decade the local production of complement components by other cells is highly debated. The aim of our study was to prove the ability of renal podocytes to produce and secrete complement components and the functionality of these produced components.

Methods: Immortalized human podocytes were analyzed by Western Blot (WB), immunofluorescence (IF) and PCR for their ability to produce components (C1r/1q, C4, C3, C4, C5, C7, C9) inhibitors (factor I, CD46, CD55, CD59) and activators (factor B, properdin, factor D) of the complement system. Secretion of components was measured in the medium, hemolytic activity was tested in a hemolysis assay and functionality of C3 was tested in a specific C3-converstase assay. Stimulation of the cells was done with either interferon-γ or interleukin 6.

Funding: Government Support - Non-U.S.

TH-OR067

Functionally Active C3 and Other Complement Components Are Secreted by Human Podocytes

Anne Karin Detman,1 Isabel Kopka,2 Christoph Licht,2 Markus J. Kemper,1 Peter F. Zippel,1 Jun Oh,1 Univ Hamburg-Eppendorf, Hamburg, Germany; 2Hans-Knöll-Institut, Jena, Germany; 3The Hospital for Sick Children, Toronto, Canada.

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

Underline represents presenting author/disclosure.

16A
Results: PCR-studies revealed that human podocytes express on mRNA level the components C1, C2, C3, C4, C5, the inhibitors factor H, CD46, CD55 and CD59, and the activators properdin and factor B. Cells expressed CD35 and CD59 on protein level. In addition, we could show that podocytes secrete the factors C2, C3, C4, C5, C7 and factor H into the medium. As expected, because of the missing secretion of factor D and B, there was no functionally active complete complement cascade resulting in hemolysis of rabbit erythrocytes, but the secreted C3 was clearly functionally active.

Conclusions: This is the first study showing the potential of human podocytes to secrete active complement components. These data suggest that podocytes might contribute to local complement activation and modify complement mediated renal diseases.

TH-OR069

Complement Pathway Inhibition by Antisense Oligonucleotide for Treatment of Renal Diseases


Background: Activation of the complement system plays a key role in normal inflammatory response to injury but may cause substantial injury when activated inappropriately. Complement contributes to injury in several forms of glomerulonephritis, chronic humoral rejection after renal transplantation and ischaemia/reperfusion injury. Genome-wide association studies have shown that polymorphisms at the complement factor H-related gene locus are associated with over activation of the alternative complement pathway and subsequent susceptibility to IgA nephropathy and systemic lupus erythematosus. Rare mutations in these genes and other complement genes are associated with familial forms of C3 glomerulopathy and hemolytic uremic syndrome.

Methods: Using second generation antisense technology, we identified and characterized novel oligonucleotides (ASOs) that block complement component 5 (C5) and complement factor B (CFB) and tested their efficacy in NZB/W and MRL/lpr mouse models for Lupus Nephritis as a representative of human renal disease.

Results: Systemic Treatment with CFB ASO (100 mpk/wk) resulted in 75-90% mRNA knockdown in the liver and 40-60% in the kidney, which led to improved survival, proteinuria, renal C3 accumulation and renal pathology in mouse models for lupus nephritis. In addition plasma C3 level, which is dramatically reduced by C3 turnover in the disease models, was corrected to normal level with treatment. Similarly, systemic treatment with C5 ASO (25 mpk/wk) resulted in 95% mRNA knockdown in the liver and 80% in the kidney and improved renal pathology and reduced renal C3 accumulation in MRL/lpr mice.

Conclusions: Our results suggest that the amplification of complement activation by the alternative pathway is necessary for glomerular C3 deposition and progression of proteinuria and that factor B and C5 play important roles for disease progression and pathology in lupus nephritis mouse models. Treatment with ASO to CFB or C5 may offer a novel treatment strategy to treat lupus nephritis and other complement related renal diseases, such as C3 glomerulopathy, hemolytic uremic syndrome and dense deposit disease.

Funding: Pharmaceutical Company Support - Isis Pharmaceuticals

TH-OR070

IgM Contributes to Glomerular Disease Progression in Complement Induced Glomerulopathy

Sarah E. Panzen,1 Brandon Renner,1 Danica Ljubanovic,1 Doris-Bogdan Borza,2 Joshua M. Thurman.1 Renal Div. Univ. of Colorado Denver, Aurora, CO; 1Dept of Pathology, Univ Hospital Dubrava, Zagreb, Croatia; 2Renal Div, Vanderbilt Univ, Nashville, TN.

Background: While glomerular IgM deposition is reported in a variety of glomerular diseases the mechanism of its deposition and the clinical significance of its presence remain controversial. Recent research demonstrates IgM binds damaged glomeruli. Clinical studies associate IgM deposition with more severe manifestations of nephrotic syndrome. We hypothesized natural IgM binds neo-epitopes exposed after insults to the glomerulus and exacerbates disease progression.

Methods: We used mice deficient in the complement regulatory protein factor H to model a non-sclerotic and non-immune-complex glomerular disease and assessed the contribution of glomerular IgM to disease expression. To test the functional importance of IgM in this model we crossed factor H deficient mice with mice that lack B cells and therefore do not produce IgM. We also injected B cell deficient mice with IgM from wild type mice to determine whether it has nephriogenic properties.

Results: We demonstrated glomerular IgM deposition occurs in factor H deficient mice and progressed from a mesangial distribution into the basement membrane of capillary loops as mice aged. In contrast, glomerular IgG deposition was not observed. Factor H deficient mice lacking B cells were protected from renal damage, as evidenced by mild histologic lesions on electron microscopy and a trend towards reduced albuminuria. IgM from wild-type mice, but not IgG, bound to cultured human mesangial cells. Injection of purified IgM into mice lacking B cells bound within the glomeruli and induced albuminuria (P= 0.05 by ANOVA, N=3).

Conclusions: These results suggest IgM plays an active role as a contributing factor to the development of glomerular damage in a non-sclerotic and non-immune complex model of glomerular disease. Natural IgM and complement may offer new therapeutic targets for slowing the progression of glomerular disease.

Funding: NIDDK Support

TH-OR071

Inflammasome in Renal Collecting Duct Cells Contributes to Inflammation and Fibrosis after Unilateral Ureteral Obstruction

Takaroni Komada,1,2 Shigeaki Muto,1 Eiji Kusano,1 Masafumi Takahashi.2 1Dept of Nephrology, Jichi Medical Univ, Tochigi, Japan; 2Div of Inflammation Research, Jichi Medical Univ, Tochigi, Japan.

Background: The inflammasome is a multiple protein complex containing Nod-like receptors (NLRs), ASC, and caspase-1. It regulates interleukin-1β (IL-1β) and contributes to the development of CKD. However, the role of each inflammasome component in the renal tubulointerstitial cells remains investigated. We investigated the role of each inflammasome ureteral unilateral obstruction (UUO) model and evaluated the localization of ASC.

Methods: C57BL/6J-background wild type (WT) and ASC-knockout (ASC-KO) mice underwent UUO. Primary mouse collecting duct (CD) cells were used in vitro study. In vivo study: ASC-KO showed a significant reduction in tubulointerstitial injury and fibrosis histologically. On the 5 days after UUO, flow cytometric analysis showed that leukocyte infiltration was abolished in ASC-KO compared with WT, indicating that inflammatory response was remarkably suppressed in ASC-KO. The mRNA expressions of IL-1β, IL-18, IL-1α, C3, C5, C7 and Tgfb showed less increase in ASC-KO. Immunohistochemistry showed that ASC expression was upregulated in the renal tubules after UUO. Double immuno-fluorescence analysis revealed that most ASC positive tubules were co-stained with AQP2, collecting duct marker. In vitro study, we identified the presence of NLRP3 and ASC in primary mouse CD cells using western blotting. After SmcATP stimulation, IL-1β secretion was prevented significantly by P2X2 receptor (A-38079), by blocking the K+ efflux, by glibenclamide, or by antioxidant N-acetyl cysteine (NAC).

Conclusions: ASC was upregulated in CD cells after UUO and related to inflammation and fibrosis. Extracellular ATP stimulated inflammasome activation in CD cells, through P2X2–potassium efflux and ROS-dependent pathways. These findings suggest that ASC in the CD cells contributes to kidney inflammation as a major component of the inflammasome.

TH-OR072

Macrophage A2A Adenosine Receptors Are Essential to Protect from Progressive Kidney Injury

Gabriela E. Garcia,1 Luan D. Truong,2 Jessica Helen Trostel,3 Richard J. Johnson,1 Lili Feng.1 Medicine, Univ of Colorado Denver, Aurora, CO; 1Pathology, The Methodist Hospital, Houston, TX; 2Medicine, Baylor College of Medicine, Houston, TX.

Background: A2A adenosine receptor (A2AR) activation attenuates inflammatory injury to the kidney.

Methods: We investigated the role of A2AR in the progression of kidney injury in a model of severe, macrophage-mediated anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) using C57BL/6J-DTR transgenic mice. In these mice, tissue Mφ can be selectively deleted by injection of diphtheria toxin (DT). GN was induced in C57BL/6J-DTR mice and Mφ were selectively depleted in the established phase of the disease and reconstituted with Mφ from WT or A2AR deficient mice and then treated with an A2AR agonist and euthanized at day 8. Mice reconstituted with WT Mφ but not with A2AR agnostic were used as a control.

Results: Mφ were tracked in vivo labeling them with PKH-26GL and found that Mφ were distributed in nephritic kidneys. In mice that received WT Mφ and were treated with an A2AR agonist against the glomerular cellularity, crescent formation, sclerotic glomeruli and tubulointerstitial (TIN) injury were significantly reduced compared with the control group. In contrast, mice reconstituted with A2AR deficient Mφ and treated with A2AR agonist, the kidney injury was worst with increased crescent formation, enhanced sclerotic glomeruli and TIN compared to the control group. In addition, collagen (Col)-I, Col-III and Col-IV deposition were increased in mice receiving Mφ deficient in A2AR compared with the control group. Importantly, the antigen-specific humoral immune response and the glomerular immunoglobulin-G deposition were not affected by DT, Mφ depletion, or Mφ reconstitution. In vitro studies, higher levels of TGF-β and tissue inhibitor of matrix metalloproteinase-1 were induced in Mφ deficient in A2AR-deficient mice compared with Mφ from WT mice.

Conclusions: These findings suggest that absence of Mφ A2AR increases Mφ pro-fibrotic activity and that endogenous Mφ A2ARs are essential to protect from progressive kidney fibrosis.

Funding: NIDDK Support

TH-OR073

NLRP3 Is a Predictor of Renal Tubular Injury in Human IgA Nephropathy

Justin Chung,1 Xiangyu (Wendy) Wang, Hyunjung Chung, Matthew T. James, Kiril Trpkov, Brenda Hemmelgarn, Daniel A. Muruve.1 Medicine, 1, Calgary, Canada.

Background: Despite efforts to identify biomarkers to classify and prognosticate kidney disease outcome, current markers are non-specific and unable to predict disease outcome. Our previous studies have demonstrated significant expression of a family of NOD-like receptors called NLRPs in various human kidney diseases. NLRP3 gene expression is increased in biopsies of patients with IgA nephropathy (IgAN), a slowly progressing form of CKD that is associated with tubulointerstitial fibrosis. Although NLRP3 mRNA expression has been linked with IgAN, little is known about the relationship between NLRP3 expression with IgAN progression.

Funding: NIDDK Support
Method: Biopsies from a total of 67 patients with IgAN were selected for analysis of NLRP3 mRNA expression by quantitative real-time PCR. Patients with advanced renal failure were excluded from the analyses to avoid patients on dialysis. Therefore, a total of 57 cases of IgAN were analyzed. NLRP3 gene expression was analyzed as a logarithmic variable due to its non-normal distribution, and displayed as tertiles in a survival curve. We used immunohistochemistry (IHC) and Western blot to study NLRP3 protein expression with correlation to a kidney injury molecule (KIM-1).

Results: Our results demonstrate that lower levels of NLRP3 gene expression is associated with a worse outcome in patients with IgAN. NLRP3 and KIM-1 had strong correlation, as reflected by the increase of NLRP3 and KIM-1 protein levels that diminished after prolonged treatment with TGF-β.

Conclusions: NLRP3 is a promising marker of epithelial burden that can be used to predict IgAN progression. Higher levels of NLRP3 mRNA and protein expression are associated with earlier manifestation of IgAN. The presence of high levels of NLRP3 in IgAN can also provide an opportunity to identify reversible or treatment-responsive inflammation.

TH-OR074

Transcriptional Regulation of Endothelial Cell Proliferation Induced by Simultaneous Antibody Targeting of AT1- and ET Receptors

Aurélie Philippe, Rusan Catar, Philine Wagner, Duska Dragan. Nephropathy and Intensive Care Medicine, Univ Hospital Charité, Berlin, Germany.

Background: Patients with systemic sclerosis (SSc) suffer from severe obliterative autoimmune vasculopathy affecting various vascular beds including kidney. Activating autoantibodies simultaneously targeting G-protein coupled receptors (GPCR) Angiotensin II type 1 receptor (AT1R) and Endothelin-1 type A receptor (ET1R), may predict vasoconstrictive mechanisms which remain to be clarified. We hypothesized that both activating antibodies may induce vascular dysfunction independent from receptor natural ligands, Angiotensin II and Endothelin-1.

Methods: Affinity purified IgG fraction derived from serum of SSc patients positive for AT1R/ET1R Abs (SSC P-IgG) served for functional, signalizing and transcriptional regulation studies in human microvascular endothelial cells (HMEC-1). Mice were passively transferred with SSC P-IgG.

Results: Both autoantibodies induced ERK1/2 phosphorylation to a similar extent as natural ligands, indicating a breakdown of their biologic activity, and induced further downstream phosphorylation of the transcription factor Ets-1. SSc P-IgG transfer induced expression of Ets-1 in kidney arteries of mice. AT1/ET1R autoantibodies, but not natural ligands Ang II or ET-1 were able to induce endothelial cell proliferation. Receptor antagonist attenuated endothelial proliferation emphasizing receptor specific effect of both activating antibodies. These effects were attributed to GPCR since pharmacologic targeting of ERK1/2 achieved similar results. Same anti-proliferative effects could be achieved by siRNA mediated blockade of Ets-1. SSc P-IgG also induced increased DNA binding to Tissue factor (TF) promoter, which contains Ets-1 binding site, in EMSA and ChIP assays. Moreover, inhibition of TF obviated endothelial cell proliferation, illustrating that antibodies activating AT1 and ET1R contribute to pathogenesis of proliferative obliterative vascular lesion via enhanced Ets-1 mediated transcriptional regulation of TF.

Conclusions: Both pathways induced by AT1R and ET1R antibodies may offer new prospects in treating obliterative vascular lesions in autoimmune vasculopathies.

TH-OR075

Increased Hedgehog-GLI Signaling Causes Stromal Cell-Mediated Ureteropelvic Junction Obstruction

Norman D. Rosenblum,1 Lijun Chi, Brian Nieman,2 Steven Potter.3 1Div Neph, Prog DSCM, Hosp Sick Child, U Toronto, Toronto, Canada; 2Dev Biol, Child Hosp Med Centre, Cincinnati; 3U Toronto Centre Phenogenomics, Toronto, Canada.

Background: Hedgehog (Hh) signaling is required during kidney morphogenesis. While increased HH-GLI signaling causes cancer in nonrenal tissues, its pathogenic role in the embryonic kidney is undefined.

Methods: We generated and analyzed mice with a constitutive increase in HH-GLI signaling activity in the metanephric mesenchyme by genetically inactivating Patched1 (Pch1), that encodes a cell surface protein that constitutively inactivates HH signaling in the absence of ligand, using Rarb2-Cre and Pch1fl/fl mouse strains.

Results: Pch1-deficient (Rarb2-Cre;Pch1fl/fl) mice were characterized by hydro nephrosis after E15.5. Dye injection into the renal pelvis revealed obstruction of dye passage beyond the ureteropelvic junction (UPJ). Serial 2 μm histologic sections revealed cells obstructing the UPJ. Analysis of Pch1-lacZ expression, a reporter of HH signaling activity, in Pch1-deficient Pch1-lacZ and Pch1-deficient Pch1-lacZ/mice revealed increased Pch1 and ectopic expression of Pch2 in the cells obstructing the UPJ. A 2-fold rescue of hydro nephrosis, measured by MRI, was observed in Pch1-deficient mice with constitutive expression of the Gli3R544Q allele that encodes GLI3 repressor, demonstrating that UOPD in Pch1-deficient mice is GLI-dependent. Pch2-positive cells (3 distinct batches of 2000 cells) were isolated distinct from Pch2-negative cells in the region of the UPJ by tissue dissection and flow sorting and analyzed by RNAseq. In comparison to Pch2-negative cells, Pch2-positive cells exhibited a 2-9-fold increase in genes expressed in renal stromal cells or pericytes/smooth muscle progenitors, or that promote smooth muscle cell development. Validation of these results using qPCR and double in situ hybridization with Pch2 mRNA established the stromal cell identity of obstructing Pch2-positive cells.

Conclusions: Increased HH-GLI signaling in the metanephric mesenchyme causes UPJO due to ectopic stromal cells. Our results provide a basis to investigate human UPOP, presently understood only at the level of histopathology.

Funding: Government Support - Non-U.S.

TH-OR076

Wnt7b Signals to Pericytes/Perivascular Fibroblasts and Regulates Microvasculature Development in the Renal Medulla

LaToya Ann Roker, Jing Yu. Cell Biology, Univ of Virginia, Charlottesville, VA.

Background: Wnt7b is expressed in the ureteric trunk epithelium and is essential for renal medulla formation. It elicited canonical Wnt signaling in interstitial cells of the prospective renal medulla, which is also vital for renal medulla formation. However, the identity of the Wnt7b target cells remains elusive. Determining the identity of these cells may help us to better understand Wnt7b functions in renal medulla development.

Methods: Therefore, we employed mouse genetics, Immunohistochemistry, and Transmission Electron Microscopy (TEM) to determine the identity of Wnt7b target interstitial cells and the effect of Wnt7b signaling on this cell population.

Results: We found that the in the nascent renal medulla, Wnt7b canonical Wnt signaling targets cells that do not constitute the embryonic mesenchyme. Rather, they are confined to 1-3 cell layers adjacent to the prospective medullary collecting ducts. Moreover, we found that they express pericyte markers and are intimately associated with endothelial cells of the microvasculature lining the prospective medullary collecting ducts, demonstrating that these cells are pericytes/perivascular fibroblasts. We further found that differentiation of this population of pericytes/perivascular fibroblasts did not depend on Wnt7b signaling from ureteric trunks; instead, ablation of Wnt7b signaling in the kidney did not affect and increased reduced reciprocal signaling from ureteric trunks. Consistent with our hypothesis, Wnt7b mutants displayed an increase in the density of vascular coverage of prospective medullary collecting ducts and in endothelial cell proliferation. Further analysis identified a defect in endothelial cell flattening and lumen formation of this population of the microvasculature.

Conclusions: Taken together, our study revealed a novel function of Wnt7b in kidney development that Wnt7b regulates peri-ureteric trunk microvasculature development in the developing renal medulla, most likely through its signaling to pericytes/perivascular fibroblasts lining the microvasculature.

Funding: NIDDK Support

TH-OR077

Wnt5a Is Crucial for Kidney Development

Liwei Huang, Sao Young Choi, Maria F. Chacon-Heszele, Weibin Zhou, Sarah McKenna, Xiaofeng Zuo, Yun Kyoung Ryu, Reji Kuruvilla, Joshua H. Lipschtz. Dept of Medicine, Univ of Pennsylvania, Philadelphia, PA.

Background: Wnt5a is a non-canonical secreted glycoprotein of the Wnt family that plays an important role in the development of various organs and postnatal cellular function.

Little is known regarding the role of Wnt5a during kidney development.

Methods: The objective of the present study is to determine the role of Wnt5a during nephrogenesis using zebrafish and murine models.

Results: By real-time RT-PCR and immunoblotting, we determined that Wnt5a mRNA was expressed in the zebrafish pronephros. Wnt5a knockdown by antisense wnt5a morpholinos results in abnormal glomerular structure and dilated renal tubules in zebrafish. In wt1-GFP fish, the pronephros can be visualized with fluorescent microscopy. Dilations are observed as 48 hours post fertilization (hpf) in the glomerular and proximal tubular region of the wt1-GFP injected with wnt5a antisense morpholinos. Wnt5a knockdown resulted in decreased w1 expression detected by wnt5a and in the w1-GFP fish detected by fluorescence microscopy. Rescue with a mouse Wnt5a mRNA showed that this was not due to global effects. In wt1-GFP global knock-out mice, by wnt5a, Wnt5a expression is localized to the entire intermediate mesoderm at embryonic day (E) 10.5, and its expression level is increased further at E11.5. At E13.5, Wnt5a is weakly expressed in the mesenchymal region of the renal medulla. Wnt5a global knockout mice showed pleiotropic kidney phenotypes, including bilateral or unilateral kidney agenesis, hydronephrosis and fused kidneys. Further histologic examination, when kidney tissue was present, revealed reduced kidney tubules, glomeruli, and medullary zones in the Wnt5a-/- embryos.

Conclusions: A strength of this study is that we utilized two different animal models each of which has specific advantages that could be exploited to investigate the role of Wnt5a in nephrogenesis. In zebrafish and mice, Wnt5a was expressed very early in nephrogenesis. Disrupted Wnt5a resulted in abnormal glomerular and tubular growth and cyst formation. Our data indicate that Wnt5a is centrally involved in kidney development.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR078

The WNT-Calcium Pathway Controls c-Ret Expression during Ureteric Bud Branching Morphogenesis

Diana Ijelesiam,1 Jeremy A. Saban,2 Rachel Pritchard1, Rachel Pritchard1, Richard R. Goodyer1,2. 1Pediatrics, Montreal Children’s Hospital Research Institute, Montreal, Canada; 2Human Genetics, Montreal Children’s Hospital Research Institute, Montreal, Canada.

Background: Normal nephrogenesis requires reciprocal signaling between the invading ureteric bud (UB) and the condensing metanephric mesenchyme (MM). Here, we examine the role of the non-canonical WNT/ Ca2+ signaling pathway in kidney development.

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

18A
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.

19A
A Transposon-Mediated System for the Generation of Nephron Progenitors from Adult Somatic Cells
Jessica May Vanslambrouck, Lauren Elizabeth Woodard, Norsaeha Suhaimi, Matthew H. Wilson, Melissa H. Little. Institute for Molecular Bioscience, Univ of Queensland, Australia; 2Dept of Medicine, Baylor College of Medicine, TX.

Background: Novel treatments for chronic kidney disease are desperately needed and cellular reprogramming may represent one such option. As all nephrons in the human kidney form prior to birth, their regeneration may require the recreation of embryonic nephron progenitors (NPs). Using a lentivirus-mediated screen, we identified 6 transcrip tion factors sufficient to re-impose a NP-like state when co-expressed in adult human proximal tubule cells (Hendry et al., JASN, 2013). Here we report the preliminary de-replication of this gene set and development of a multistracock transposon construct to improve this reprogramming.

Methods: De-replication involved removal of individual lentiviral constructs from NP cell transductions. A transposon-mediated system was generated by engineering all 6 genes into a piggyBac construct with intervening 2A sequences, a tetracycline response element for doxycycline inducibility and a reporter (mCherry) for cell enrichment. FuGENE6 was used to co-transfect HK2 cells with transposon, a tetracycline activator transposase and a piggyBac transposase construct. Gene expression was induced with 2μg/ml doxycycline. Reprogramming was assessed via morphologic change (epithelial-to-mesenchymal transition) and expression of key NP genes. Results: A NP-like state was achieved without EYA1 or HOXA11. Transposon integration into HK2 cells was most efficient with the hyperactive piggyBac transposase (m7pB). Following integration, HK2 cells displayed tightly regulated doxycycline-inducible mCherry expression and NP-like characteristics, including increased expression of key NP markers. The expression of these genes was influenced by the length of doxycycline exposure.

Conclusions: These results further refine the genes required for NP reprogramming and demonstrate the feasibility of a transposon-based approach for inducible reprogramming to a NP. In the long term, this approach will facilitate patient-specific reprogramming to NP cells. Such cells may also prove invaluable for bioengineering and nephrotoxicity screening. Funding: Government Support - Non-U.S.

Mycofenolate Mofetil Therapy in IgA Nephropathy: Histological Changes after Treatment

Background: Endocapillary hypercellularity independently predicts renal outcome in IgA Nephropathy (IgAN). Mycofenolate mofetil (MMF) treatment is offered to patients presenting to the Imperial College Kidney and Transplant Institute with IgAN and histological evidence of endocapillary inflammation. Clinical trials of MMF in IgAN have inconclusive results. Evidence of histological improvement following MMF treatment would support its therapeutic use. We therefore reviewed histological changes after MMF therapy in a cohort of IgAN patients.

Methods: Eleven IgAN patients with repeat native renal biopsies before and after MMF treatment were identified. Patients were excluded if they had received any other immunosuppression therapy, including corticosteroids. Based on the Oxford classification of IgAN, we reviewed histological changes after MMF treatment.

Results: Seven patients (60%) were male. At diagnostic renal biopsy, median age was 42 (range 24-71) years. Median serum creatinine was 172 μmol/L (137-235), serum creatinine ratio (SCR) was 1.6 (1.1-2.2), mean ESR was 39 (23-67), serum C3 was 0.85 (0.67-1.1), and proteinuria was 7.6 (1.5-62). Median time between biopsies was 29 months (14-41). Following MMF treatment, repeat biopsy demonstrated statistically significant improvement in the mean percentage of glomeruli showing endocapillary hypercellularity and cellular/fibrillary crescents. A significant reduction in IgA deposition (p=0.04) and a trend towards improved mesangial hypercellularity (p=0.05) was also demonstrated. There was no change in tubular atrophy. Median serum creatinine remained stable at 3 years follow-up at 100μmol/L (59-421).


Abnormal STAT3 Signaling Enhances Production of Autoantigen in an Autoimmune Disease
Colin Reilly, Koshi Yamada, Zhi Qiang Huang, Milen Raska, Hitoshi Suzuki, Bruce A. Julian, Christopher D. Willey, Jan Novak. Program in Pharmaceutical Sciences, Oklahoma Medical Research Foundation; 2Microbiology, Univ of Alabama at Birmingham; 3Medicine, Univ of Alabama at Birmingham; 4Radiation Oncology, Univ of Alabama at Birmingham; 5Palacky Univ in Olomouc; 6Huntingdon Univ Faculty of Medicine.

Background: IgA Nephropathy (IgAN) is an autoimmune disease characterized by IgA1-containing mesangial immunodeposits. These deposits are likely derived from circulating immune complexes formed from IgA1 with galactose-deficient O-glycans (GD1a; autoantigens) and antigen autoantibodies. Disease activity (macroscopic hematuria) frequently manifests after an upper respiratory tract infection, suggesting that immune activation via cytokines may be involved in disease exacerbation. This concept is supported by the observation that serum IL-6 levels are elevated in some IgAN patients. Using immortalized IgA1-secreting cells derived from or circulation of IgAN patients and healthy controls (HC), we characterized signaling mechanisms involved in GD-IgA1 production induced by IL-6.

Methods: IgA1-secreting cells were stimulated with IL-6, and IgA1 production and O-glycansylation were assessed. siRNA knock-down (si) and specific kinase inhibitors confirmed the role of IL-6-STAT3 pathway in GD-IgA1 production. Association of a possible co-factor, HDAC6, with STAT3 was assessed by using immunoprecipitation and Western blot analysis.

Results: IgA1-producing cells from IgAN patients but not HC stimulated with IL-6 secreted more GD-IgA1 (P<0.05). IL-6 stimulation induced more robust and prolonged STAT3 phosphorylation in cells from IgAN patients than from HC. siRNA k/d and kinase

Contrasting Roles for M1 and M2 Type Macrophages in Childhood IgA Nephropathy
Colin Reilly, Toshiaki Suzuki, Takeshi Yamada, Hiyori Hasegawa, David J. Nikkole-Paterson, Akiko Saitoh. 1Dept of Pediatrics, Nippon Univ Medical and Dental Hospital, Nippon, Japan; 2Monash Univ Dept of Medicine, Monash Medical Centre, Clayton, Victoria, Australia.

Background: We have previously shown that M2-type macrophages (MQ) are dominant in chronic lesions, such as glomerular matrix expansion and interstitial fibrosis, in IgA nephropathy (IgAN). However, the role of M1-type activated MQ has not been elucidated. Therefore, we examined activated M1-type MQ in biopsies of childhood IgAN.

Methods: Biopsies taken from 81 cases of childhood IgAN (11±3 years) were examined for histologic changes and by immunofluorescence staining for activated M1-type MQ (CD86+ cells) and M2-type MQ (CD163+ cells). Nine biopsies from children with thin basement membrane disease (TBMD) were used as control.

Results: Histopathologic assessment of IgA-renewed significant accumulation of both M1 and M2 type MQ in glomeruli, while most interstitial MQ were CD163+ (M2-type). CD86+ M1-type MQ correlated with: endocapillary proliferation and cellular crescent formation (both p<0.001); the degree of hematuria (p<0.001) and proteinuria (p<0.014), but not correlate with glomerular matrix expansion (p=0.14). In contrast, CD163+ M2-type MQ correlated with glomerular matrix expansion (p<0.01) and interstitial fibrosis (p<0.001).

Conclusions: We have identified contrasting roles for M1 and M2 type MQ in childhood IgAN. Activated M1-type MQ appear to be involved in the development of acute lesions (endocapillary proliferation and cellular crescents), whereas M2-type MQ are involved in chronic lesions such as mesangial matrix expansion and interstitial fibrosis. The prognostic significance of these findings warrants further study. Funding: Government Support - Non-U.S.
inhibitors confirmed the central role of STAT3 activation in the enhanced production of Gd-IgA1 in response to IL-6 (P<0.05). HDAC6 showed no association with STAT3 regarding IL-6 stimulation.

Conclusions: IL-6-mediated activation of STAT3 plays an important role in the enhanced production of Gd-IgA1 in IgAN. Further analysis is needed to determine a potential role of acetylation in STAT3 activation. STAT3 signaling is exacerbated in IgAN patients and may offer a target for disease-specific therapy.

Funding: NIDDK Support, Other NIH Support - T32 grant training

TH-OR088

Tonsillar Cells in Patients with IgA Nephropathy Produce Aberrantly Glycosylated IgA1 and Anti-Glycan Antibodies

Hitoshi Suzuki,1 Yusuke Suzuki,1 Yoko Makita,1 Bruce A. Julian,2 Jan Novak,3 Yashuhiko Tomino,1
1Nephrology, Juntendo Univ Faculty of Medicine, Tokyo, Japan; 2Medicine and Microbiology, Univ of Alabama at Birmingham, Birmingham, AL.

Background: IgA1 in circulating immune complexes and mesangial deposits of patients with IgA nephropathy (IgAN) is aberrantly glycosylated, galactose-deficient in O-glycans (Gd-IgA1), and is bound to anti-glycan IgG/IgG autoantibodies. However, the origin of cells producing Gd-IgA1 and the autoantibodies is not certain. Upper respiratory tract infections and tonsillitis are frequently associated with clinical flares of IgAN, suggesting a link with disease pathogenesis. Levels of gene transcription for specific glycosyltransferases are dysregulated in tonsillar B cells from patients with IgAN, resulting in production of Gd-IgA1. In some patients, tonsillolcystectomy and glucocorticoids (TSP) may slow disease progression in early clinical stages. Therefore, we assessed whether tonsillar cells produce Gd-IgA1 or anti-glycan IgG.

Methods: Tonsillar cells obtained from 29 patients with IgAN were cultured 72 hours. Gd-IgA1 and anti-glycan IgG secreted by these cells were measured by ELISA. Proteinuria and hematuria, and serum levels of Gd-IgA1, Gd-IgA1-specific IgG and IgA, and IgG/IgA immune complexes (IC) were measured before and after TSP.

Results: Proteinuria and hematuria improved after TSP (P<0.05). Eighteen of 29 patients had proteinuria <0.3 g/day and 5 red blood cells/HPF after TSP (Remission group). Eleven patients did not clinically improve (non-Remission group). Serum levels of Gd-IgA1, Gd-IgA1-specific autoantibodies, and IgG/IgA IC decreased during glucocorticoid therapy after tonsillolcystectomy (P<0.01). The rate of decrease in the levels of Gd-IgA1, Gd-IgA1-specific autoantibodies, and IgG/IgA IC were greater in the Remission group (P<0.01). Tonsillar cells from Remission group produced more Gd-IgA1 and anti-glycan IgG than those from non-Remission group (P<0.01).

Conclusions: Tonsillar cells may contribute to the circulating Gd-IgA1 and anti-glycan IgG in patients with IgAN. These biomarkers may be useful for guiding therapy of IgAN.

Funding: NIDDK Support

TH-OR089

Understanding the Structure of PLA2R: Insights into Formation of the Immunodominant Epitope Recognised by Autoantibodies in Patients with Idiopathic Membranous Nephropathy

Marlyne Fresquet, Thomas A. Jowitt, Jennet O. Gummadova, Edward A. McKenzie, Rachel Lennon, Paul E. Brenchley. Faculty of Human and Medical Sciences, Univ of Manchester; Manchester; United Kingdom.

Background: 75% of patients with idiopathic membranous nephropathy (IMN) have autoantibodies against the phospholipase A2 receptor (PLA2R). The epitope(s) within PLA2R and its 3D structure are unknown. The objective is to understand how autoantibodies to PLA2R interact with the receptor.

Methods: To identify the dominant epitope, PLA2R was trypsin digested, separated on unreduced gels and peptides reacting to patient sera were identified by western blotting. Bands of 16, 20 and 37kDa were excised, reduced and analysed by MS. The structure of bands of 16, 20 and 37kDa was determined by SAXS, sedimentation, SAXS and 3D electron tomography. A SPR method was developed to assess binding kinetics of patient antibodies to PLA2R and NCTLD3. Antibody affinity to full-length PLA2R and NCTLD3 PLA2R.

Results: Bands of 16, 20 and 37kDa were excised, reduced and analysed by MS. The structure of the extended conformation at neutral pH and a bent conformation at lower pH possibly involved in the regulation of ligand recognition or receptor oligomerization. This has implications for formation of neo-epitopes that may become immunogenic and induce autoimmunity.

Funding: NIDDK Support, Other NIH Support - T32 grant training

TH-OR090

APOL1 Risk Variants in PLA2R-Positive Membranous Glomerulopathy

Christopher Patrick Larsen, Patrick D. Walker, Josephine M. Ambruzs, Nidia Cordeiro Messias. Nephropath, Little Rock, AR.

Background: The APOL1 disease spectrum includes non-diabetic ESKD, FSGS and collapsing glomerulopathy (CG) associated with HIV and SLE. It is currently unknown if the presence of APOL1 risk alleles modifies the morphologic phenotype of other glomerulonephritides. We sought to determine if there were any morphologic alterations correlated with the presence of APOL1 risk alleles in a homogeneous cohort of patients with PLA2R-positive membranous glomerulopathy (PLA2rMG).

Methods: 118 renal biopsies were identified in the case file of our institution from AA patients with PLA2rMG. A blinded morphologic evaluation was performed to evaluate for changes associated with the presence of 2 APOL1 risk alleles. Features examined included global and segmental glomerulosclerosis, subtype of FSGS, degree of interstitial fibrosis and tubular atrophy, subtype of tubular atrophy, degree of interstitial inflammation, degree of arteriolar sclerosis, evidence of acute tubular injury, and the presence of microcystic tubular dilatation (MCTD). DNA was genotyped for APOL1 risk alleles using TaqMan assays.

Results: Six (6) cases of CG were identified including 4/18 in the group with 2 risk alleles, 2/45 in the group with 1 risk allele, and 0/40 in the group with no risk alleles. APOL1 associated with CG such that in a recessive model, APOL1 risk alleles conferred a 19.9 fold higher odds of developing CG (P=0.01). Odds ratio CG = 2.0-79.0. APOL1 risk alleles were also found to be associated with MCTD (P<0.04), interstitial inflammation (P<0.03), and segmental sclerosis (P<0.01). The cases with 2 risk alleles also showed a trend toward more interstitial fibrosis and tubular atrophy. Other morphologic features were not found to be associated with APOL1.

Conclusions: Collapsing glomerulopathy is an aggressive nephropathy with no currently available efficacious treatment. We have evaluated the changes associated with APOL1 risk alleles in a cohort of patients with PLA2R-positive MG and found that there is significantly more CG with the presence of 2 APOL1 risk alleles. These results raise the possibility that APOL1 risk alleles modulate and potentially accelerate glomerular diseases though the development of collapsing lesions.

TH-OR091

The Prevalence of Circulating Monoclonal Protein in Proliferative Nephropathy with Monoclonal Deposits

Gauri Bhutani,1 Fernando C. Fervenza,1 Sanjeev Sethi,2 Samih H. Nasr,3 Nelson Leung.1 1Nephrology & Hypertension, Mayo Clinic; 2Anatomic Pathology, Mayo Clinic, Rochester.

Background: Monoclonal gammapathy of ‘Renal’ significance (MGRS) was recently described as a new classification of monoclonal gammapathy which results in renal disease but is not diagnostic of multiple myeloma. MGRS is defined as a kidney disease with monoclonal protein deposits or where the monoclonal protein acts as a C3 nephritic factor. This study was undertaken to evaluate the hematologic characteristics of these patients.

Methods: The pathology database at Mayo Clinic was reviewed for patients with MGRS associated proliferative kidney diseases from 2008 to 2012. Circulating monoclonal protein testing included serum protein electrophoresis (SPEP/IF) and serum free light chain assay (FLC). Methods to detect the pathological clone included bone marrow biopsy and PET scan. Fisher’s exact test was used for statistical analysis.

Results: In total 56 patients, biopsy displayed mesangioproliferative (8 = 14%), membranoproliferative (MPGN) (22 = 40%), diffuse proliferative (DPG) (11 = 20%), a mixed MPGN- DPG (10 = 18%) and proliferative GN with membranous features (5 = 9%). Monoclonal deposits were IgGk in 59%, IgGk in 25% and IgAK and / or IgM / or IgGk in the remaining 10%. IgGk subclassing showed IgGk in 14 (64%), IgGk in 25% and IgGk and IgG2 in 3 (14%) out of 22 biopsies. Table 1 notes pertinent diagnostic workup.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Patients</th>
<th>Proteinuria</th>
<th>Hypertension</th>
<th>ANCA</th>
<th>Membrane (O\approx)</th>
<th>APOL1 Positive</th>
<th>C3 nephritic factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10 (91%)</td>
<td>6 (60%)</td>
<td>4 (40%)</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>1 (9%)</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Majority of patients with a proliferative nephropathy and monoclonal deposits lack a detectable serum monoclonal gammapathy. Detection of a serum monoclonal protein is associated with significantly high detection rate of the pathologic clone (p < 0.05) and, hence, a more direct method. Serum free light chain ratio is normal in most patients and an abormal result does not appear to increase the likelihood of finding a pathologic clone.

TH-OR092

Toward a Working Definition of C3 Glomerulopathy by Immunofluorescence


Background: An impediment to the diagnosis of C3G is the lack of a working IF definition developed and validated in a disease cohort. While “C3 only” is applied as a theoretical construct, its practicality is untested. We aimed to test hierarchical IF criteria with the varying stringency for C3G using dense deposit disease (DDD) as gold standard; determine if “C3 only” is a practicable criterion; apply these criteria to analyze the incidence of C3G in MPGN types 1 and 3; and explore clinical correlates.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Intramembranous deposits. The pathophysiological basis of both diseases is dysregulation of some combination of subepithelial, subendothelial and/or less dense, discontinuous glomerular basement membrane dense deposits while C3GN is associated with immunoactivity.

**Results:** On analysis of the initial bx in 22 patients (200 MPGN1, 42 DDD and 77 MPGN3), the most restrictive criterion of “C3 only” captured only 50% of DDD (compared to 8% MPGN1 and 10.4% MPGN3), whereas criterion 3 identified 88.1% of DDD (compared to 30.5% MPGN1 and 39% MPGN3). Broadening to criterion 4 added only 4.8% of DDD cases but added 26.5% MPGN1 and 13% MPGN3 cases, suggesting loss of specificity. Therefore criterion 3 was chosen as working definition of C3GN. Among MPGN3, 90% of C3G cases were Strife and Andrews variant. Repeat bx in C3G revealed a change in IF criterion class in 10 of 23 cases, indicating fluidity between subgroups. The prevalence of low scores in C3 and/or C4 at bx did not significantly change from the 3 proposed IF criteria. A nephritic presentation was more common in criterion 1 cases.

**Conclusions:** “C3 only” is an impractical definition of C3G. We propose a less restrictive definition of C3 dominant and at least 2 orders of magnitude more intense than any combination of IgG, IgM, IgA, IgCq (Criterion 3); C3 dominant and ≥1 IgM or IgG (Criterion 4).

**TH-OR093**

**Biomarker Profiling of Dense Deposit Disease and C3 Glomerulonephritis**

Yuzhou Zhang, Tara Maga, Bertha Martin, Nicole Meyer, Dingwu Shao, Xue Xiao, Carla M. Nester, Richard J. Smith. 

**Univ of Iowa, Iowa City, IA.**

**Background:** Dense Deposit Disease (DDD) and C3 Glomerulonephritis (C3GN) are prototypical C3 glomerulopathies (C3G). On renal biopsy, both are C3 dominant by immunofluorescence while on electron microscopy DDD is defined by intramembranous glomerular basement membrane dense deposits while C3GN is associated with some combination of subepithelial, subendothelial and/or less dense, discontinuous intramembranous deposits. The prevalence of low scores between DDD and C3GN include a significant reduction in both pyronin-g (p<.005) and C7 (p<.01) in C3GN and a significant elevation of SMAC (p<.05) in C3GN. Biomarker profiling distinguishes DDD and C3GN and is a valuable metric for defining the degree of complement dysregulation that is present. These results have clinical implications and can be used to guide and follow response to different anti-complement therapies.

**Funding:** NIDDK Support

**TH-OR094**

**Recurrent C3 Glomerulonephritis: Clinicopathological Findings and Outcomes**

Ladan Zand,1 Elizabeth C. Lorenz,1 Fernando G. Cosio,1 Fernando C. Fervenza,2 Samih H. Nasr,3 Richard J. Smith,2 Sanjeev Sethi.2

1 Mayo Clinic, Rochester, MN; 2Carver College of Medicine, Iowa City, IA.

**Background:** C3 glomerulonephritis (GN) is a proliferative glomerulonephritis characterized by bright C3 staining and the absence of significant Ig staining on IF microscopy. C3GN results from abnormalities in the alternative pathway of complement.

In a significant number of C3GN patients, the disease progresses to end-stage DDD and C3GN patients to test the hypothesis that these two diseases can be differentiated by biomarker profiling.

**Methods:** We examined a panel of biomarkers that are reflective of alternative and terminal complement pathway activity in 17 DDD patients and 17 C3GN patients.

**Results:** As compared to controls, in both DDD and C3GN patients, serum levels of C3, factor B, properdin and C5 are significantly elevated (p<.005). In C3GN patients but not in DDD patients, SMAC is elevated (p<.005) and C7 is reduced (p<.01) as compared to controls. Significant biomarkers differed between DDD and C3GN included an increase in p40 (p<.05) and C7 (p<.01) in C3GN and a significant elevation of SMAC (p<.05) in C3GN.

**Conclusions:** Biomarker profiling distinguishes DDD and C3GN and is a valuable metric for defining the degree of complement dysregulation that is present. These results have clinical implications and can be used to guide and follow response to different anti-complement therapies.

**Funding:** NIDDK Support

**TH-OR095**

**Small Molecule Agonists of CD11b Reduce Leukocyte Activation and Recruitment to Promote Kidney Allograft Survival**

Samia Khan,1 Mohd Hafeez Faridi,1 Anupam Agarwal,2 James George,3 Vinnet Gupta.1

1 Dept of Internal Medicine, Rush Univ Medical Center, Chicago, IL; 2Biochemistry & Molecular Genetics, The Univ of Alabama at Birmingham, Birmingham, AL.

**Background:** Graft loss remains a major obstacle in kidney transplantation and the severity of allograft rejection is often associated with inflammatory infiltrates of leukocytes including myeloid cells expressing β2 integrin CD11b/CD18. Recently, we reported that activation of CD11b by a small molecule compound, leukadherin-1 (LA-1), increases leukocyte cell adhesion to the inflamed endothelium, prevents transmigration and inhibits leukocyte tissue recruitment, which resulted in improved kidney function in a murine model of nephritis.

**Methods:** Here we tested whether targeting of CD11b/CD18 using LA-1 prolongs kidney allograft survival in a mouse model of fully major histocompatibility complex-mismatched orthotopic kidney transplant, where C57BL/6 (H-2b) recipients receive a kidney allograft from a Balb/c animal (H-2d) along with daily cyclosporine for 2 weeks to sustain the transplant (control group). In addition to standard cyclosporine therapy, the recipient C57BL/6 mice in the test group were administered LA-1 injections daily during week 1 and every other day from weeks 2-8 after receiving the transplant. Renal allograft rejection was considered at the time animals displayed signs of ill health and high serum creatinine.

**Results:** Combination therapy with LA-1 and cyclosporine resulted in a significant prolongation of median graft survival from 28 days (cyclosporine only) to 60 days (cyclosporine and LA-1). At week 5 after transplantation, cyclosporine treated controls accumulated creatinine values near 0.6 mg/dl while LA-1 and cyclosporine treated mice had baseline values near 0.2 mg/dl. The mice in the combination therapy group showed significantly reduced leukocyte infiltration and neointimal hyperplasia.

**Conclusions:** These findings indicate a crucial role for CD11b/CD18 in the control of leukocyte migration to transplanted kidney and identify leukadherins as potential, novel therapeutics for use in renal allotransplantation.

**Funding:** NIDDK Support

**TH-OR096**

**Myeloid Derived Suppressor Cells Induced by Apoptotic Donor Cells Suppress Transplant Rejection via Indolamine 2,3-Dioxygenase and IDO-Mediated Recruitment to Promote Kidney Allograft Survival**

Jane Bryant,1 Nadine M. Lerro,2 Jiaoqiu Wang,2 Zheng Jenny Zhang,2 Xun-Rong Luo.1,2

1 Medicine, Northwestern Univ Feinberg School of Medicine; 2Surgery, Northwestern Univ Feinberg School of Medicine.

**Background:** We have previously shown that pre- and post-transplant infusions of apoptotic donor splenocytes induced by 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (ECDI-SPs) provide significant donor-specific protection to full MHC-mismatched donor cardiac allografts, and with a short course of rapamycin provides indefinite cardiac allograft survival in 100% of the recipients. The mechanisms of protection are not fully elucidated.

**Methods:** The current study focuses on the role of apoptotic donor ECDI-SPs in the induction of myeloid derived suppressor cells and their mechanism of suppression of subsequent transplant rejection in a murine cardiac transplant model. BALB/c ec/c donor cardiac grafts are transplanted to C57BL/6 recipients treated with infusions of donor (BALB/c EC/c) ECDI-SPs, and cells from the graft and spleen are used as controls.

**Results:** We show that infusions of donor ECDI-SPs induce a significant increase of both the CD11b Gr1 Ly6C+ and the CD11b Gr1 Ly6C+ populations in the spleen in a PGE2 dependent manner, and that deletion of these cell populations abolishes graft protection induced by donor ECDI-SPs infusions. Interestingly, both splenic CD11b Gr1 Ly6C+ and the CD11b Gr1 Ly6C+ populations suppress T cell proliferation in vitro, with more robust suppression towards CD8+ T cells, whereas the same populations when trafficking to the cardiac allograft become less suppressive. Furthermore, the suppression by these myeloid-derived suppressor cells (MDCs) is mediated through an interleukin-1 dependent induction of the tryptophan metabolizing enzyme indoleamine 2,3-dioxygenase (IDO). Consequently, treatment with the IDO inhibitor 1-MT abolishes T cell suppression in vitro as well as cardiac graft protection in vivo.

**Conclusions:** These findings reveal a novel link between apoptotic donor cell infusions and the induction of IDO-producing MDCs as a mechanism for transplant graft protection, and provide several targets amenable to therapeutic manipulations for tolerance induction for cardiac transplantation.

**Funding:** NIDDK Support

**TH-OR097**

**Protection from Apoptosis during Extreme Cold Ischemia and Reperfusion Is Mediated by XIAP and Akt**

Swati Jain, Daniel Keys, Charles L. Edelstein, Alkesh Jani.

UC Denver.

**Background:** Cold ischemia (CI) followed by warm reperfusion (WR) during hibernation is a natural model we have used to understand DGF. Hibernating ground squirrels (GS) kidneys survive CI for several days in torpor (LT) followed by WR in Arousal (IBA) without AKI or tubular cell (RTEC) apoptosis seen in mouse & human kidneys after CW. The molecular mechanism of protection against apoptosis & AKI during hibernation has long been sought. We hypothesized that upregulation of anti-apoptotic proteins XIAP, pAkt & pBAD during hibernation prevents RTEC apoptosis.

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

22A
tube formation on matrigel served to study endothelial neoangiogenic response. 

Activation by qRT-PCR, western blot, EMSA and knockdown, VEGF secretion by ELISA. 

transcriptional regulation was studied by promoter deletion assay, transcription factor.

IgG isolated from patients' sera with transplant peritubular pathology (KTx-IgG). VEGF tube formation. Upon treatment with several pharmacologic antagonists, VEGF secretion was further con...

Kidneys subjected to prolonged CI/WR.

Akt1 survive prolonged CI/WR far in excess tolerable by human kidneys, using survival factors.

atrophy and interstitial...

angiogenesis and identi...

hypothesized that autoimmune GPCR targeting process may disturb VEGF induced...

the G-Protein Coupled Receptor (GPCR) PAR-1 is closely involved in VEGF regulation.

mediates PTC homeostasis. Thrombin, a serin protease which elicits its cellular effects via...

Deregulates VEGF and Disturbs Neoangiogenesis

TH-OR098

Autoimmune Targeting of Protease Activated Receptor-1 (PAR-1) Derugulates VEGF and Disturbs Neoangiogenesis Rusan Catar, Isa Annett Schramm, Michele Simon, Oskar Wischnewski, Aurèle Philippe, Angelika Kusch, Dunka Dragan. Univ Hospital Charite, Berlin, Germany.

Background: Early loss of peritubular capillaries (PTC) with initiation of tubular atrophy and interstitial fibrosis is central to progressive nephron loss in native kidneys and transplants. VEGF is crucial for endothelial growth, differentiation and survival and mediates PTC homeostasis. Thrombin, a serin protease which elicits its cellular effects via the G-Protein Coupled Receptor (GPCR) PAR-1 is closely involved in VEGF regulation. Functional anti-GPCRs autobodyes are able to induce endothelial dysfunction. We hypothesized that autoimmune GPCR targeting process may disturb VEGF induced angiogenesis and identified PAR-1 as a novel activating autobody target.

Methods: Human microvascular endothelial cells (HMEC-1) were stimulated with IgG isolated from patients’ sera with transplant peritubular pathology (KTx-IgG). VEGF transcriptional regulation was studied by promoter deletion assay, transcription factor activation by qRT-PCR, western blot, EMSA and knockdown, VEGF secretion by ELISA. Tubule formation on matrigel served to study endothelial neoangiogenic response.

Results: Treatment with KTx-IgG increased ERK1/2 dependent VEGF secretion and tubule formation. Upon treatment with several pharmacologic antagonists, VEGF secretion could be only normalized by pretreatment with specific PAR-1 inhibitor. Specificity was further confirmed by the use of PAR-1 2nd extracellular loop peptide which rescued endothelial tube formation. KTx-IgG increased cFos protein expression and its binding to VEGF-promoter contributing to deregulate neoangiogenesis by reducing VEGF-promoter activity, AP-1 inhibition of cFos siRNA-induced knockdown reconstituted VEGF levels and increased its promoter activity. 

Conclusions: We identified the PAR-1 receptor as a new target for functional antibodies in the context of kidney transplantation with disturbed PTC homeostasis. We showed that KTx-IgG disturbs VEGF transcriptional regulation resulting in reduced VEGF secretion and inability of endothelial cells to form tubes. PAR-1 mediated VEGF regulation could offer new possibilities for treatment of kidney transplants to obviate loss of PTCs.

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

Underline represents presenting author/disclosure.
TH-OR101
CTLA4 Is Required For Rapamycin-Induced Augmentation of the CD8+ T Cell Response to a Latent Viral Infection
David F. Pinelli, Mandy L. Ford. Emory Univ.

Background: Latent viral infections are a major concern among immunosuppressed transplant patients. Treatment with belatacept, a CTLA4-Ig fusion protein, was shown to reduce toxicity in kidney transplant recipients compared to CNI therapy, but is contraindicated in EBV patients. We next sought to more fully assess how gadolinium precipitated in draining lymph nodes. Similarly, CD4+ and CD8+ T effector memory/T reg ratios were increased (p < 0.05). We next sought to more fully assess how gadolinium precipitated in draining lymph nodes. Similarly, CD4+ and CD8+ T effector memory/T reg ratios were increased (p < 0.05).

Methods: Mice were infected with gammaherpesvirus 68 (gHV), the murine homolog of EBV, treated with rapa +/- CTLA4-Ig, and MHC tetramers were used to track virus-specific CD8 T cells. We also performed ex vivo restimulation with gHV peptide to assess CD8 T cell IFN-γ production.

Results: Rapa treatment alone enhanced the T cell response to gHV, with a significant increase in the number of gHV tetramer positive CD8 T cells per 10^6 PBMCs at Day 20 compared to mice that received no treatment (4.5E4±9E3 vs. 2.4E4±8E3) and also led to an increase in the percentage of CD8 T cells in contrast, CTLA4-Ig treatment prevented rapa from significantly enhancing CD8 T cell responses (CTLA4-Ig 2.6E4±8E3 vs. +Rapa 2.6E4±6E3). Interestingly, when an anti-CTLA4 blocking antibody was used, which leaves CD28 signals intact, rapamycin was also unable to augment the response (anti-CTLA4 4.2E4±5E3 vs. +Rapa 4.6E4±5E3). To determine the impact of rapamycin on T cell function, we performed an ex vivo restimulation with gHV (Anti-CTLA4 4.2E4±5E3 vs. +Rapa 4.6E4±5E3).

Conclusions: Taken together, these results suggest that the ability of rapamycin to enhance virus-specific memory T cell function requires signals through the CTLA-4 co-inhibitor. Further work is necessary to dissect the interactions of these two signaling pathways and to understand the mechanism by which CTLA4 blockade diminishes the ability to promote the generation of CD8 T cell memory.

Funding: Pharmaceutical Company Support - Pfizer

TH-OR102
Gadolinium Accelerates Cardiac Allograft Rejection through Macrophage Activation and Blockade of Phagocytosis
Martina M. McGrath, Melissa Y. Yeung, Nader Najafian. Renal Div, Brigham and Women’s Hospital, Boston.

Background: Phagocytosis is a crucial mechanism for the maintenance of self-tolerance. Defects in phagocytic mechanisms predispose to autoimmunity. Gadolinium has been used as a tool to impair macrophage phagocytosis in experimental models. In this study we sought to examine the effect of blockade of macrophage phagocytosis by gadolinium, on allograft outcomes.

Methods: B6 recipients of fully mismatched heart transplants were treated with CTLA4-Ig 500ug on D0, 300ug gadolinium ip on D-2, D5 and D12 post transplant and assessed for survival and mechanistic studies.

Results: Treatment with gadolinium led to accelerated allograft rejection (MST 10d vs 20d, pт0.001). Mechanistic studies revealed increased Annexin V+ apoptotic cells in spleens of gadolinium treated recipients (p<0.05). Furthermore, gadolinium treated recipients showed increased production of pro-inflammatory IFNγ, IL4, IL6, IL17 and reduced IL10 levels in draining lymph nodes. Similarly, CD4+ and CD8+ T effector memory/T reg ratios were increased (p<0.05). We next sought to more fully assess how gadolinium precipitated allograft rejection. In vitro and in vivo phagocytosis assays confirmed an increased impairment in macrophage and macrophage phagocytosis after treatment with gadolinium. DC phagocytosis was unaffected in vivo. Incubation with gadolinium increased macrophage expression of MHC Class II molecules and CD68. Macrophage production of pro-inflammatory TNFα, IL12 and IL17 also increased significantly in response to gadolinium treatment in vitro.

Conclusions: These data indicate that gadolinium promotes an activated macrophage phenotype with impaired phagocytosis, increased costimulatory molecule expression and proinflammatory cytokine production. In vivo treatment of recipients of fully mismatched cardiac allografts precipitates acute rejection, characterised by markedly increased pro-inflammatory T cell infiltrate in graft, spleen and draining lymph nodes and splenic accumulation of apoptotic cells. Further studies are required to fully elucidate the mechanisms of rejection induction and evaluate the translational significance of these findings in humans exposed to gadolinium.

Funding: Private Foundation Support

TH-OR103
Prevention of Acute Antibody Mediated Rejection by MLN9708, Alone and in Association with Low Dose Cyclosporine in Sensitized Rats
Shannon Reece,1 Nancy A. Wilson Schleifer,2 Gengshen Huang,1 Wexiang Zhou,1 Arjang Djamali.1 1Medicine, Univ of Wisconsin; 2Pathology, Univ of Wisconsin.

Background: We designed a study to evaluate the activity of proteasome inhibitor, Ixazomib Citrate (MLN9708) alone and in combination with low dose cyclosporine in the prevention of acute antibody mediated rejection (ABMR) in a rat kidney transplant model.

Methods: To develop a robust model of ABMR, full MHC mismatch (Brown Norway to Lewis) kidney transplants were performed in recipients that were sensitized to donors via bone marrow or tumor cell allo-antigen (B6 to all groups). Histopathological grading was performed in accordance with BANFF criteria using H&E, PAS and C4d staining. Flow-cytometry was used to evaluate the effect of treatment on circulating Donor Specific Antibody (DSA). The presence of graft infiltrating B cells, complement regulatory proteins (CD35 and CD55) and M1 macrophage transcription factor (IRF5) were assessed by western blot analysis. Serum creatinine was measured as an indicator of kidney function.

Results: One week after transplant, MLN9708, alone or in combination with low dose CsA, was associated with a significant prevention of ABMR as evidenced by inhibition of microvascular inflammation (miNV) and the absence of C4d deposition in the allograft. Treatment with Ixazomib was more effective in preventing acute ABMR in an experimental rat model. Further mechanistic studies are needed to understand the therapeutic synergy between proteasome inhibition and calcineurin inhibition in CNI minimization protocols.

Funding: Pharmaceutical Company Support - Takeda Millennium

TH-OR104
High Salt Intensifies Alloimmune Response
Kassem Safa, Tetsunosuke Noguchi, Ciara N. Mager, Avi Arad, G. Gandhakur, Leonardo V. Riella. Renal Div/ Transplantation Research Center, Brigham and Women’s Hospital, Boston, MA.

Background: Recent reports suggest that a high salt diet (HSD) exacerbates autoimmune disease in mice (Nature, 2013). Whether HSD exerts a similarly deleterious effect in alloimmunity is unknown. Herein, we sought to examine the effect of NaCl on the alloimmune response both in vitro and in vivo, using mixed lymphocyte cultures (MLC) with allo-stimulation and a murine model of solid organ transplantation.

Methods: B6 mice were sensitized with fully MHC-mismatched BALB/c skin grafts; to perform MLCs, splenocytes were isolated from these mice and cultured with irradiated BALB/c splenocytes in media enriched with NaCl at gradual increments from 0 to 80 mM. To examine the effect of HSD in vivo, B6 mice were fed either HSD (3% NaCl, 0.9% Na, chow, regular water) starting 3 days prior to receipt of a BALB/c cardiac graft; a single dose of CTLA-4-Ig was administered to control the initial alloimmune response.

Results: An increase in the in vitro [NaCl] from 5-10 mM effected a corresponding increase in IFNγ secretion, as measured by ELISPOT (311 vs 342 SFC; p=0.03); however, further increase in [NaCl] from 10-40 mM reduced IFNγ secretion (342 vs 275 SFC; p<0.001). Similarly, increased cellular proliferation, as measured by thymidine incorporation, was seen as [NaCl] increased from 0-20 mM (923 vs 1377 cpm; p=0.046), while further increase from 20-40 mM NaCl decreased proliferation (1377 vs 776 cpm; p=0.001).

Conclusions: These results indicate that HSD may indeed influence the alloimmune response. Further mechanistic experiments will provide greater insight into this fascinating observation that has significant clinical implications in transplantation.

TH-OR105
Epigenetic Programming of Postnatal Renal Transcription Rates by Maternal Malnutrition
Oleg N. Denisenko,1 Carol Bomsztyk,1 Tom Patrick Fleming,2 Medicine, Univ of Washington, Seattle, WA; 2Univ of Southampton, Southampton, United Kingdom.

Background: Adverse exposures during pregnancy result in intrauterine growth restriction, IUGR, and increased risk of chronic diseases later in life, a phenotype that can be transferred through generations. A diverse set of conditions that cause this phenomenon suggests that common mechanisms of programming may be operative. We recently reported that transcription rates were globally decreased in fetal kidneys in two animal models of IUGR, maternal protein restriction in pigs and placental insufficiency in sheep, together representing IUGR in two major species of IUGR in humans. Here we examined mechanisms of transcription changes in a mouse model of maternal malnutrition.

Methods: Pregnant animals were fed low protein (LPD, 9% protein) or normal protein (NPD, 18% protein) diets during the entire gestation period, after birth all offspring were fed normal diet. RNA and DNA purified from embryonic (17 dpc) and adult (fmo) kidneys were analyzed by RT qPCR and methylated DNA IP (MeDIP) respectively.

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

24A
Results: We found that maternal LPD results in increased cellular RNA content in adult kidneys, in contrast to the reduced RNA levels in LPD fetal kidneys (p<0.05). Moreover, even before exposure to LPD during the periconceptional period (0-3.5 dpc) was sufficient to consistently increase renal cellular RNA levels in kidneys after transition to normal diet. To explore epigenetic contribution, we examined levels of DNA methylation known to repress transcription. Ribosomal RNA transcribed from ribosomal DNA (rDNA) loci represented 3% of cellular RNA. Dot-induced changes in cellular RNA content inversely correlated with levels of rDNA methylation, and were matched by changes in expression levels of Rn3, a key DNA transcription factor.

Conclusions: These observations identify rDNA methylation and transcription factor Rn3 as putative targets of dietary programming of rDNA transcription. Because ribosome production consumes up to 70% of cell resources, upregulation of rDNA transcription in LPD offspring may have adverse consequences for kidney function. Funding: NIDDK Support, Private Foundation Support

TH-OR106
Effect of N-3 Fatty Acids on Kidney Function after Myocardial Infarction: The Alpha Omega Trial
Ellen K. Hoogeveen,1 Johanna M. Geleijnse,2 Daan Kromhout,3 Theo Stijnen,4 Eugenie Gemen,4 Ron Kusters,5 Erik Giltay,6 1Nephrology, Jeroen Bosich Hospital, Den Bosch, Netherlands; 2Human Nutrition, Wageningen Univ, Wageningen, Netherlands; 3Medical Statistics and Bioinformatics, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Kidney function gradually decreases with age, and a myocardial infarction accelerates this deterioration.

Methods: We examined in an ancillary study the effect of marine n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and plant-derived alpha-linolenic acid (ALA) on kidney function in the Alpha Omega Trial: a multicenter, double-blind, randomized, placebo-controlled trial with a 2x2 factorial design.

Results: We randomly assigned free-living Dutch patients with a history of myocardial infarction, aged 60-80 years (79% men), to margarines supplemented with targeted additional intake of 400mg/day EPA and DHA, 2g/day ALA, EPA-DHA plus ALA, or placebo for 40 months. In 4262 patients the treatment effect parameters cystatin C- and creatinine- and creatinine-cystatin C-based eGFR were assessed with CKD-EPI equations. Patients consumed 19.8g margarine/day, providing an additional amount of 238mg/day EPA with 15mg/day DHA, 1.98g/day ALA, or both, in active-treatment groups. In the placebo-group, cystatin C-based eGFR was 5.57 ml/min/1.73m2 (SE=0.04) lower after 40 months. Compared to placebo the decline (95%-CI) in cystatin C-based eGFR was reduced by 1.90 (0.26 to 2.94) ml/min/1.73m2 for EPA-DHA, 1.03 (0.21 to 2.28) ml/min/1.73m2 for ALA, and 1.28 (0.04 to 2.51) ml/min/1.73m2 for EPA-DHA plus ALA. Creatinine- and creatinine-cystatin C-based eGFR in the placebo-group declined by 1.33 (SE=0.39) and 2.22 (SE=0.39) ml/min/1.73m2, respectively. Decline of creatinine- and creatinine-cystatin C-based eGFR was not affected by EPA-DHA and/or ALA treatment.

Conclusions: Supplementation with modest amounts of EPA-DHA, with or without ALA, significantly attenuated the decline of cystatin C-based eGFR in post-myocardial infarction patients. However, a beneficial effect was not observed for creatinine-based and creatinine-cystatin C-based eGFR. Funding: Other NIH Support - Dutch Kidney Foundation, Dutch Heart Foundation, US National Institutes of Health (NIH), Pharmaceutical Company Support - Unilever R&D

TH-OR107
Effects of a Low Protein Diet on Skeletal Muscle Protein Synthesis and Degradation in Patients with Chronic Kidney Disease
Giacomo Garibotto, Antonella Sofia, Valeria Cademartori, Emanuele L. Parodi, Daniela Verzola. Div of Nephrology, Dialysis and Transplantation, Genoa Univ and AOU San Martino-IST, Genoa, Italy.

Background: Chronic kidney disease (CKD) is characterized by progressive loss of muscle mass, an effect which could be accelerated by a low protein diet (LPD). However, to what extent skeletal muscle protein metabolism adapts to a LPD in CKD patients is still unexplored.

Methods: To assess the effect of LPD on muscle protein metabolism in CKD patients, forearm [2H]phenylalanine kinetics and amino acid balance were evaluated in six CKD patients (5M/1F, age 54±5 yrs, eGFR 18±2 ml/min) assigned to a usual-protein diet (1.2 g/kg/day, 32 kcal/Kg/day) or a LPD (0.55 g/kg, 32 kcal/Kg/ day) period. Studies were performed after an overnight fast (post-absorptive state) and results express basal rates of protein turnover.

Results: After LPD: (a) whole body protein turnover declined only slightly (from 0.65±2 to 0.57 ±2 mmol/min/kg, usual protein diet vs, LPD, p<0.06); (b) forearm protein net balance, i.e. the difference between protein synthesis and degradation, decreased markedly (-41%, from -21±2 to -21 ±2 mmol/min/100 ml, p<0.02); (c) the efficiency by which amino acids are recycled back from protein degradation into protein synthesis increased by 30% (p<0.05); (d) muscle protein degradation underwent a marked decline (from 65±4 to 48 ±4 mmol/min/100 ml , p<0.02), (e) Protein synthesis was unchanged (from 37±3 to 37±4 mmol/min/100 ml, p= NS).

Conclusions: Our data show that CKD patients achieve muscle protein metabolism adaptation to a LPD through a marked decrease in muscle protein degradation and enhanced recycling of amino acid derived from catabolism. Protein synthesis appears to be remarkably preserved, which suggests that a 0.55 g/kg LPD is nutritionally safe.
TH-0R110
Effect of Restriction of Foods Containing Phosphorus Additives on the Phosphatemia of Patients with End-Stage Renal Disease

Margarete M. M. Fornasari, Yvoty As Sens. Santa Casa de São Paulo - School of Medical Sciences, São Paulo, SP, Brazil.

Background: Hyperphosphatemia control in chronic renal disease involves restriction of foods which naturally contain phosphorus. However, this restriction must also be extended to processed foods with phosphorus additives, the percentage of which varies from country to country. The purpose of the study is to verify the effect of restricting foods containing phosphorus additives on the serum phosphorus in patients on hemodialysis.

Methods: This study was done on adults with end-stage renal disease on hemodialysis for ≥6 months at a single center in São Paulo, Brazil. A total of 248 patients with phosphorus ≥5.5 mg/dL were evaluated, and 134 were selected according to the inclusion criteria and randomized into 2 groups: intervention (n=67) and control (n=67). Clinical-laboratory, nutritional status, calories, protein, phosphorus intakes and nPNA evaluations were made at the beginning of the study and after 90 days. The intervention group received orientation to substitute processed foods with phosphorus additives for foods without these additives, but having similar nutritional value. The control group maintained the nutritional orientation given prior to the study. The prescription of phosphorus binders was not modified for either group.

Results: There was no initial difference between the groups for serum phosphorus, nutritional status, protein and calories intake and nPNA. After 3 months, there was a decline in phosphorus levels in the intervention group (from 7.2±1.4 mg/dL to 5.0±1.3 mg/dL, p<0.001), while there was no significant difference in the control group (from 7.1±1.2 to 6.7±1.2 mg/dL, p=0.50). In the intervention group 65.7% of the patients reached the target of ≤5.5 mg/dL serum phosphorus versus 18.5% in the control group (p<0.001). There was no difference between groups for nutritional status, protein intake and nPNA.

Conclusions: The restriction of food with phosphorus additives reduced the serum phosphorus without interfering in the nutritional status of end-stage renal disease patients on hemodialysis.

TH-0R111
Safety and Efficacy of Bariatric Surgery in Obese Patients with CKD

The London Renal Obesity Network (LORON) Experience

Helen L. MacLaughlin, Iain C. Macdougall, Ahmed R. Ahmed, Ameet G. Patel, Avril Chang, Aine Burns, Nick Finer, Harvinder Chahal, George Tharakan, Andrea Pucci, Frederick W.K. Tam, Tina Johansson, Jan Flint, Andrew H. Frankel. 1Fresenius Medical Care, Germany; 2Fresenius Medical Care North America; 3Fresenius Medical Care Asia Pacific.

Background: While bariatric surgery is effective for weight loss in obese patients with CKD, the adverse event and mortality rates are high. Identifying which patients with CKD are at the highest risk for adverse outcomes could impact clinical decision-making.

Methods: We performed a prospective study in patients with CKD stage 1-5 (NCT00441623). Intestinal PC uptake, under steady state conditions, was estimated from 24 hr urinary excretion of PCS. Primary endpoint was time to first CV event, i.e. cardiac death, myocardial infarction/sclerosis, ventricular arrhythmia, CV surgery, cerebrovascular accident or symptomatic peripheral arterial disease. Statistical analysis was done using Kaplan Meier estimates and Cox proportional hazard analyses.

Results: In a cohort of 200 patients, median 24hr urinary excretion of PCS was 547.47 μM (IQR 252.68-697.17). After a median follow-up of 52 months, 25 patients reached the primary endpoint (tertile 1/2/3: 5/6/14 events, see figure). Higher urinary excretion of PCS was related with CV events (univariate HR per 100 μM increase: 1.112, P=0.0015). In multivariate analysis, urinary excretion of PCS remained a predictor of CV events, independent of markers of renal function (HR 1.120, P=0.0022) and in different models with other CV risk factors (Framingham, CV history, diabetes mellitus and biochemical parameters). The independent association between urinary excretion of PCS and outcome persisted after correction for serum PCS.

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

Underline represents presenting author/disclosure.

TH-0R112
Cardiovascular Disease Relates to Intestinal Uptake of p-Cresol in Patients with Chronic Kidney Disease


Background: Serum p-cresyl sulfate (PCS) associates with cardiovascular (CV) disease in patients at different stages of chronic kidney disease (CKD). PCS concentrations are determined by intestinal uptake of p-cresol (PC), human metabolism to PCS and renal clearance. Whether intestinal uptake itself is associated with CV disease in patients with CKD has not been studied to date.

Conclusions: Intestinal uptake of PC associates with CV disease. Insights into mechanisms governing intestinal generation and absorption of PC may lead to identification of novel therapeutic targets to reduce CV disease risk in patients with CKD.

Funding: Government Support - Non-U.S.

TH-0R113
Sagittal Abdominal Diameter Is an Independent Predictor of Mortality in Incident Peritoneal Dialysis Patients

Mi Jung Lee, Shin-Wook Kang, Hyung Jung Oh, Sung Jin Moon, Tae Ik Chang, Dae-Suk Han, Tae-Hyun Yoo. 1Brain Korea 21; Internal Medicine, College of Medicine, TaeSei Univ, Seoul, Korea; 2Internal Medicine, KwanDong Univ, Gyeonggi-do, Korea; 3Internal Medicine, NHIC Ilsan Hospital, Gyeonggi-do, Korea.

Background: Sagittal abdominal diameter plays a crucial role in the development and progression of cardiovascular (CV) disease. However, the impact of sagittal abdominal diameter (SAD), as an index of visceral fat, on clinical outcomes has never been explored in dialysis patients. In this prospective observational study, therefore, we elucidated the prognostic value of SAD in incident peritoneal dialysis (PD) patients.

Methods: SAD was determined by lateral abdominal X-ray at PD initiation in 418 incident PD patients. SAD was defined as the anterior-posterior distance, from skin to skin, at the L4-L5 intervertebral disc level. Cox proportional hazard analysis was performed to ascertain the independent prognostic values of SAD for all-cause and CV mortality.

Results: The mean SAD was 24.5±4.3 cm. During a mean follow-up duration of 39.4±21.3 months, 97 patients (23.2%) died. SAD was a significant independent predictor of all-cause (HR (hazard ratio) = 1.081, 95% CI [confidence interval] = 1.015-1.151, P=0.019) and CV mortality (HR = 1.022, 95% CI = 1.022-1.255, P=0.015). In addition, SAD provided significantly higher predictive values for all-cause (AUC=0.691 vs. 0.547, P<0.001) and CV mortality (AUC=0.644 vs. 0.483, P<0.001) than body mass index (BMI). Subgroup analysis revealed that higher SAD (≥24.2 cm) was significantly associated with all-cause mortality in men, women, younger patients (<65 years), and patients with lower BMI (<22.3 kg/m²).

Conclusions: SAD on lateral abdominal X-ray at the time of PD start was a significant independent predictor of all-cause and CV mortality in incident PD patients, suggesting that estimating visceral fat by SAD could be useful to stratify mortality risk in these patients.

Funding: Government Support - Non-U.S.

TH-0R114
Relationship between Body Composition Evaluated by Whole Body Bioimpedance and Survival in Hemodialysis Patients

Danielle Marcelli, 1 Len A. Usvyat, 2 Cristina Marelli, 2 Michael Eter, 1 Jeroen Kooman, 2 Aileen Grassmann, 1 Laura Scatizzi, 1 Inga Bayh, 2 Peter Kotanko, 3 Bernard Canaud. 1Grassmann, 1 Laura Scatizzi, 1 Inga Bayh, 2 Peter Kotanko, 3 Bernard Canaud. 1Fresenius Medical Care, Germany; 2Fresenius Medical Care North America; 3Renal Research Institute, N.Y.; 4Fresenius Medical Care, Argentina; 5Fresenius Medical Care Asia Pacific; 6Maastricht Univ Medical Centre, Netherlands.

Background: It is unknown which components of body composition contribute to the reported protective effect of high body mass index (BMI) in chronic HD patients. This international observational study explores the independent and joint associations of fat and lean tissue mass (FTM, LTM) with mortality.

Methods: We performed a prospective study in patients with CKD stage 1-5 (NCT00441623). Intestinal PC uptake, under steady state conditions, was estimated from 24 hr urinary excretion of PCS. Primary endpoint was time to first CV event, i.e. cardiac death, myocardial infarction/sclerosis, ventricular arrhythmia, CV surgery, cerebrovascular accident or symptomatic peripheral arterial disease. Statistical analysis was done using Kaplan Meier estimates and Cox proportional hazard analyses.

Results: In a cohort of 200 patients, median 24hr urinary excretion of PCS was 547.47 μM (IQR 252.68-697.17). After a median follow-up of 52 months, 25 patients reached the primary endpoint (tertile 1/2/3: 5/6/14 events, see figure). Higher urinary excretion of PCS was related with CV events (univariate HR per 100 μM increase: 1.112, P=0.0015). In multivariate analysis, urinary excretion of PCS remained a predictor of CV events, independent of markers of renal function (HR 1.120, P=0.0022) and in different models with other CV risk factors (Framingham, CV history, diabetes mellitus and biochemical parameters). The independent association between urinary excretion of PCS and outcome persisted after correction for serum PCS.

Conclusions: Intestinal uptake of PC associates with CV disease. Insights into mechanisms governing intestinal generation and absorption of PC may lead to identification of novel therapeutic targets to reduce CV disease risk in patients with CKD.

Funding: Government Support - Non-U.S.
Conclusion: LTM, not FTM, seems to be the main determinant of the inverse relationship between BMI and mortality. FTM seems to be only protective if accompanied by an appropriately higher LTM. Patients with low LTM relative to FTM appear to be at higher risk.

TH-OR115

International Comparisons Illustrate Effect of Payment and Regulatory Changes on Anemia Practice in U.S. Hemodialysis Patients: The Dialysis Outcomes and Practices Patterns Study

Douglas S. Fuller,1 Brian Bieber,1 Hal Morgenstern,1 Tadao Akizawa,2 Stefan H. Jacobson,4 Francesco Locatelli,5 Ronald L. Pisoni,1 1Arb Res Collab Hlth, Ann Arbor; 2Univ of MI, Ann Arbor; 3Showa Univ, Tokyo; 4Danderyd Hosp, Stockholm; 5Hosp A Manzoni, Lecco.

Background: In the US in 2011, an erythropoiesis-stimulating agent (ESA) label change and Quality Incentive Program (QIP) update removed the 10 g/dL lower hemoglobin (Hb) target, and a new dialysis payment system began. To assess the impact, we compared recent anemia management practices in the US to Europe (EUR) and Japan (JP).

Methods: Linear spline regression adjusted for age, black race, sex, vintage, and catheter use was used to assess trends from Aug 2010 to Dec 2012 for ESA-managed Hb (HbESA), serum ferritin, TSAT, and ESA and IV iron use in US, EUR, and JP.

Results: In Aug '10, mean HbESA in US (11.3 g/dL) was similar to that in EUR but then diverged after Jun '11 US ESA label change. By Dec '12, mean HbESA was 10.7, 10.7, and 11.1 g/dL in US, JP, and EUR. ESA use (any time over 3 months) changed from 95% to 89% in US, 91% to 89% in EUR, and 87% to 91% in JP. Median prescribed IV epoetin (EPO) dose fell 41% in US to 102 u/wk/kg (Dec '12) vs little change in EUR and JP (92 and 63 u/wk/kg, Dec '12). US monthly IV iron use over the study rose from 55 to 68% while stable in EUR and JP. US mean ferritin rose 35% to 825 ng/mL (Dec '12; median: 794), with an 8% rise in EUR to 514 ng/mL and no rise in JP. Higher ferritin in US may be due to higher IV iron doses used in US vs most other countries.

Conclusions: Recent US trends of lower ESA doses and Hb and higher ferritin levels are not observed among male and female subgroups. A similar pattern of association between increased Kt/V level and decreased mortality was observed among both male and female subgroups.

TH-OR116

Linear Relationships between Non-Volume-Scaled Dialysis Dose and Mortality Risk among Male and Female Hemodialysis Patients

Connie Rhee,1 Vanessa A. Ravel,1 Jongha Park,1 Elani Streja,1 Allen R. Nissenson,2 Csaba P. Kovessy,3 Kamyar Kalantar-Zadeh,4 1Harold Simmons Center, Orange, CA; 2DaVita Inc, El Segundo, CA; 3Memphis VA Medical Center, Memphis, TN, 1Univ of Ulsan College of Medicine.

Background: Dialysis dose has typically been defined as the dialyzer clearance of urea multiplied by dialysis duration (Kt/V) scaled to the volume of distribution of urea in the body (V). Using this classic metric (Kt/V), prior observational studies have shown that women receiving lower dialysis doses have higher mortality than women receiving higher doses, whereas men receiving higher doses have slightly increased mortality. However, V may have been a proxy for body size, which is associated with mortality independent of urea clearance. Kt (dialysis dose non-scaled to V), may be a more optimal approach to examining the association between dialysis dose and hemodialysis (HD) patient mortality.

Methods: Using DaVita clinical data, we identified 104,219 maintenance HD patients who underwent treatment from 2001-2009. Associations between time-averaged Kt and all-cause mortality were examined in the overall cohort and within subgroups of males (n = 57,156) and females (n = 47,063) using Cox regression models.

Results: In the overall cohort, there was a graded inverse association between higher time-averaged Kt levels and mortality risk in unadjusted, case-mix, and case-mix and malnutrition-inflammation-complex syndrome adjusted analyses (reference Kt =90-109). A similar pattern of association between increased Kt level and decreased mortality was observed among men and women.

TH-OR117

Effect of Medicare Part D Plan on Adoption on Renal Medications by Dialysis Patients on Renal Transplant Wait List

Marie D. Philipneri, Krista L. Lentine, Mark Schnitzler. Saint Louis Univ, Saint Louis, MO.

Background: Medicare Part D Prescription Drug Benefit Program came into effect on January 1, 2006. There is limited data on the adoption of renal medications post Medicare Part D implementation among dialysis patients.

Methods: A novel database wherein OPTN identifiers for kidney transplant (KT) wait list patients were linked to pharmacy fill records from a large U.S. pharmaceutical claims clearinghouse (2005 to 2010) was evaluated. For this study, we selected dialysis patients with at least one Medicare pharmaceutical fill per quarter in 2006 and at least one pharmaceutical fill per quarter in 2005 (N=1,648).

Results: 34.0% of the sample did not have pharmacy fills for any binder in 2005 and of these 27.8% filled at least one binder in 2006. African American patients were 1.65 times more likely to adopt binders after the start of Medicare Part D compared to Caucasians after adjusting for gender, education level, and employment status (p<0.05). 82.2% of the sample did not have pharmacy fills for cinacalcet in 2005 and of these 15.7% filled cinacalcet at least once in 2006. African American and middle-aged (31-65 year old) patients were more likely to adopt cinacalcet use compared to Caucasian and older (over 65 years) patients after adjusting for gender, level of education, and employment status. The patients who attained college education were 40% less likely to adopt use of cinacalcet compared to those who did not receive college education (p<0.05).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Outpatient Dialysis Treatments in the Week Post-Discharge and Readmissions

Eduardo K. Lacson, Weiling Wang, Franklin W. Maddux.
Fresenius Medical Care, North America, Waltham, MA.

Background: 30-day hospital readmissions in dialysis patients are thought to be influenced by outpatient dialysis facility care. Contact with facility staff to draw labs and implement interventions are necessary to influence outcome. Laboratory results are often received by the second (or third) treatment and could be acted upon. We evaluated the frequency of hemodialysis (HD) treatments within the 1st week post-discharge, before readmission events.

Methods: All adult in-center HD patients treated 3x/week as of 1/1/2011 in Fresenius Medical Care, North America facilities with at least one hospital discharge in 2011 were included. Days to readmission and the number of HD treatments before readmission were recorded until 12/31/2011.

Results: There were 164,258 hospital events in 64,128 patients in 2011. 50,380 (30.7%) 30-day readmissions occurred in 23,575 patients. 17,797 (35.3%) of 50,380 readmissions were within 7 days post-discharge, with only 5,810 (32.6%) having 2 or more days to receive the second (or third) treatment.

Conclusions: The results of this study suggest that Medicare Part D Plan was particularly helpful for the African American, middle-aged, and those without college education. Future studies are needed to see if this trend is sustained and the findings could help policy makers focus their efforts on special populations in the implementation of new health care reforms.

TH-OR119

Evaluation of Calciphylaxis Incidence in the United States Renal Data System

Saagar U. Nigwekar,1 Craig Solid,2 Elizabeth D. Ankers,1 Ravil I. Thadhani,1 Charles A. Herzog.1 Massachusetts General Hospital; 2CIVIC, US Renal Data System, Minneapolis, MN.

Background: Exact incidence of calciphylaxis, a highly fatal condition seen in maintenance hemodialysis (MHD) patients, is unknown. This study is designed to develop a strategy to accurately identify calciphylaxis cases in the United States Renal Data System (USRDS) and to examine calciphylaxis incidence.

Methods: Using the USRDS database, we identified those receiving MHD during 2007-2011 (n=1,203,240). ICD-9 code 275.49 refers to Other Disorders of Calcium Metabolism with calciphylaxis included along with other diagnoses such as nephrocalcinosis, chondrocalcinosis, etc. Since accurate diagnosis of calciphylaxis requires a skin biopsy and other disorders covered under 275.49 do not require a skin biopsy for diagnosis, we theorized that applying ICD-9 code 275.49 plus skin biopsy procedure codes simultaneously to claims in the USRDS will accurately identify calciphylaxis cases. We planned a systematic validation of this strategy in Partners Healthcare System’s Research Patient Data Registry (RPDR) that contains 11,451 MHD patients using natural language processing and by an independent query of pathology department records.

Results: Application of surrogate strategy to RPDR identified 69 calciphylaxis cases. Chart review confirmed 66 cases to be true positives. An independent query of pathology records identified 8 calciphylaxis cases missed by the surrogate strategy. This yielded sensitivity 87%, specificity 99%, and C statistic 0.96 for the surrogate strategy. Application of this validated strategy to the USRDS database identified 527 calciphylaxis cases. Annual incidence of calciphylaxis increased over the study period from 3.7 per 10,000 HD patients to 5.7 per 10,000 HD patients.

Conclusions: Calciphylaxis is rare but its incidence is rising. Further research is needed to investigate reasons for this rise.

Funding: Private Foundation Support

TH-OR120

Provider Characteristics and Hemodialysis Patient Outcomes

Yelena Slinin,1 HaiFeng Guo,1 Saiying Li,2 Jiannong Liu,2 Areef Ishani.1,2 Veterans Administration Health Care System, Minneapolis, MN; 2Chronic Disease Research Group, Minneapolis, MN.

Background: Physician characteristics are associated with differential performance on quality measures and patient outcomes in several medical fields. We aimed to determine whether hemodialysis provider characteristics were associated with patient morbidity, mortality, and quality of care (defined by influenza vaccination and wait-listing for kidney transplant).

Methods: Using USRDS data for patients who initiated in-center hemodialysis 10/01/2003-9/30/2006 (n = 91,276), we defined patient characteristics and identified physicians from Part B Medicare claims for outpatient dialysis submitted during months 4-6 of hemodialysis. We obtained physician characteristics from the AMA Physician Master File. We determined associations of physician characteristics with 1-year patient mortality and first hospitalization using Cox proportional hazards analysis, and with vaccination and wait-listing using logistic regression.

Results: Physician characteristics were not associated with patient mortality. After adjustment for patient and other provider characteristics, longer practice duration (AHR 1.03(1.01-1.05) for 9-21 years in practice compared with 0-8), and administrative, research, or teaching practice (1.08(1.00-1.16) compared with office-based practice) were associated with greater risk of patient hospitalization. Practice in smaller metropolitan service areas (MSAs) was associated with lower risk of hospitalization (0.95(0.92-0.97)). Longer practice duration was associated with higher chance of wait-listing for kidney transplant (AOR 1.15(1.05-1.25) for ≥ 22 years in practice compared with 0-8), and practice in smaller MSAs was associated with lower chance (0.80(0.79-0.99) for population 100,000-249,999 and 0.84(0.74-0.95) for < 100,000, compared with ≥ 1,000,000). Graduation from a foreign medical school was associated with higher odds of influenza immunization 1.07(1.00-1.14), as was practice in smaller MSAs (AOR 1.29(1.20-1.38) for population 100,000-249,999).

Conclusions: Several characteristics of physicians following patients for outpatient hemodialysis were associated with patient hospitalizations and quality of care.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
TH-OR121
Comparison of Hospitalization between For-Profit and Nonprofit Dialysis Facilities
Lorien S. Dalrymple,1 Kirsten L. Johansen,2 Patrick S. Romano,1 Glenn M. Chertow,3 Yi Mu,4 Julie H. Ishida,5 Barbara A. Grimes,6 George A. Kaysen,7 Danh V. Nguyen,81 UC Davis; 2San Francisco VAMC; 3UCSF; 4Stanford; 5UC Irvine.

Background: The vast majority of US dialysis facilities are for-profit and profit status has been associated with processes of care and outcomes in patients on dialysis. Our study examined whether dialysis facility profit status was associated with the rate of hospitalization in patients starting dialysis at a single dialysis center.

Methods: We conducted a retrospective cohort study of Medicare beneficiaries starting dialysis between 2005 and 2008 using data from the United States Renal Data System. We examined and compared all-cause hospitalization between for-profit and nonprofit dialysis facilities through 2009 using Poisson regression. We conducted companion analyses of cause-specific hospitalization that are likely to be influenced by dialysis facility practices including hospitalizations for heart failure and volume overload, access complications, or hyperkalemia.

Results: The cohort included 150,642 patients. Of these, 12,985 (9%) were receiving care in non-profit dialysis facilities. In adjusted models, patients receiving hemodialysis in for-profit facilities had a 15% (95% CI 13 - 18%) higher relative rate of hospitalization compared to those in nonprofit facilities. Among patients receiving peritoneal dialysis, adjusted analyses showed a non-significant trend toward higher rate of hospitalization in for-profit facilities (RR 1.07, 95% CI 0.97 - 1.17). Patients on hemodialysis receiving care in for-profit dialysis facilities had 17% (95% CI 13 - 44%) higher rates of hospitalization for heart failure or volume overload and 15% (95% CI 11 - 20%) higher rates of hospitalization for vascular access complications.

Conclusions: Hospitalization rates were significantly higher for patients receiving hemodialysis in for-profit dialysis facilities.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc.

TH-OR122
Primary Care Nephrology versus Subspecialist Care for ESRD Patients: The Southern California Kaiser Permanente Experience
Dean A. Kujubu,1 Miwa Takayanagi,2 Jean Q. Wang,3 Antoine C. Abcar,4 Scott A. Rasgon,5 Kaiser Permanente, Los Angeles, CA; 2Research and Evaluation, Kaiser Permanente, Pasadena, CA.

Background: Since most dialysis patients see their nephrologists more often than their generalists, many nephrologists serve as de facto primary care physicians. Alternatively, other nephrologists prefer to manage ESRD issues only and defer non-dialysis issues to the patients’ primary care physicians. Which practice pattern results in better clinical outcomes, more efficient use of medical resources, or higher patient satisfaction is unclear.

Methods: We reviewed the number of emergency room (ER) visits, hospitalizations, hospital days, ambulatory visits, and mortality of ESRD patients in the Southern California Kaiser Permanente (SCKP) Health System from 1999-2009. In 2 of the 13 medical centers, nephrologists serve as primary care physicians (PC) for ESRD patients; in the other 11 medical centers, ESRD patients see nephrologists who do not provide primary care (NPC). Demographic data and the presence of co-morbidities (CAD, CHF, HTN, DM, cirrhosis) were collected.

Results: From 1999-2009, there were 1932 ESRD patients in the PC group and 9192 patients in the NPC group. The PC group had more PD patients (10.9% vs 9.1%), more men (60.2% vs 57.1%), fewer Blacks (14.5% vs 23.7%), more Asians (15% vs 8.7%), and fewer cirrhotics (5.8% vs 3.7%) compared to NPC group. Age and the presence of other co-morbidities were not significantly different. Compared with NPC patients, PC patients had fewer ER visits (4.0 vs 4.7, p<0.01), fewer hospitalizations (2.8 vs 3.1 p<0.03), and fewer clinic visits (10.7 vs 11.4, p<0.001). Hospitalization days, death rate, and time to death were not significantly different. Nephrologists who provided PC received higher patient satisfaction scores (9.55 vs 9.46, p<0.01).

Conclusions: Within SCKP, patients of PC nephrologists had significantly fewer ER and clinic visits, fewer hospitalizations, and better satisfaction with their physicians compared with those ESRD patients whose nephrologists who did not provide PC. An ESRD patient-centered medical home with nephrologists serving as primary care physicians may improve both patient care and patient satisfaction.

Funding: Clinical Revenue Support

TH-OR123
Cost Analysis of Provider-Patient Visit Frequency during In-Center Hemodialysis
Benjamin B. Morgan,1 Suying Li,2 Jiannong Liu,2 Areef Ishani,1,2,3

Background: In 2004, CMS linked physician payment for HD services to the number of times/month providers see their patients. It is unknown whether increased HD visits correlate with Medicare cost savings.

Methods: Using USRDS data, a retrospective cohort of 130,892 in-center HD patients was created, including patients starting HD between October 31st, 2003 & September 30th, 2006. During a 3 month run-in phase, provider visit frequency was defined as the average number of provider visits/month, and expressed as ≥4 or <4 provider HD visits/month. Total individual Medicare costs, inpatient Medicare costs, and hospital length of stay (LOS) were summed over the course of a 12 month observational phase. A multi-linear regression model was constructed to estimate the association of provider visit frequency on total Medicare monthly expenditures for patients with ≥4 provider visits/month. Logistic regression models showed a 4% reduction (C.I. 0.93-0.98) in the odds of incurring any inpatient costs or LOS among the ≥4 provider visits/month group as compared to <4 visits/month. On average, patients with <4 visits/month, incurred $232/month higher expenses and stayed in the hospital 0.21 days/month longer than patients with ≥4 provider visits/month.

Conclusions: A non-significant difference in total expenditures along with the observed reduction in hospitalization rates among the higher provider frequency group support the current CMS dialysis provider reimbursement policy strategy.

Funding: NIDDK Support

TH-OR124
Can We Compare Laboratory Results from Different Dialysis Units?
Panapong Lisawat,1 Jeffrey M. Rimmer,1 FAHC/UVFM

Background: Calcium and albumin concentrations are important in management of hemodialysis patients and may be used as quality indicators. Difficulty achieving targets for serum calcium and albumin in our patients led to the hypothesis that differences in laboratory measurements influence assessment of population outcomes.

Methods: All patients at the our dialysis unit were offered inclusion in the study. Specimens were collected on the day of monthly testing in the usual manner. After routine testing was complete, the remaining sample in each specimen was divided equally into 2 plastic transport tubes. These samples were stored and then analyzed the same day at Fletcher Allen Laboratory (FAL) and Spectra Laboratories (SL). Both laboratories use similar indicator techniques for albumin and calcium but different analytic instruments and formulae for calculated corrected calcium.

Results: Samples were obtained from 66 patients. Results for paired values of serum albumin, calcium and calculated corrected calcium were significantly different between laboratories with p-values of <0.001, 0.001 and <0.001. Bland-Altman analysis showed the systematic bias between laboratories for albumin, calcium and corrected calcium to be 0.08 g/dl, 0.24 mg/dl and -0.26 mg/dl. Albumin and calculated corrected calcium values categorized among the ranges in the DOPPS are shown in the figure.

Funding: Private Foundation Support

TH-OR125
In Vivo Modulation of Per1 Target Gene Expression in the Kidney by Pharmacological Blockade of Circadian Clock-Regulatory Kinases CK1δ/ε
Jacob Richards,1 Sean All, Kit-Yan Cheng, Michelle L. Gunz. Medicine, Univ of Florida, Gainesville, FL.

Background: Mounting evidence suggests that the circadian clock plays an important role in the regulation of renal function and blood pressure (BP). We previously showed that the circadian clock protein Per1 coordinately regulates expression of several genes encoding products that function in the regulation of sodium (Na) reabsorption in the kidney. Per1 positively regulates the alpha subunit of the renal epithelial Na channel (eNaC) and Fxyd 5, a gamma-like subunit of the Na+ K+ ATPase. Per1 negatively regulates the lipid raft protein Caveolin-1 (Cav-1) and Endothelin-1 (ET-1), a potent inhibitor of ENaC channel activity. This coordinate regulation of Na transport genes predicts that knockdown of Per1 would result in renal Na wasting and subsequent decreased blood volume and BP. Indeed, we have shown that Per1 KO mice have significantly lower BP than control mice (Stow et al. Hypertension 2012). To understand more about the mechanism of how Per1 results in these effects, we investigated if modulation of other circadian genes results in changes in blood pressure. We have previously demonstrated that the circadian kinase inhibitor CK1δ/ε resulted in decreased eNaC expression and decreased ENaC Channel activity (Richards et al. AJP Renal 2012).

Distributions of SL (Salb) and FA (Faalb) albumin values are different (p=0.02) as are distributions of values for SL corrected calcium (SCCa) and FA corrected calcium (FACCa) (p=0.002).

Conclusions: Measurements of serum albumin, calcium and calculated calcium made on the same serum sample differ significantly between laboratories. A small systematic bias results in significant differences in categorized laboratory outcomes. Differences in quality of care may be mistakenly inferred from differences resulting from laboratory measurement.

Funding: Private Foundation Support

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

29A
Methods: Wild type 129/uv mice were injected with vehicle or the CK1ε inhibitor PF670462 every 12 hr for 2.5 days, a previously reported effective dose and time. Mice were euthanized at midnight and kidneys were harvested. Total RNA was isolated and checked for integrity. PCR was used to assess changes in gene expression of eNOS, Fxdy5, Cav-1, and ET-1 in the renal inner medulla and cortex. Results: Because the BP phenotype of Per1 KO mice suggests that Per1 is a viable target for the treatment of hypertension, we tested the in vivo effects of pharmacological inhibition of Per1 nuclear entry on the expression of Per1 target genes in the kidney. CK1ε inhibition led to decreased eNOS and Fxdy5 and increased Cav-1 and ET-1 in the inner medulla and cortex, consistent with our previous in vitro data. Conclusions: These results support the use of PF670462 for in vivo inhibition of Per1 activity and may have implications for the treatment of hypertension.

TH-OR126
A Novel Mouse Model Expressing Cre Recombinase along the Entire DCT
Juliette Hadehoul1,2, Christelle Soukaseam1,2, James A. McCormick1, Nicolas Picard3, David H. Ellison.1

1INSERM U970, Paris Cardiovascular Research Center, Paris, France; 3Oregon Health and Science Univ, OR.

Background: The distal nephron, composed of the cortical Thick Ascending Limb (TAL), the Distal Convoluted Tubule (DCT), the Connecting Tubule (CNT) and the Collecting Duct (CD), is a key player in maintaining Na+, K+ and Cl− homeostasis. Since many important regulators of ion transport are expressed in several segments, the development of segment-specific models is critical. While transgenic mouse lines expressing Cre recombinase along the CNT and CD have been created, only one transgenic line allowing targeting of the DCT is available, using the parvalbumin promoter. However, this model only targets the proximal part of the DCT. Our goal was to develop a transgenic mouse expressing Cre along the entire DCT, using the promoter of the Na-C1 co-transporter, NCC.

Methods: Our previous attempt with an NCC-based transgene was unsuccessful. We therefore chose to introduce the iCre cDNA into the endogenous Slc12a3 locus, encoding NCC. To preserve the NCC expression and activity, we used the viral iCre cDNA introduced between the iCre cDNA and the first coding amino acid of NCC. Using homologous recombination in ES cells, we have generated two independent mouse lines with the iCre-2A cassette targeted into the Slc12a3 locus.

Results: Immunofluorescence data showed that Cre recombinase is expressed along the DCT in NCC-iCre mice. We further demonstrated by RT-PCR that iCre is expressed only in the kidney. We are currently assessing whether the knock-in of iCre into the Slc12a3 locus affects NCC activity by measuring NCC expression and phosphorylation, and by performing thiazide-response tests in vivo.

Conclusions: Many studies have highlighted the crucial role of the DCT in the maintenance of normal sodium balance. However, our understanding of the mechanisms regulating DCT function has been hampered by several issues, such as the lack of a good cellular model and the difficulties of microinjection. This iCre model using Cre recombinase is a key tool to specifically target the entire DCT.

Funding: Government Support - Non-U.S.

TH-OR127
A Western Diet Activates NCC to Promote Sodium Retention
Andrew Terker, Chao-Ling Yang, David H. Ellison. Nephrology & Hypertension, Oregon Health & Science Univ, Portland, OR.

Background: To maintain blood pressure homeostasis, the thiazide-sensitive Na-Cl cotransporter (NCC) is suppressed by diets that are high in salt, promoting natriuresis. Since this is a key player in maintaining Na+, K+ and Cl− homeostasis, the NCC also plays a key role in potassium (K+) homeostasis. Diets that are low in K+ increase NCC abundance, reducing distal sodium delivery, and suppressing sodium-dependent potassium secretion along the distal nephron. A Western diet is typically high in salt and low in potassium. To determine the effects of a typical Western diet on NCC, we analyzed effects of opposing sodium and K+ signals.

Methods: Several models were used to generate opposing sodium/potassium signals: 1) Fludrocortisone (F) was administered via drinking water at a dose of 17 mg/L for one week; 2) Amiloride (A) was administered via drinking water at a dose of 50 mg/L for one week. 3) Indicated diets were administered for 7-10 days; high salt/normal K+ (HS/NK), high K+/normal salt (HKS/N), high salt/high K+ (HSK/EK), low salt/low K+ (LSK/LEK).

Results: 1) We confirmed that F (to model primary aldosteronism/Liddle syndrome) increased total and phosphorylated NCC; when NCC activation could not occur (NCC knockout (KO)), F caused profound hypokalemia. 2) Surprisingly, A (to model pseudohypoaldosteronism, PAH, DH), which causes hyperkalemia as expected, decreased total and phosphorylated NCC significantly. 3) HKS/LK dramatically increased total and phosphorylated NCC, compared with HSK/NK. Further, HS/NK increased WKY and SPAk, and redistributed WKY in DCT to cytoplasmic punctae. These effects were preserved in SPAr and angiotensin II receptor 1a (AT1a) KO mice. Lastly, HS/LK mice showed decreased urinary sodium compared with a HSK/NK diet in WT, but not in NCC KO mice.

Conclusions: Increased NCC activity caused by F attenuates K+ wasting. Decreased NCC caused by a likely results from hyperkalemia; such a similar effect may contribute to salt-wasting in PAH. 1. A HS diet, LK greatly increases NCC, compared with NK, independent of SPAr or AT1aR. Changing from a HS/NK to a HS/LK diet promoted sodium retention, an effect that requires NCC. Lastly, HS/LK moves WKY into cytoplasmic punctae. The results suggest that a Western diet promotes hypertension in an NCC-dependent manner; this hypothesis should be tested in humans.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR128
The Application of a Novel Phosphoprotein Technology to Study the WNK Kinase Signaling Network
Jesse Rinehart, Natasha L. Pirman. Cellular and Molecular Physiology, Systems Biology Institute, Yale Univ, New Haven, CT.

Background: Recent work has identified phosphorylation sites in the WNK kinases and has shown that mechanistic insight into WNK kinase phosphorylation will be a key to understanding their role in renal sodium transport and hypertension.

Methods: While many of the phosphorylation sites on mammalian proteins have been identified, and most others are within reach via phosphoarrays, there remains a substantial knowledge gap in the connections between kinases and substrates. We have recently made substantial progress in transforming phosphoprotein research by introducing a new technology that enables site-specific incorporation of phosphoserine into proteins. Our technology adds phosphoserine to the genetic code of E. coli by using the rare TAG stop codon (Amer codon). Phosphoproteins can then be synthesized and studied without the corresponding upstream kinase.

Results: We have an new optimized version of our technology that enables robust production of stoichiometrically phosphorylated proteins at single or multiple sites. This new technology was used to produce and study WKY with its physiologically relevant phosphorylation sites and a combinatorial library of WKY variants with phosphoserine introduced at activation loop residues. Previous work showed that phospho-mimetic substrate substitutions in these same positions produced an inactive WKYN. In contrast, our technology introduced native phosphoserines and produced fully activated WKYN. We used these activated WKYN proteins to reconstitute the WKY-SPAk-NKCC sub-network which showed robust WKYN dependent SPAk activation. Quantitative phosphoproteomic analysis of this network and WKYN auto-phosphorylation have been investigated and suggest new functional roles for WKYN phosphorylation.

Conclusions: Our technology provides unprecedented resolution into the role of protein phosphorylation in WNK kinase function, as well as recapitulates physiologically relevant signaling networks. Our studies provide the basis for a general strategy to study the role of protein phosphorylation in kidney physiology and a novel platform to develop targeted therapies.

Funding: NIDDK Support

TH-OR129
WK4N Modulates the WKIN/WNK3-Mediated Activation of the NaCl Cotransporter
Maria Chavez-Canales1,2, Christelle Soukaseam1,3, Maria Castañeda-Bueno1, Norma Hilda Vázquez1, Lorena Leonor Rojas1, Xavier Jeunemaitre5, David H. Ellison3, Gerardo Gamba1, Juliette Hadehoul2.

1INSERM U970, Paris Cardiovascular Research Center, Paris, France; 2Univ Paris-Descartes, Paris Sorbonne Cité, Paris, France; 3Oregon Health and Science Univ, OR.

Background: Increased renal salt reabsorption is a key pathogenic factor in the development of Arterial Hypertension. Familial Hyperkalemic Hypertension (FHHt) is a monogenic form of salt-sensitive hypertension caused by mutations in genes encoding WNK1, WNK4, Cullin 3 or kelch-like 3 that belong to the same salt reabsorption regulatory locus. While many of the phosphorylation sites on mammalian proteins have recently made substantial progress in transforming phosphoprotein research by introducing a new technology that enables site-specific incorporation of phosphoserine into proteins. Our technology adds phosphoserine to the genetic code of E. coli by using the rare TAG stop codon (Amer codon). Phosphoproteins can then be synthesized and studied without the corresponding upstream kinase.

Methods: Several models were used to generate opposing sodium/potassium signals: 1) Fludrocortisone (F) was administered via drinking water at a dose of 17 mg/L for one week; 2) Amiloride (A) was administered via drinking water at a dose of 50 mg/L for one week. 3) Indicated diets were administered for 7-10 days; high salt/normal K+ (HS/NK, 6%NaCl/0.8%K+), high salt/low K+ (HS/K/EK, 6%NaCl/0% K+).

Results: 1) We confirmed that F (to model primary aldosteronism/Liddle syndrome) increased total and phosphorylated NCC; when NCC activation could not occur (NCC knockout (KO)), F caused profound hypokalemia. 2) Surprisingly, A (to model pseudohypoaldosteronism, PAH, DH), which causes hyperkalemia as expected, decreased total and phosphorylated NCC significantly. 3) HKS/LK dramatically increased total and phosphorylated NCC, compared with HSK/NK. Further, HS/NK increased WKY and SPAk, and redistributed WKY in DCT to cytoplasmic punctae. These effects were preserved in SPAr and angiotensin II receptor 1a (AT1a) KO mice. Lastly, HS/LK mice showed decreased urinary sodium compared with a HSK/NK diet in WT, but not in NCC KO mice.

Conclusions: Increased NCC activity caused by F attenuates K+ wasting. Decreased NCC caused by a likely results from hyperkalemia; such a similar effect may contribute to salt-wasting in PAH. 1. A HS diet, LK greatly increases NCC, compared with NK, independent of SPAr or AT1aR. Changing from a HS/NK to a HS/LK diet promoted sodium retention, an effect that requires NCC. Lastly, HS/LK moves WKY into cytoplasmic punctae. The results suggest that a Western diet promotes hypertension in an NCC-dependent manner; this hypothesis should be tested in humans.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR130
WK4N Regulates NKCC in the Fly Tubule through a SPAk Intermediate
Aylin R. Rodan, Chou-Lang Huang. Dept of Medicine, UT Southwestern, Dallas, TX.

Background: The main segment of the Drosophila melanogaster renal tubule is K+-secreting. We have previously shown that the fly NKCC, Nce69, mediates approximately 1/3 of normal K+ flux. In the mammalian nephron, the WKSPNK kinase cascade regulates the Nce69-related transporters NCC and NKCC2. Here, we examined whether this pathway is conserved in the fly tubule.

Funding: Government Support - Non-U.S.
Methods: We genetically manipulated the fly WNK and SPAK kinases in wild-type and Ncc69 mutant flies and measured K+ flux in isolated tubules. We measured wnk transcript levels using quantitative RT-PCR.

Results: Knockdown of wnk with RNAi in the cation-secreting cells of the fly renal tubule decreased K+ flux (80±5 pmol/min/tubule in control vs 49±5 in wnk knockdown tubules, p<0.0001). Similarly, expression of WNK3 [1], a kinase-best isoform with low expression in WNK4 and also decreased K+ flux (68±3 in control vs 0.05 for wnk knockdown vs. control and fray204-flx expression). Activated Fray expression on its own did not change K+ flux (57±6 in control vs 68±8 in fray204-expressing tubules, NS). Wnk knockdown in an Ncc69 null mutant background did not result in decreased K+ flux (65±5 in controls, 62±4 in Ncc69 mutant tubules with wnk knockdown, NS). Wnk transcript levels were similarly decreased by wnk knockdown in both the wild-type and Ncc69 mutant backgrounds, to 37±9% and 50±17% of control (NS).

Conclusions: Decreasing WNK activity in the fly renal tubule impairs K+ flux. This phenotype is rescued by expression of constitutively active Fray (fly SPAK), suggesting that Fray acts downstream of WNK and that WNK activates Fray. Ncc69, the fly NKCC, appears to be the target of WNK/SPAK signaling, as the wnk knockdown phenotype is abolished in Ncc69 mutant tubules. We have thus established that the WNK/SPAK/NKCC pathway is conserved in the fly renal tubule, laying the groundwork for further dissection of the mechanisms by which this occurs, as well as the discovery of new genes in this regulatory pathway.

Funding: NIDDK Support

TH-OR131

SPAK-Independent Activation of Na-(K)-Cl Cotransporter by WNK4 Requires Cab39 as an Adaptor Protein

José Ponce-Coría,1 Paul A. Welling,2 Eric J. Delpire.1

Background: SPAK (STE20/SPS1-related proline alanine rich kinase), OSR1 (oxidative stress kinase 1) and WNK (with no K-lysine) kinases modulate distal Na+ transport by affecting the activities of the thick ascending limb of Henle Na-K-2Cl cotransporter (NKCC2) and of the distal convoluted tubule Na-Ci cotransporter (NCC). WNK4 is thought to affect the cotransporters through two different pathways: 1) by regulating their trafficking to the plasma membrane; and 2) by phosphorylating and activating SPAK which then phosphorylates and activates the cotransporters. Here, we demonstrate a third mode of action consisting of a direct stimulatory effect of WNK4 on the cotransporters.

Methods: We measured K+ influx in Xenopus oocytes injected with cotransporter, wild-type and mutant kinase, and Cab39 cRNAs to assess the role of the kinases and adaptor protein in modulating cotransporter activity.

Results: When Cab39 or Cab39l cRNA was injected with WNK4 and NKCC1, we observed a significant increase in the level of K+ influx. This increase was bumetanide-sensitive indicating that the WNK/SPAK/NKCC regulatory pathway.

Funding: NIDDK Support

TH-OR132

Aβ Targets Ring Finger Protein 2 (Rnf2) to the eENaC Promoter to Regulate Basal and Aldosterone-Stimulated eENaC Transcription

Zhiyuan Yu, Qun Kong, Bruce C. Kone.

The Univ of Texas Medical School at Houston, Houston, TX.

Background: Aβ is an aldosterone-sensitive regulator of eENaC transcription required for enhanced renal tubular Na transport. Aβ binds to a cis-element in the eENaC promoter to recruit histone methyltransferase Dote1 to a epigenetically repress basal eENaC transcription (collecting duct cells). Aldosterone downregulates this repressor complex to de-repress eENaC transcription. Rnf2, a central component of Polycomb repressive complex 1 involved in epigenetic silencing of target genes, lacks DNA-specific binding activity, so that other factors must mediate its site-specific chromatin recruitment. We tested the hypotheses that Aβ interacts with and recruits Rnf2 to the eENaC promoter, and contributes to basal eENaC repression and aldosterone de-repression of eENaC transcription in mMDM3 cells.

Methods: Immunofluorescence microscopy, co-immunoprecipitation, and GST pull-down assays were used to identify Aβ-Rnf2 interactions in mMDM3 cells. Chromatin immunoprecipitation (ChIP)p/qPCR and re-CHIP assays, promoter-lucerase assays, overexpression and siRNA knockdown of Rnf2 were used to assay functionally relevant interactions of Rnf2 with the eENaC promoter in vehicle and aldosterone-treated mMDM3 cells.

Results: Rnf2 and Aβ co-localized in the nucleus, and they interacted in co-immunoprecipitation and GST-pull-down assays. Rnf2 knockdown enhanced basal and aldosterone-stimulated eENaC mRNA levels and eENaC promoter activity. Conversely, Rnf2 overexpression inhibited aldosterone-stimulated eENaC mRNA expression and eENaC promoter activity. ChIP-re-ChIP assays showed that Aβ and Rnf2 co-occupy the R3 subregion (−57/+494) of the eENaC promoter. Aldosterone inhibited Rnf2 occupancy of the eENaC promoter and trimethylation of histone H3K27, a chromatin mark of repressed genes, coincident with induction of eENaC transcription.

Conclusions: We conclude that Aβ mediates site-selective physical and functional recruitment of Rnf2 to the eENaC promoter to constrain basal eENaC transcription. Aldosterone de-represses eENaC transcription by inhibiting Dot1a, Aβ, and Rnf2 association and action at the eENaC promoter.

Funding: NIDDK Support

TH-OR134

Calveolin-1 Is Required for Src-Family Protein Tyrosine Kinase (SFK)-Induced Regulation of the Basolateral K Channel in the Early Distal Convoluted Tubule (DCT1)

WenHui Wang, Pharmacology, New York Medical College, Valhalla, NY.

Background: The basolateral K channels in the DCT1 play an important role in determining the membrane potential which is essential for sustaining C1 exit across the basolateral membrane and Na-K-ATPase activity.

Methods: We performed the whole-cell recording to measure the Ba2+-sensitive K currents in the cells transfected with KCNJ10-transfected cells and a 20 pS K channel in the cells transfected with KCNJ10/16+calveolin-1 or with calveolin-1+KCNJ10. Immunostaining showed that CA9 mediates site-selective physical and functional interaction.

Funding: NIDDK Support

TH-OR135

Renal SGK1 Plays a Crucial Role in the Control of Potassium Homeostasis, by NEDD4-2 Dependent Regulation of ENaC and NCC

Lama Al-Qusairi,1 Matteo Stifanelli,2 Anne Debonneville,1 Nouridine Faresse,1 Johannes Loffing,2 Olivier Staub.1 1Univ of Lausanne; 2Univ of Zurich.

Background: Dietary K+ load results in increased kaliuresis, leading to aldosterone (aldo) release thereby stimulating K+ secretion in the ASDN. However, the mechanisms of this regulation are unclear.

Methods: Here, we identified the specific role of the aldosterone inducible SGK1 kinase in the tight regulation of potassium secretion using an inducible nephron specific SGK1 KO (SGK1fi) mouse model.

Results: We find that lack of SGK1 has no obvious effect on potassium homeostasis under normal diet. However, under high K+ diet for 48 hours, mutant mice exhibit a 35% decrease in urinary K+ excretion, accompanied with sever hyperkalemia and increased plasma aldol levels. At the molecular level, we observe a decrease in cleavage of alpha and gamma ENaC, indicating that ENaC activity is reduced. Moreover, phosphorylation of the Na-Ci-cotransporter NCC is strongly reduced under these conditions, indicating reduced NCC activity. The ubiquitin-protein ligase NEDD4-2, a well-known substrate of SGK1 kinase, and implicated in the positive regulation of both ENaC and NCC, is less phosphorylated on the SGK1-dependent phosphorylation sites S222 and S328, as evidenced by immunoblotting.

Conclusions: Our data indicate that renal SGK1 is a key regulator of potassium homeostasis in the kidney, which affects the activity of both NCC and ENaC, likely via regulation of NEDD4-2.
TH-OR135
The Rapidly Rising Global Burden of End-Stage Renal Disease – An Analysis of the Change in Maintenance Dialysis Prevalence between 1990 and 2010
Bernadette A. Thomas,1 Sarah Wulf,2 Rajnish Mehrotra,1 Jonathan Himmelfarb,1 Mohsen Naghavi,3 Christopher JI Murray.2
1Kidney Research Institute, Univ of Washington, Seattle, WA; 2Institute for Health Metrics and Evaluation, Univ of Washington, Seattle, WA.

Background: Rapidly rising global rates of chronic diseases portend a consequent rise in end-stage renal disease (ESRD). However, the change in global burden of treated ESRD has never before been quantified. This study was undertaken to accurately report the trajectory of treated prevalent ESRD rates at the global and regional level between 1990 and 2010.

Methods: We extracted data from the Global Burden of Disease database, the largest existing database for global causes of morbidity and mortality. The prevalence estimates were calculated from data from national and regional ESRD registries and a structured literature review for years 1990 and 2010. Data from 26 countries that lack routine access to dialysis were excluded. Data from twenty-three countries providing 100% dialysis access and 138 countries providing partial dialysis access were included. A negative binomial Bayesian regression tool was used to estimate the prevalence of chronic dialysis in 161 countries stratified by year and sex.

Results: Within the past two decades, there has been a global increase in maintenance dialysis of 165%. The global prevalence of treatment with maintenance dialysis for countries with universal dialysis access increased by 134% after population growth and aging adjustment; 145% in women versus 123% in men. For countries whose populations lack universal dialysis access, adjusted prevalence increased by 102%; 116% for women versus 90% for men. The five world regions not experiencing substantial increase in maintenance dialysis prevalence include Oceania, South Asia, central sub-Saharan Africa, eastern Europe, and tropical Latin America.

Conclusions: The significant growth in maintenance dialysis therapy far out of proportion to population growth for a majority of regions in the world. This emphasizes the need for early chronic kidney disease detection and treatment targeting ESRD prevention, since increased rise in prevalence of maintenance dialysis may not be sustainable.

Funding: Private Foundation Support

TH-OR136
Oral Activated Charcoal Absorbent, AST-120, Induced Continuous Reduction of Protein-Bound Uremic Toxins in Maintenance Hemodialysis Patients: A Randomized Cross-Over Trial
Suguru Yamamoto,1 Kentaro Omori,2 Koji Matsuoi,1 Kazuko Kawamura,1 Minako Wakisaki,1 Hiroki Manuya,1 Junichiro J. Kazama,1 Ichiehi Narita.1
1Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan; 2Omori Clinic, Niigata, Japan.

Background: An accumulation of protein-bound uremic toxins (PBUT) is one of the reasons why patients undergoing dialysis treatment have high risk of cardiovascular events. Oral activated charcoal absorbent, AST-120, has been shown to decrease serum indoxyl sulfate in non-dialysis CKD patients. The aim of this study is to examine whether AST-120 decreases PBUT in maintenance hemodialysis patients.

Methods: Twenty maintenance hemodialysis patients were individually randomized in a crossover design between treatment with 6 g/day of AST-120 and non-treatment for 4-week periods. Ten participants followed the AST-120 treatment first for 2 weeks and then switched to non-treatment for another 2 weeks; the other 10 subjects followed the same treatment in reverse order. Serum level of indoxyl sulfate at pre-post dialysis session before and after the AST-120 treatment was measured by mass spectrometry. Data were presented as medians (interquartile range: IQR). Wilcoxon signed-rank test was used for the statistical analysis.

Results: At the baseline, serum levels of indoxyl sulfate were 3.27 (2.17 to 3.89) and 2.20 (1.38 to 2.89) mg/dl in pre- and post-dialysis sessions respectively while it returned to the previous level before the next dialysis sessions. However, AST-120 treatment for 2 weeks dramatically decreased serum indoxyl sulfate levels in both pre-[1.64 (1.25 to 1.98) mg/dl, p=0.0004 vs. baseline] and post-[1.24 (0.87 to 1.49) mg/dl, p=0.002 vs. baseline] dialysis treatment.

Conclusions: Use of AST-120 showed a continuous and powerful effect to remove protein-bound uremic toxins in maintenance hemodialysis patients.

Funding: Government Support - Non-U.S.

TH-OR137
Prevalence and Predictors of Blood Pressure Variability in Hemodialysis Patients

Background: Blood pressure variability (BPV) predicts cardiovascular mortality in general population and patients with kidney disease. We hypothesized that variation in pre-dialysis systolic blood pressure (Pre-SBP) and mean BP change are independent predictors of mortality in hemodialysis patients.

Methods: We used clinical and biochemical data derived from the DaVita database. The study population (N=420,255) included subjects undergoing hemodialysis in DaVita facilities across the US during the period of 2004 to 2011. Pre-SBP variability is described by the SBP-DV examined before every dialysis during a month; mean BP change during dialysis is described by the mean of the difference between post-dialysis mean BP and pre-dialysis mean BP over a month. Repeated measurement model were built to examine the factors that influence BPV variability. Cox proportional hazard model with time-dependent covariates were fitted to test if SBP variability is a significant predictor of time to death and time to hospitalization.

Results: The mean pre-dialysis systolic blood pressure was 148±53 mm of Hg. Low, medium and high BPV was found in 35%, 34%, and 30% of the patients respectively. Patients’ gender, race, BMI, weight gain during dialysis, lack of insurance, exposure to heart disease or Diabetes mellitus are significant predictors to both SBP variability and mean BP change during dialysis (p<0.001). Both Pre-SBP variability and mean BP change during dialysis were significant predictor of time to death (HR (pre-SBP)=1.009, 95% CI (1.008, 1.010) p<0.001, HR (BP change)=1.028, 95% CI (1.027, 1.028), p<0.001) and time to hospitalization (HR (pre-SBP)=1.005 95% CI (1.0046, 1.0058) p<0.001, HR (BP change)=1.100, 95% CI (1.0992, 1.1000), p<0.001).

Conclusions: Pre-SBP variability and mean BP change are very common and they are associated with distinct clinical predictors. Both SBP variability and mean BP change during dialysis are significant predictors of time to death and time to hospitalization. Further studies are needed to confirm our results and to find ways to decrease BP variability in patient with ESRD.

TH-OR138
Greater Endothelial Cell Fluid Associated with Increased Mortality in Hemodialysis Patients: A Nationwide Cohort Study in Japan
Takeshi Hasegawa,1 Ikuto Masakane,1 Kunitoshi Iseki,1 Yoshiharu Tsabakihara,2 Tadao Akizawa.1 1Div of Nephrology, Showa Univ Fujigaoka Hospital, Yokohama, Japan; 2Dept of Epidemiology and Healthcare Research, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 3Committee of Renal Data Registry, The Japanese Society for Dialysis Therapy, Tokyo, Japan; 4Div of Nephrology, Showa Univ School of Medicine, Tokyo, Japan.

Background: There has been wide variation in targeted endotoxin level of dialysis fluid among countries, however, evidences for the effectiveness of dialysis fluid purity for mortality of patients on hemodialysis (HD) are lacking. The aim of this research is to evaluate the impact of water quality by dialysis fluid endotoxin level (dET) on mortality of HD patients.

Methods: The design of this investigation is a cohort study using a nationwide annual survey of the Japan Renal Data Registry. We analyzed 130,781 patients on HD at the end of 2005; 101,081 patients on HD > half a year, three times session per week, during 2007: no changing facilities and treatment modalities). The main outcome measure was all-cause death. Main exposure to be tested was dET reported by 2,746 facilities at the end of 2006 (categorized into 5 groups: <0.001, 0.001 to 0.01, 0.01 to 0.05, 0.05 to 0.1, and 0.1~EU/mL). Cox regression was employed to estimate the hazard of all cause death adjusted for potential confounders.

Results: During one year follow-up, 8,978 (6.9%) patients died of all-causes. The rate of all-cause mortality at one year was the highest of patients in the greatest dET (0.1EU/mL~) category (88.0 deaths/1,000 person-years). After multivariable adjustment, patients who were exposed to the greatest dET (0.1EU/mL~) displayed a 28% (95% CI, 15%-41%) increased risk of all-cause death compared to those who with the lowest dET (<0.001EU/mL).

Conclusions: These results suggested that greater dET was related to increased risk of cause death in HD patients. Correcting this modifiable water management practice may improve outcomes of HD patients.

TH-OR139
Convective Therapies versus Low-Flux Hemodialysis for Chronic Kidney Failure: A Meta-Analysis of Randomized Controlled Trials
Paareeewa Susantiphong,1,2 Bertrand L. Jaber.1 1Medicine, St. Elizabeth’s Medical Center, Boston, MA; 2Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: Convective therapies have gained popularity for the optimal removal of uremic solutes. However, their benefits and potential risks have not been fully elucidated. We conducted a meta-analysis of all randomized controlled trials (RCTs) comparing convective therapies vs. low-flux hemodialysis in patients with chronic kidney failure and our results. The main outcome measure was all-cause mortality at one year was the highest of patients in the greatest dET (0.1EU/mL~) category (88.0 deaths/1,000 person-years). After multivariable adjustment, patients who were exposed to the greatest dET (0.1EU/mL~) displayed a 28% (95% CI, 15%-41%) increased risk of all-cause death compared to those who with the lowest dET (<0.001EU/mL).

Methods: We searched MEDLINE (through December 2012), Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, scientific abstracts from meetings, and bibliographies of retrieved articles for randomized controlled trials comparing the effects of convective therapies (including high-flux hemodialysis, hemofiltration, and and

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

32A
Compared to the rest of the week, excess emergency admissions were seen after the 2 day gap (21.3 vs 15.7 deaths per 100 patient years, P<0.001) was primarily due to the 32% of pulmonary disease (RR 1.97 vs 1.65 without, P=0.002) and Pre-HD systolic blood pressure increases were seen in heart failure (RR 1.82 vs 1.64 without, P=0.012), chronic obstructive pulmonary disease (RR 2.05 vs 1.90 without, P=0.001), and comorbidity. Laboratory and clinical measurements were obtained from the nearest analysed. Hospitalisation data was used to identify HD attendance patterns, admissions and 2006 in England with available data until 2009 from the UK Renal Registry were estimated. Change in Medicare Costs Associated with the New Medicare Payment Policy Allan L. Collins,1 Suying Li,1 Jiannong Liu,2 David T. Gilbertson,1 Robert N. Foley,1 James P. Ebben,1 Craig Solid,1 Shu-Cheng Chen.1,1 USRDS Coordinating Center, MMRF, Mpls, MN; 2Medicine, Univ of MN, Mpls, MN.

Background: Starting in January 2011, several outpatient dialysis services, including laboratory services performed by nephrologists and injectable medications, were transferred to the new Medicare prospective payment system (PPS). We aimed to examine trends in Medicare costs 2001-2011 and estimate change in Medicare costs associated with the new PPS in hemodialysis (HD) patients.

Methods: Yearly cohorts, 2001-2011, included point prevalent HD patients on January 1, with a 90-day rule applied and Medicare Parts A/B eligibility required. Patients were followed from January 1 to December 31 each year and censored at transplant, change in modality, death, or loss to follow-up. Medicare payment per person-year (MPPY) consisted of inpatient (IP), outpatient (OP)/physician services, and other costs. Dialysis facilities were characterized as 100% bundle or 25% blend based on their decisions regarding the new PPS in 2011. We estimated change in Medicare costs associated with the new PPS using the difference-in-difference approach.

Results: Total MPPY increased from $75008 in 2001 to $79758 in 2010 and decreased to $78864 in 2011. The cost changes (PPS) from 2010 to 2011 were: -$238 for IP-, -$880 for OP/physician, and $224 for others. Among the change in OP/physician cost, the reduction in categories related to the new PPS (HD and routine lab services, injectable medications, and lab services performed by nephrologists) was $51,106 (PPS). The estimated change (2011 vs. 2010) in Medicare cost (PPS) associated with new PPS (100% bundle vs. 25% blend) was -$215 (95% CI, -$1617 to $1187).

Conclusions: The PPS44 (PPS) saving in Medicare costs in 2011 implies an approximate saving of $220 million in total Medicare costs for HD patients included in this study. This reduction may contribute to a low rate of growth in per capita general Medicare spending in 2011. Although the new PPS bundle associates with stabilization of Medicare total costs in 2011, providers may reduce their expenses, generating previously unrealized savings.

Funding: NIDDK Support TH-OR141 Factors Influencing Hospital Admissions and Deaths over the Two Day Gap in a Week Hemodialysis James Farghany,1 Dannaian G. Fogarty,1 Michael J. Campbell,1 Meguid El Nahas,1 Ken Farrington.2 'School of Health and Related Research, Univ of Sheffield, Sheffield, South Yorkshire, United Kingdom; 2The UK Renal Registry, Bristol, United Kingdom; 3Global Kidney Academy, Sheffield, United Kingdom.

Background: Excess mortality and hospitalization has been identified after the 2 day gap in 3 times a week hemodialysis (HD) patients compared to 1 day intervals. Thus far additional risk factors and potential interventions have not been formally explored in dialysis scheduling related units. Greater understanding of mortality and hospitalisation events is required.

Methods: Incident renal replacement therapy patients starting treatment between 2002 and 2006 in England with available data until 2009 from the UK Renal Registry were analysed. Hospitalisation data was used to identify HD attendance patterns, admittance and comorbidity. Laboratory and clinical measurements were obtained from the nearest recorded period in the 6 months before the week of analysis. Rates were compared with rate ratios of events after the 2 day gap compared to the rest of the week (RR). Results: 9,255 patient years were identified in 5790 patients across 36 centres. Compared to the rest of the week, excess emergency admissions were seen after the 2 day gap (2.29 vs 1.36 per patient year, P<0.001). Admission RR remained constant for the first 2 years of dialysis, the 2 years approaching death and across centres. Greatest admission increases were seen in females, those >75 years, and those with comorbidities.

Conclusions: Faster K mobilization and a larger central distribution volume are associated with lower body size. Using BSA, RER or TEE based dialysis prescription would result in higher dose delivery in these settings.

TH-OR143 Determinants of Potassium Kinetics during Hemodialysis Baris U. Akoz,1 J. Ken Leyboldt,1 Richard J. Fluck,2 Bruce F. Culleton.1 'Medical Products, Baxter Healthcare Corporation, Deerfield, IL; 2Dept of Renal Medicine, Royal Derby Hospital, Derby, United Kingdom.

Background: Both hyperkalemia and hypokalemia are associated with elevated mortality in hemodialysis (HD) patients, and low dialysate potassium (K) concentration (K<2.5 mEq/L) during HD treatments are associated with a higher incidence of sudden cardiac arrest if predialysis serum K levels are ≤5 mEq/L. Improved control of serum K levels in HD patients, particularly those treated by frequent HD sessions, may benefit from improved understanding of K kinetics. We have recently shown (2013 ERA-EDTA Congress) that K kinetics during HD can be described using a pseudo one-compartment model and that K mobilization clearance (Km) and predialysis K central distribution volume (V) are relatively independent of dialysate K concentration.

Methods: We determined Km and V from kinetic modeling sessions in 437 patients during a 2013 NKF Study with a dialysate K concentration of approximately 2 (1.6-2.5) mEq/L. By optimal fitting of pseudo one-compartment model predictions of serum K levels to those measured predialysis, 1 hour after treatment, postdialysis and 30 minutes after stopping the treatment. The determinants of these kinetic parameters were determined by univariate and multivariate linear regression.

Results: The patients were 59±14 (mean±standard deviation) years old with predialysis body weight (BW) of 72.6±15.1 kg; predialysis serum K concentration (Kp) was 5.3±1.0 mEq/L and treatment time (T) was 206±29 minutes. Fifty-five percent of patients were female; 45% were diabetic and 34% were of black race. On univariate analyses, Km and V were associated (P<0.001) positively with BW and T but negatively with Kp. Only V was associated positively with BW quartile compared to the highest quartile (p<0.003). On multivariate analyses, Km and V were associated positively with BW and negatively with Kp, only V was associated positively with T. In total, V was 27±9% of BW.

Conclusions: Faster K mobilization and a larger central distribution volume are expected for bigger patients, providing further support for the validity of a pseudo one-compartment model. The larger central distribution volume with longer treatment times may indicate more effective K removal.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation
TH-OR144

Potential Application of Exhaled Breath Monitoring in Renal Replacement Therapy
Kelly M. Paschke,1 Sevag Demirjian,2 Jaime T. Newman,1 Lauren L. Chen,1 Raed A. Dweik,3 Robert J. Heyka,2 1Pathobiology/Lerner Research Institute, Cleveland Clinic, Cleveland, OH; 2Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH; 3Pulmonary, Allergy, and Critical Care Medicine/Respiratory Institute, Cleveland Clinic, Cleveland, OH.

Background: Uremic retention solutes are a systemic consequence of Chronic Kidney Disease (CKD) and contribute to disease progression. Urea removal is used for monitoring adequacy of solute removal in hemodialysis (HD). However, this does not always correlate with symptoms of uremia or removal of retained solutes. In end stage renal disease (ESRD), the unique breath profile composed of volatile organic compounds and inorganic amines represents accumulations of end products of metabolic reactions, gut bacteria, and exogenous volatiles. However, no standardized breath test exists for monitoring CKD or the efficacy of HD.

Methods: Selected ion flow tube mass spectrometry (SIFT-MS) was used to quantify the exhaled breath of 15 ESRD patients before and after HD. An additional 15 healthy subjects were recruited as a baseline control. Selected ion monitoring of 21 known breath volatiles and mass scanning for high intensity peaks of unknown volatiles was applied.

Results: ESRD patients pre HD had elevated breath ethanol, ammonia, trimethylamine, 2-propanol, and acetone compared to healthy controls (p<0.05) and 43 peaks in the mass spectra (p<0.01). HD reduced breath trimethylamine, 2-propanol, acetaldehyde, acetone, benzene, dimethyl sulfide, pentane, 1-normco, 3-methylhexane (p<0.01), and 13 peaks in the mass spectra (p<0.01). Breath ammonia, ethanol (p<0.05), and 21 peaks in the mass spectra (p<0.01) remained elevated post HD compared to healthy controls. Post HD breath composition more closely resembled healthy controls.

Conclusions: Breath testing may serve as a novel modality for CKD monitoring, in particular for HD adequacy. A potential advantage of breath tests is the ability to measure multiple volatiles simultaneously for a disease state which may provide a more robust method for monitoring CKD and HD.

Funding: Pharmaceutical Company Support - American Society of Nephrology

TH-OR145

Gene-Targeted Deletion of the Angiotensin II Type 1 Receptor-Interacting and Functionally Modulating Protein Enhances Renal Sodium Reabsorption and Exacerbates Angiotensin II-Mediated Hypertension
Kouichi Tamura, Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan.

Background: The angiotensin II (Ang II) type 1 receptor (AT1R)-associated protein (ATRAP/Atrap), a molecule which specifically interacts with the AT1R. We hypothesize that a down-regulation of ATRAP at local tissue sites that enhances the pathological activation of tissue AT1R signaling in response to certain stimuli without any evident effect on baseline physiological AT1R signaling. Functional significance of ATRAP in renal sodium handling and blood pressure (BP) regulation in response to pathological stimuli is not fully resolved.

Methods: We generated mice with a gene-specific disruption of ATRAP (ATRAP-KO mice). We examined the effects of chronic Ang II infusion on BP and renal sodium handling in ATRAP-KO mice and their littermate wild-type control mice (WT mice).

Results: Although ATRAP was abundantly distributed along the renal tubules in WT mice, there was no ATRAP expression in any of the nephron segments in ATRAP-KO mice. ATRAP-KO mice exhibited no apparent renal morphological alterations under baseline conditions and BP of ATRAP-KO mice was comparable to that of their littermate wild-type control mice (WT mice) at baseline. However, the Ang II-mediated BP elevation was significantly augmented in the ATRAP-KO mice. Consequently, the heart weight/body weight ratio and urinary albumin excretion in the Ang II-infused ATRAP-KO mice were significantly increased compared with those in Ang II-infused WT mice. Metabolic cage analysis disclosed the increased cumulative sodium balance during the Ang II infusion period in the ATRAP-KO mice, along with an increase in the expression of α-subunit of the epithelial sodium channel in the kidney of ATRAP-KO mice.

Conclusions: In summary, these results indicated that the gene-targeted deletion of ATRAP provoked the exacerbation of Ang II-mediated hypertension and its associated end-organ injury, along with an inhibition of natriuresis, without any evident effect on baseline physiological function. Therefore, ATRAP is a potential target of interest in the regulation of BP.

Funding: Government Support - Non-U.S.

TH-OR146

Somatic and Germline CACNA1D Calcium Channel Mutations in Aldosteronism-Producing Adenomas and a Mendelian Syndrome Featuring Primary Aldosteronism
Ute I. Scholl,1 Gerald S. Goh,2 Gabriel Stöltig,3 Regina Campos de Oliveira,2 Murim Choi,4 Annabelle L. Fonseca,4 Erum A. Hartung,5 Matthew Benson,6 Carol J. Nelson-Williams,7 Steven Libutti,8 Shrikanth M. Mane,9 Per Hellman,10 Peyman Björklund,10 Tobias Carling,10 Christoph W. Musahl,2 Patricia Hidalgo,2 Richard P. Lifton,7 Genetics, HHMI, Yale School of Medicine, New Haven, CT; 2Institute of Complex Systems, Forschungszentrum Jülich, Germany; 3Neurophysiologie, Medizinische Hochschule Hannover, Germany; 4Surgery, Yale School of Medicine, New Haven, CT; 5Children’s Hospital of Philadelphia, Philadelphia, PA; 6Nemours Children’s Clinic, Jacksonville, FL; 7Surgery, Albert Einstein College of Medicine, Bronx, NY; 8Surgical Sciences, Uppsala, Sweden.

Background: Adrenal aldosterone-producing adenomas (APAs) are benign, hormone-producing tumors found in ~5% of patients referred to hypertension specialists. ~40% of these tumors are caused by mutations in the potassium channel KCNJ5, resulting in sodium permeability, depolarization and calcium influx.

Methods: We here use exome and targeted sequencing to identify additional recurrent mutations in APAs and evaluate their functional impact by using patch clamp electrophysiology.

Results: We describe seven novel somatic mutations in the voltage-gated calcium channel CACNA1D in 43 non-KCNJ5-mutant APAs (16.3%). Four alter G403, and one each alter I770, F767 and V1373. Six of seven mutations are located within the 56 domains of the channel and are shown by electrophysiology or inferred to be gain-of-function, resulting in activation at less depolarized potentials. G403 mutations also impair inactivation. Remarkably, we identify de novo mutations at the identical residues in two patients with a novel Mendelian syndrome featuring primary aldosteronism and neuromuscular abnormalities, including seizures. CACNA1D is expressed in human adrenal cortex. Excess calcium influx through mutant channels is expected to result in aldosterone production and proliferation by activation of the same pathways upregulated in KCNJ5-mutant tumors.

Conclusions: These findings explain a significant fraction of primary aldosteronism and have diagnostic and therapeutic implications.

Funding: Other NIH Support - Centers for Mendelian Genomics, Private Foundation Support, Government Support - Non-U.S.

TH-OR147

Mutation of Anti-Aging Gene Klotho Causes Hypertension via Upregulation of Adrenal CYP11B2 Expression and Plasma Aldosterone Levels
Zhongjie Sun, Physiology, Univ of Oklahoma Health Sciences Center.

Background: Klotho is a recently discovered anti-aging gene. The purpose of this experiment is to assess if klotho deficiency affects blood pressure.

Methods: One group of KL mutant heterozygous (+/-) mice and one group of wild-type mice were used.

Results: Interestingly, klotho (-/-) mice demonstrated a significant and persistent increase in blood pressure starting form 3-4 months of age, indicating that klotho deficiency causes hypertension. Plasma level of aldosterone was elevated in KL(-/-) mice. Two groups of KL(+/-) mice and 2 groups of wild-type mice were used. When BP was elevated in KL(-/-) mice, 1 group of KL(+/-) mice and 1 group of WT mice were treated with aldosterone receptor blocker, eplerenone (6 mg/kg/day), while the remaining groups received DMSO and serve as controls. Eplerenone decreased hypertension to the control level. Eplerenone also abolished KL-deficiency-induced kidney damage (glomerulonephritis, fibrosis). Klotho deficiency causes renal inflammation as evidenced by significant increases in inflammatory cytokines (IL-6, TNFa and MCP-1) and T cell and macrophage infiltration in kidneys of KL(-/-) mice. Eplerenone significantly attenuated KL deficiency-induced inflammation. Note that NCC and SGK1 levels were increased in kidneys in KL(+/-) mice, which could be abolished by eplerenone. Further analysis indicated that klotho co-localized with CYP11B2, a key enzyme for aldosterone synthesis, in the adrenal cortex. Klotho deficiency upregulated CYP11B2 protein expression.

Conclusion: KL deficiency caused hypertension via upregulating adrenal CYP11B2 protein expression and plasma aldosterone levels which led to inflammation and upregulation of NCC signaling in kidneys.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-OR148

Hypertensive Response to Angiotensin II (Ang II) Infusion Is Blunted in IL-17a-/- Mice Associated with Depressed Na/H Exchanger 3 (NHE3) Abundance
Nikhil Kamat,1 David G. Harrison,2 Alicia A. McDonough,1 Vell and Neurobiology, Keck School of Medicine of USC, Los Angeles, CA; 3Vanderbilt Vascular Biology Center, Vanderbilt Univ Medical Center, Nashville, TN.

Background: Previous studies (Harrison lab), establish that CD8 T cells are essential for the hypertensive response to AngII infusion and that CD8 cells accumulate in the kidney of hypertensive animals where they produce the cytokine IL-17A. AngII infusion hypertension is blunted in IL-17a-/- mice compared to wild-type (WT) mice (18 vs. 38 mmHg). The aims of this study were to test the hypothesis that the blunted hypertensive response to AngII infusion in IL17a-/- mice is associated with blunted renal Na+ transporter stimulation, and to define the transporter(s) involved.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: Wild-type (WT) mice (n=12), previously salt resistant, became salt sensitive after L-NAME exposure. L-NAME increased WT systolic blood pressure (SBP) from 110±2 to 135±3 mmHg (p<0.01). SBP returned to baseline during the washout and increased again in response to L-NAME. SBP of ACE 10/10 mice was 106±5 mmHg (NS). In addition, basal renal Ang II level (by IHC) was similar between WT and ACE 10/10. However, sodium load induced an accumulation of renal Ang II that was greater in WT compared to ACE 10/10 (26±2 vs. 13±2%/area; p<0.01). Finally, sodium balance studies revealed an enhanced natriuretic response of ACE 10/10 vs. WT during the HS diet. For instance, sodium excretion after day 1 (before returning to balance) was 1076±67 μmol/day in WT vs. 1533±52 μmol/day in ACE 10/10 mice (p<0.01).

Conclusions: These results demonstrate that renal ACE is required to increase local Ang II, trigger anti-natriuresis and to induce SS hypertension in response to renal inactivation.

Funding: Other NIH Support - R00 DK083455

TH-OR151
Role of Collecting Duct Renin in Blood Pressure Regulation
Nirupama Ramkumar,1 Deborah Stuart,1 Sara Rees,1 Curt D. Sigmund,1 Donald E. Kahn.1 1Nephrology and Hypertension, Univ of Utah, Salt Lake City, UT; 2Univ of Iowa, Iowa City, IA.

Background: Recent studies propose that collecting duct (CD) renin is an important modulator of blood pressure regulation, especially in conditions such as angiotensin-II infused hypertension.

Methods: We used gene targeting to generate a CD-specific renin knockout (KO) to assess if CD-derived renin can regulate BP utilizing the Cre-loxP system, exon 1 of the renin gene was ablated specifically in the CD. BP was recorded via telemetry and plasma and urine were collected in metabolic cages on normal, high and low Na diets.

Results: DNA recombination showed kidney specific recombination in KO mice. Compared to floxed mice, CD renin KO mice had 70 % lower medullary renin mRNA levels and 90% lower renin mRNA in micro-dissected cortical and inner medullary CD tubules. Urinary renin levels were significantly lower in the KO mice on normal and low Na diets (45% of floxed levels) but not with high Na intake. Plasma renin concentration was significantly higher in the KO mice on all three diets. While BP was similar between the two groups on all three diets, infusion of Ang-II delayed the increase in BP in the CD renin KO group for at least 4 days post-infusion.

Conclusions: These findings suggest that CD renin likely plays a role in normal BP regulation (evidenced by an increase in PRC) and in response to AngII infusion.

Funding: Private Foundation Support

TH-OR152
Salt Overload Aggravates Hypertension and Promotes Severe Renal Injury in Rats Subjected to NF-κB Inhibition during Nephrogenesis

Background: We showed recently that NF-κB inhibition by pyrrolidine dithiocarbamate (PDTC) during rat lactation leads to hypertension (HTN) in adult life, with no renal injury. Here we investigated whether challenging this new model with a high-salt diet (HS) would exacerbate HTN and promote renal injury.

Methods: Munich-Wistar dams were kept with their offspring (males only, n=49), receiving no treatment or PDTC, 280 mg/kg/day in drinking water during lactation only. The offspring underwent uninephrectomy (UNx) at 10 wks of age, and received normal salt diet (NS) until 12 wks of age, when they were divided into: C; NS, control (C); CHS, receiving 3.2% NaCl chow and 0.5% NaCl to drink; PDTC+HS, rats that had received neonatal PDTC; PDTC+HS, HS; PDTC+HS on HS. Tail-cuff (TCP, mmHg), glomerulosclerosis index (GSI), % cortical interstitium (% INT), % injured microvessels (% IMV), INT macrophage infiltration (IMF, cells/mm²), plasma renin activity (PRA, ng/ml/h), and INT angiotensin II (AIIG, cells/mm²), were assessed 12 wks later.

Results:

<table>
<thead>
<tr>
<th>Group</th>
<th>CHS</th>
<th>PDTC+HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>107±3</td>
<td>120±3</td>
</tr>
<tr>
<td>PRA (ng/ml)</td>
<td>0.6±0.1</td>
<td>0.8±0.2</td>
</tr>
</tbody>
</table>

Mean(SE); *p<0.05 vs C; †p<0.05 vs NS

Moderate HTN was seen in Groups C+HS and PDTC+HS+NS, while Group PDTC+HS exhibited marked HTN, GS, glomerular thrombi and aneurysms, INT expansion, severe Vasc, intense Mβ infiltration, and INT AngII dissociated from PRA.

Conclusions: HS and UNX uncovered a renal dysfunction not apparent in PDTC+HS rats on NS, indicating that an intact NF-κB system is required to enable developing rat kidneys to avoid HTN and deal properly with salt excess in adult life.

Funding: FAPESP/CNPq.

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

35A
The Endoplasmic Reticulum Stress Inhibitor, 4-Phenylbutyrate, Reduces Hypertension in the Spontaneously Hypertensive Rat Model of Essential Hypertension

Kaitlyn Werner,1,2 Victoria Yum,1,2 Chao Lu,1 Jeffrey G. Dickhoff,1,2 1Medicine, Div of Nephrology, McMaster Univ, Hamilton, Canada; 2Nephrology, St. Joseph’s Healthcare Hamilton, Hamilton, Canada.

Background: We have shown that endoplasmic reticulum (ER) stress is important in angiotensin II-mediated hypertension, and that the low molecular weight chemical chaperone, 4-phenylbutyrate (4-PBA), can inhibit endoplasmic reticulum stress in the kidney via oral dosing. Therefore, we tested the ability of 4-PBA to lower blood pressure in the most frequently used animal model of essential hypertension, the spontaneously hypertensive rat (SHR).

Methods: 12 week old male SHRs with established hypertension were used and treated with 4-PBA or vehicle for 5 weeks. Blood pressure was measured 1 week before the treatment using tail cuff plethysmography and was 181±118 initially. These animals were randomized into either 4-PBA or vehicle treatment groups. Treatment with 4-PBA proceeded for 5 weeks. Aortas and mesenteric resistant vessels were collected after 5 weeks for functional and structural analysis. Final blood pressures were measured directly through carotid artery cannulation.

Results: We found 4-PBA treatment significantly lowered blood pressure in the SHR (Vehicle 206.1±4.4 vs. 4-PBA 179.0±4.3, systolic; vehicle 143.6±4.4 vs. 4-PBA 121.2±4.3, diastolic) at 5 weeks. This was reflected in both tail cuff and direct blood pressure measurement. Examination of aortic and mesenteric resistant artery contractility found 4-PBA diminished mesenteric resistant artery contractility but had no effect on that of the aorta. 4-PBA treatment also augmented endothelial vasodilation in the resistant vessels, but not the aorta. 4-PBA treatment had no effect on the ability of nitric oxide to evoke vasorelaxation in either mesenteric vessels or the aorta, as shown by sodium nitroprusside treatment. 4-PBA treatment did not change the structure of mesenteric resistant vessels, as shown by a three dimensional vascular reconstruction.

Conclusions: The ER stress inhibitor, 4-PBA, reduces hypertension in the spontaneously hypertensive rat by improving resistant blood vessel endothelial dependent vasodilation without changing smooth muscle mass or vessel structure.

Funding: Government Support - Non-U.S.

Mesenchymal Stem Cells (MSC) Prevent the Progression of Renovascular Hypertension, Improved Renal Function and Architecture Elizabeth B. Oliveira-Sales,1 Edgar Maquigussa,1 Patricia Semedo Kuriki,1 Luciana Guilhermino Pereira,1 Vanessa Melo Barreto,1 Niciels O.S. Camara,2 Cassia T. Bergamaschi,2 Ruy Campos,2 Mirian A. Boim.1 1Dept of Medicine, Federal Univ of Sao Paulo, Sao Paulo, Brazil; 2Dept of Physiology, Federal Univ of Sao Paulo, Sao Paulo, Brazil.

Background: Renovascular hypertension induced by 2 Kidney-1 Clip (2K-1C) is a renin-angiotensin-system (RAS) dependent model, leading to renal vascular rarefaction and renal failure. RAS inhibitors are not able to reduce arterial pressure (AP) and/or preserve the renal function, and thus, alternative therapies are needed.

Methods: Three weeks after left renal artery occlusion, fluorescently tagged mesenchymal stem cells (MSC) (2x10^5 cells/animal) were injected weekly into the tail vein in 2K-1C hypertensive rats.

Results: Flowcytometry showed labeled MSC in the cortex and medulla of the clipped kidney. MSC prevented a further increase in the AP, significantly reduced proteinuria and decreased sympathetic hyperactivity in 2K-1C rats. Renal function parameters were unchanged, except for an increase in urinary volume observed in 2K-1C rats, which was not corrected by MSC. The treatment improved the morphology and decreased the fibrotic areas in the clipped kidney and also significantly reduced renal vascular rarefaction typical of 2K-1C model. Expression levels of IL-1β, TNFα, angiotensinogen, ACE, and Ang II receptor AT1 were elevated, whereas AT2 levels were decreased in the medulla of the clipped kidney. MSC normalized these expression levels.

Conclusions: In conclusion, MSC therapy in the 2K-1C model (i) prevented the progressive increase of AP, (ii) improved renal morphology and microvascular rarefaction, (iii) decreased fibrosis, proteinuria and inflammatory cytokines, (iv) suppressed the intrarenal RAS, (v) decreased sympathetic hyperactivity in anesthetized animals and (vi) MSC were detected at the CNS suggesting that the cells crossed the blood-brain barrier. This therapy may be a promising strategy to treat renovascular hypertension and its renal consequences in the near future.

Funding: Government Support - Non-U.S.

Loss of p47^phox Ameliorates Kidney Fibrosis and Proteinuria Xiuxi Chen, Paisit Pauksakon, Ming-Zhi Zhang, Raymond C. Harris, Roy Zent, Ambria Pozzi. Medicine, Vanderbilt Univ, Nashville, TN.

Background: Reactive oxygen species (ROS) play an important pathogenic role in the development of various diseases, including kidney disease. The major generator of ROS in the glomerulus of the kidney is the NADPH oxidase complex which consists of five different subunits. Among these subunits, the p47^phox is a critical regulatory subunit of NADPH oxidase and its expression is upregulated in the course of renal injury. The contribution of p47^phox has been widely investigated in diabetic nephropathy; however whether it also plays a role in non-diabetic-mediated glomerular injury is unclear.

Methods: To address this issue, we analyzed the contribution of the p47^phox in glomerular disease since it is a critical regulatory subunit of NADPH oxidase. To this end, we crossed the p47^phox-null mice with integrin α1-null mice, a model of exacerbated NADPH-mediated ROS production and glomerulosclerosis after injury, to generate wild type, p47^phox-null, integrin α1-null, and p47^phox-null/integrin α1-null mice. These mice were then subjected to either ROS-dependent (adriamycin) or ROS-independent (partial mesangial resection) renal injury and the outcome was analyzed over time.

Results: We provide evidence that in both models, deletion of p47^phox significantly reduced proteinuria and kidney fibrosis, and these effects were more accentuated on the integrin α1-null background. This protection is accompanied by decreased production of ROS and consequent glomerular injury. Moreover, in vitro analysis of primary mesangial cells isolated from different types of mice revealed that loss of p47^phox leads to reduced basal levels of superoxide and collagen production.

Conclusions: Our study suggests that the NADPH oxidase is major source of ROS in kidney glomeruli and contributes to kidney injury. Moreover, our study points to the p47^phox as a potential target for antioxidant therapy in fibrotic disease.

Funding: NIDDK Support, Veterans Affairs Support

miR-182 Inhibits FoxO3-Mediated Atrophic Signaling in Muscle, and Glucocorticoid Administration and Acute Diabetes Down-Regulate Muscle miR-182 Matthew B. Hudson,1 Myra Woodworth-Hobbs,2 Bin Zheng,1 Jill Rahnett,1 Harold A. Franch,1 Russ Price.1,3 1Renal Div, Dept of Medicine, Emory Univ, Atlanta, GA; 2Nutrition and Health Sciences Graduate Program, Emory Univ, Atlanta, GA; 3Atlanta VA Medical Center, Decatur, GA.

Background: Skeletal muscle atrophy occurs in response to a variety of conditions including chronic kidney disease, diabetes, metabolic acidosis, and elevated glucocorticoids. Preclinical studies demonstrate the protective effects of the Forkhead box O (FoxO) pathway in several models of skeletal muscle wasting. FoxO transcription factors induce skeletal muscle atrophy by increasing the expression of components for the ubiquitin-proteasome and autophagy-lysosome systems.

Methods: To identify potential modulators of the atrophy process, an in silico target scan analysis of known microRNAs was performed. miR-182 was predicted to target the FoxO proteins. To test whether miR-182 regulates expression of the FoxOs, C2C12 myotubes were transfected with miR-182 and levels of FoxO1 and FoxO3 protein were evaluated.

Results: miR-182 reduced FoxO3 protein 64% (P=0.05 vs Con) whereas FoxO1 was unaffected. Treatment of C2C12 myotubes with dexamethasone (1 µM, 6 hr) to induce muscle atrophy decreased miR-182 expression by 46% (P=0.05 vs Con). Overexpression of miR-182 prevented the glucocorticoid-induced upregulation of FoxO3 gene targets including MAFB/Atrogain-1, ATG12, Catenasip L, and LC3. To determine if miR-182 is altered in an in vivo model of muscle atrophy, miR-182 was measured in the gastrocnemius muscle of rats with acute diabetes (3-d) induced by streptozotocin. miR-182 was suppressed by 45% in the gastrocnemius of diabetic mice (P<0.05 vs Con).

Conclusions: These data identify miR-182 as a new and important regulator of FoxO3-mediated signaling during muscle atrophy induced by catabolic disease states.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Affairs Support

The Paraoxonase PON2 Modifies Lipid Peroxidation at the Slit Diaphragm Henning Hagemann,1,2 Donschtsb Kotjashski,2 Stuart E. Dryer,3 Bernhard Schermer,1,3 Thomas Benzing,1 Paul T. Brinkkoetter.1 1Dept of Nephrology, Univ of Cologne, Cologne, Germany; 2Dept of Clinical Pathology, Univ of Vienna, Vienna, Austria; 3Dept of Biochemistry, Univ of Houston, Houston.

Background: The mammalian slit diaphragm is a site of highly active intercellular signalling between adjacent podocytes. Signalling pathways e.g. via TRPC6 depend on the distinct lipid composition of the plasma membrane. Interestingly the signalling-complex at the slit diaphragm shares close homology with the neuronal mechanosensory complex of C. elegans. The Podocin homologue MEC-2 orchestrates protein-lipid supercomplexes in the plasma membrane of C.elegans touch neurons to allow for proper signalling via the degenerin cation channel MEC-4/10. Part of the mechanosensory complex is also the MEC-6-modifying enzyme MEC-6, which interacts with MEC-4/10 and enhances its channel activity.

Results: We identified the mammalian homologue of MEC-6, the paraoxonase family protein PON2, as a novel slit diaphragm protein. PON2 localizes to the slit diaphragm in the rat glomerulus and immuno-gold-labeling studies. In addition it not only co- localizes with Podocin in cholesterol-rich resistant membrane domains but also interacts directly with slit diaphragm proteins like Nephrin, Podocin and TRPC6 in pull-down experiments. We were able to show that PON2 is an integral transmembrane protein that localizes to the plasma membrane with its enzymatically active domain facing extracellular. To address the functional role of PON2 in the plasma membrane we employed in vitro enzyme assays with recombinant protein and analysed the lipid profile of PON2-proficient and -deficient cells using mass spectrometry. We found that PON2 affects the content of glycolipids and the overall peroxidation state of membrane lipids.

Conclusions: In conclusion we show that PON2 is a novel slit diaphragm protein which modifies the lipid content and peroxidation state of the plasma membrane. It is therefore well conceivable that it is an important regulator of signal transduction e.g. via the cation channel TRPC6.

Funding: Private Foundation Support

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

Underline represents presenting author.

36A
FR-OR004

Involvement of Nitric Oxide and Endothelin Systems in the Pathogenesis of Endothelial Dysfunction in Diabetic Nephropathy. Nizor Abu-Saleh,1 Mohger Khamaisi,2 Hoda Awa1, Suheir Assady,2 Ravit Cohen,1 Zaher Armary,1 Zaid Abassi,1 Technion, Haifa, Israel; 3 Joslin Diabetes Center, Boston; 4 Rambam Medical Center, Haifa, Israel; 5 Nazareth Hospital-EMMS, Israel.

Background: Endothelial dysfunction (ED) is a major cause of vascular complications characterizing diabetic nephropathy. Diabetic patients who also exhibit hyperlipidemia suffer from accelerated vascular complications. While the deleterious effects of hyperglycemia (HG) and hyperlipidemia alone on ED is well established, the effects of combined hyperlipidemia and HG has not been thoroughly studied.

Methods: We applied cultured human umbilical vein endothelial cells (HUVECs), and LDL receptor knockout mice (LDLR–/–) to investigate the mechanisms underlying combined hyperlipidemia and HG in ED.

Results: Exposed to ED HG and HG+LDLr–/–, cultured HUVECs displayed a higher blood pressure (135±2 vs. 113±8 and 97±4mmHg, respectively) plasma glucose (308±52.7 vs. 159.2±18.8 and 105±10.51mg%), triglycerides (180±15 vs. 12.65±1.24 and 12.76±2.17μM), LDL (106±11 vs. 49±1.94 and 49±1.94μM), and CRP (0.3±0.1 vs. 0.1±0.05 and 0.1±0.05μg/ml).

Conclusions: Combined hyperlipidemia and HG attenuate eNOS and Nrf2. These results suggest that perturbations in these systems may contribute to diabetic nephropathy.

FR-OR005

Human Kidney Proximal Tubular Epithelial Cells Are Not Protected against Oxidative Stress by PPARγ Agonists. David M. Small,1,2 Glenda C. Gobe.1 Centre Kidney Disease Research, Univ of Queensland; 2Dept Nephrology, PH Hospital, Brisbane, Australia.

Background: Peroxisome proliferator activated receptor-gamma (PPARγ) agonists are renoprotective in diabetic nephropathy but the mechanisms are not well understood. Mitochondrial dysfunction and oxidative stress contribute to diabetic nephropathy; PPARγ upregulates proteins required for mitochondrial biogenesis. Our aim is to determine the role of PPARγ in protecting kidney proximal tubular epithelium (PTE) against mitochondrial destabilisation and oxidative stress.

Methods: HK-2 cells were treated with 0.2-1.0mM hydrogen peroxide (H2O2) for 2h and 18h. Treated and untreated controls were compared for: apoptosis, mitosis (morphology); cell viability (MTT); superoxide (dihydroethidium /DHE); mitochondrial function (Mitotracker Red; JC-1); ATP (luminescence); and mitochondrial ultrastructure (electron microscopy). Western immunoblotting was used to study PPARγ function (Mitotracker Red; JC-1); ATP (luminescence); and mitochondrial ultrastructure (electron microscopy). Western immunoblotting was used to study PPARγ,

Results: At 2h and 18h, mitochondrial destabilisation increased with H2O2 concentration: MitoTracker Red and ATP decreased (p<0.05); JC-1 green; and DHE increased (18h; p<0.05). Mitochondria were sparse and had disrupted cristae. Pak2 increased, p62 decreased (2h), and p62 and LC3-II increased (18h) (all p<0.05) indicating increased oxidative stress.

Conclusions: PPARγ agonists protect HK-2 cells from oxidant-induced mitochondrial destabilisation in kidney PTE, in association with PPARγ activation. PPARγ agonists failed to protect the cells. Despite positive effects in other tissues, PPARγ activation appears to be detrimental to kidney PTE health when oxidative stress induces damage.

Funding: Government Support - Non-U.S.

FR-OR006

Circulating Oxidized Albumin Is a Mediator of Endothelial Dysfunction in Uremia. Fajba Magal,1,2,3 Saimi Tani,1,2 Andrea Szuchnan-Sapir,1 Shifra Selia,1 Batya Kristal,1,2 Nephrology and Hypertension Dept, Western Galilee Hospital, Israel; 2Faculty of Medicine in the Galilee, Bar Ilan Univ, Safed, Israel; 3Laboratory of Human Health and Nutrition Science, Migsal, Israel; 4Eliachar Research Laboratory, Western Galilee Hospital, Israel; 5Nutrition Dept, Tel Hai College, Israel.

Background: Oxidative stress and inflammation prevalent among hemodialysis patients under atherosclerosis and cardiovascular (CV) morbidity and mortality. We suggest that modified human serum albumin (HSA) mediates endothelial dysfunction, a process that may initiate CVD. Our study aims to characterize the modifications of uremic HSA, reveal their effects on endothelial function and establish a “finger-print” of modified HSA as a potential novel tool to predict CV disease.

Methods: Albumin enriched fraction from 5 healthy controls (HC) and 5 Hemodialysis (HD) patients were evaluated by electrospay ionization mass spectrometry (Q-TOF LC/ MS). Human umbilical vein endothelial cells (HUVEC) were exposed to albumin separated from sera of HC or HD. Endothelial mRNA was extracted to determine expression of Interleukin 6 (IL-6), TNF-alpha and e-NOS.

Results: We revealed the existence of reversible and irreversible post-translational modifications, present in HC and HD patients. Each group is characterized by an unique exclusive pattern of the post-translational modifications present only in HD patients. Unmodified Albumin showed a molecular mass of 66440.6±0.14 Da. The Known-post-translational modifications observed were: Cysteinylation (66558.60±0.74 Da), N-tosylation (66467.80: 2.59 Da), Nitration (66483.57±3.31), Glycation (66601.0.70 Da). Exposure of endothelial cells to HAS separated from HD patients resulted in an increase in the cytokine and e-NOS expression by 1.2, 1.5 and 2.4 fold, respectively, in comparison to HAS of HC.

Conclusions: We suggest that modified albumin plays a pivotal role in endothelial dysfunction underlying atherosclerosis. Further studies are needed to enable the use of these exclusive modifications as a “finger-print” for evaluation and follow-up of the atherosclerotic process.

Funding: Government Support - Non-U.S.

FR-OR007

FGF23 Enhances Nitric Oxide Synthesis, and Reduces Production of Reactive Oxygen Species in Human Endothelial Cells In Vitro. Maren Leifheit-Nestler, Jacqueline Haller, Dieter Haffner. Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.

Background: Oxidative stress and uremic toxins are well known risk factors for cardiovascular diseases (CVD), associated with comorbidity of patients with chronic kidney disease (CKD). Patients with CKD exhibit excessive serum concentration of phosphaturic hormone fibroblast growth factor 23 (FGF23) as a result of disordered calcium and phosphate homeostasis. FGF23 binds primarily to FGF receptor (FGFR) 1 and its cofactor klotho. Klotho is a transmembrane protein and after cleavage the extracellular domain functions as a humoral factor (sorulable a-klotho) as well. Klotho has been associated with aging and bone loss and klotho-deficient mice indicate accelerated arteriosclerosis suggesting an influence of klotho on the cardiovascular system.

Methods: To examine the impact of FGF23 on endothelial function, human coronary artery endothelial cells (HCAEC) were stimulated with FGF23 in a time- and concentration-dependent manner. Cells were evaluated for protein expression and activation of FGF23, FGFR1-4, klotho and endothelial nitric oxide synthase (e-NOS). To analyze endothelial function, the formation of reactive oxygen species (ROS) was detected by fluorescence microscopy and FACS analysis and FGF23 dependent nitric oxide (NO) production was quantified using modified Griess assays.

Results: FGF23 receptors 1 and 2 as well as klotho were detected in HCAEC. Incubation of HCAEC with FGF23 for 60 minutes induced the release of soluble a-klotho (3.6-fold; p=0.02) and increased NO production (1.4-fold; p<0.025). Klotho was at least partly mediated by FGFR1-2. We revealed the existence of reversible and irreversible post-translational modifications of uremic HSA, reveal their effects on endothelial function and establish a “finger-print” of modified HSA as a potential novel tool to predict CV disease.

Conclusions: Vascular endothelial cells are a target of FGF23 as HCAEC express receptors required for FGF23 signaling. FGF23 reduces oxidative stress (i.e. ROS production) and increases eNOS activity, and NO production in cultured HCAEC. This study suggests that at least partly mediated by FGFR1-2.

FR-OR008

A Novel Approach for the Management of Cardiovascular Disease in CKD. Ashutosh M. Shukla,1 Chhanda X. Bose,2 Oleg K. Karaduta,2 Sudhir V. Shah,2 Div of Nephrology, Univ of Florida & NF/SG VA, Gainesville, FL; 2Div of Nephrology, Univ of Arkansas for Med. Sc. & CAHV, Little Rock, AR.

Background: At the present time we lack an effective strategy to manage cardiovascular disease associated with chronic kidney disease(CKD). Atherosclerosis is an inflammatory process and hydroxycholesterol(IGU) has multiple pleiotropic properties that are anti-inflammatory.

Methods: In the present study we examine the effects of HClQ in ApoE-/- mice with CKD. Males 6-8 weeks old ApoE-/- mice(C57BL/6 background) were grouped by 2 x 2 design into those with and without CKD, and those who received HClQ or placebo. CKD was created by a two-step surgical technique. All mice remained on a high-fat diet for next 16 weeks and uremia was confirmed by serial lab values. Atherosclerosis was assessed through premortem(small intravalulad ultrasound echography-IUE & cytokine studies), as well as postmortem studies(pathological-en face staining with Sudan IV of whole aorta and Oil Red O staining of aortic bulb, & immunohistochemical studies).

Results: In CKD model, HClQ reduced at least partly mediated by FGFR1-2. This study was supported in part by grants from the National Institutes of Health (R01HL063139, R01DK067884, and R01DK067884). The authors thank Dr. K. M. Lee for providing the atherogenic diet and Dr. D. G. M. Sloane for providing the apoE-/- mice. Further studies are needed to enable the use of these exclusive modifications as a “finger-print” for evaluation and follow-up of the atherosclerotic process.

Funding: Government Support - Non-U.S.
 Childhood Chronic Kidney Disease (CKD) Impairs Normal Vasoprotective Factors in High Density Lipoprotein (HDL)  

**Background:** HDL's beneficial effects encompass not only reverse cholesterol transport relevant to atherosclerosis but also modulation of cellular inflammation and protection of the endothelium relevant to vasculopathy. Since early intervention can impact CKD in PD, n=14), CKD (stage III-IV, n=15) and normal kidney function (Control, n=7). Cytokine response of LPS-activated THP-1 cells ± HDL was assessed by mRNA expression of inflammatory markers. Chemotaxis of THP-1 cells to monocyte chemoattractant protein-1 (MCP-1) was assessed in a transwell chamber. THP-1 cells labeled calcein adherence to HUVEC was assessed by fluorescence and microscopy.

**Results:** HDL of CKD and ESRD-PD heightened the inflammatory cytokine response: TNF-α: Control:0.47±0.04, CKD:1.03±0.08*, ESRD-PD:1.07±0.19*, IL-1β: Control:1.41±0.20, CKD:2.60±0.24*, ESRD-PD:2.31±0.36*, (P<0.01 and P<0.05 vs Control). Control HDL reduced chemotaxis of THP-1 while HDL from CKD and ESRD-PD had no beneficial effect (ratio compared to medium: MCP-1:2.0±0.2, Control:0.9±0.2, CKD:1.9±0.2*, ESRD-PD:1.7±0.3). HDL of CKD and ESRD-PD has reduced ability to protect HUVEC against macrophage adhesion (% decrease: Control:-8.9±2.3, CKD:-3.1±1.2*, ESRD-PD:-7.1±1.6*).

**Conclusions:** Even in the absence of long-standing concomitant diseases/risk factors prevalent in adults such as diabetes, obesity and smoking, children with CKD have HDL that dramatically increases the inflammatory and chemotactic response of macrophages while impairing its endothelial protective ability. The impairment is evident even pre-dialysis, in children with moderate CKD. The results indicate that CKD per se causes dysfunctional HDL. Dysfunction of HDL is thus an early therapeutic target that may forestall subsequent vascular complication of CKD.

**Funding:** NIDDK Support

---

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

---

**FR-OR009**

**Podocyte B7-1 Inhibition as a Therapeutic Strategy for Diabetic Nephropathy**

**Methods:** Podocyte B7-1 single-nucleotide polymorphisms (SNPs) were performed on the Kidney Function cohort of TH2 and soluble (s) CD28 (B7-1 ligand) was measured by Platinum ELISA. Podocytes were cultured at 10mM glucose (normal glucose) and 30 mM (high glucose) for 7, 14 days and treated with CTLA4-Ig at 10 μg/ml. Mice were treated with CTLA4-Ig using 500 μg per day and 250 μg per day at 2, 4, 6, 8, 10; 250 μg twice a week thereafter.

**Results:** Kidney biopsies from T2D patients showed glomerular B7-1 upregulation compared to controls. Two SNPs at the B7-1 gene were associated with progression to end stage renal disease (ESRD, OR=1.56, p=0.008) and sCD28 serum baseline levels predicted ESRD progression in T2D patients. B7-1 was upregulated in *vivo* in murine podocytes when cultured in high-glucose and *in vivo* on glomerular podocytes of diabetic db/db and streptozotocin (STZ)-C57BL/6 mice. Pharmacological targeting of B7-1 with CTLA4-Ig, protected podocytes in *vitro* from high glucose-induced damage (deregulation of podocyte-specific cytoskeleton proteins) and CTLA4-Ig treatment of db/db and STZ-C57BL/6 mice was able to prevent urinary albumin excretion rise (UA; db/db, STZ-C57BL/6, untreated 7μgks vs. 25μgks; p<0.01, p<0.0001; CTLA4-Ig-treated 7μgks vs. 25μgks; p=ns) and glomerular alterations such as mesangial expansion and collagen I deposition.

**Conclusions:** Targeting B7-1 with CTLA4-Ig (clinically available as Abatacept) is a novel therapeutic strategy for diabetic nephropathy.

**Funding:** Private Foundation Support

---

**FR-OR011**

**A Randomized, Double-Blind, Placebo Controlled Trial of FG-4592 for Correction of Anemia in Subjects with Chronic Kidney Disease in China**

**Methods:** Subjects with CKD not on dialysis with hemoglobin (Hb) <10 g/dL were randomized 1:1:1 to FG-4592 low or high dose or placebo orally 3 times a week (wk) for 8 wks. The primary efficacy endpoint was maximum change of Hb from baseline (BL) by wk 9.

**Results:** 91 subjects enrolled, 90 completed 8 wks dosing; 88 were evaluable for efficacy. BL characteristics for FG-4592 and placebo groups are comparable. In FG-4592-treated subjects, Hb increased from BL in a dose-related fashion. The proportion of Hb responders (ΔHb >1 g/dL from BL) and subjects achieving Hb ≥11.0 g/dL was significantly higher in FG-4592 vs placebo subjects (Table). Significant decreases in total and low-density lipoprotein cholesterol (ΔTC & ΔLDL-C) occurred in FG-4592 subjects. The incidences of treatment emergent adverse events (AEs) and serious AEs (SAEs) were nearly identical for FG-4592-treated and placebo subjects. AEs were generally mild or moderate and typical for CKD patients.

**Conclusions:** This study suggests that FG-4592 effectively corrects CKD anemia and is well-tolerated in CKD patients. FG-4592 may also lower cholesterol. P3 trials of FG-4592 in CKD patients are underway.

**Funding:** Pharmaceutical Company Support - Fibrogen, Inc.
FR-OR013
A Systematic Exploration of Individual Haemodialysis Patient Preferences for Treatment Outcome: Symptoms or Survival Zoe C.L. Pittman,1 Chris W. McIntyre,1,2 *Royal Derby Hospital, United Kingdom; 2Univ of Nottingham, United Kingdom.

Background: In many chronic diseases, patients treatment outcome preferences vary between symptom control and survival. This has not been formerly investigated in kidney disease. We therefore aimed to systematically explore haemodialysis (HD) patients’ outcome preferences, utilising established methodology to compare and quantify the subconscious trade off in decision making.

Methods: Prevalent HD patients completed a full profile conjoint analysis outcome preference data set comprising 25 proposed treatment outcome profiles each scored for overall acceptability. All profiles contained the same 6 attributes (pain, tiredness, breathlessness, depression, survival and treatment burden (TB)), variable across 4 levels of severity. Standard conjoint analysis techniques were used to derive part worths (utilities) and importance weights for each attribute, allowing the relative contribution of each attribute to be determined per individual. Additional demographic data were collected.

Results: 22 patients were studied, mean age 63±15 years, 59% male, 52% diabetic. Overall importance weights (%) were higher for survival (20.6%), pain (20.3) and breathlessness (18.2), than for tiredness (14.4), depression (13.7) or TB (12.8). Pain ranked 1st or 2nd in 15/22, survival 8, breathlessness 6, tiredness 5, depression 4, and TB 3.

Conclusions: There are a variety of difference outcome preferences in this cohort however the majority of patients showed a preference for symptom control, as opposed to survival, and were able to consider increased treatment burden in order to achieve this. Understanding of individual patient preferences for treatment outcome may allow a more informed discussion about changes to therapy, including potential for increased uptake of more intensive therapy.

FR-OR014

Background: Medications prescribed to patients with Chronic Kidney Disease (CKD) may contribute to hyponatremia. We sought to explore which prescribed medication is most frequently associated with hyponatremia in this setting.

Methods: Cross-sectional baseline analysis of hyponatremia (<135mmol/l) and concomitant medication of patients enrolled in the Chronic Renal Insufficiency Standards Implementation Study (CRISIS), a prospective observational outcome study in all-cause CKD stages 3-5 managed in secondary care, was undertaken. We examined the association of drugs known to cause hyponatremia in a multivariate logistic regression (LR) adjusting for diabetes,eGFR,history of heart failure and liver disease.

Results: 22 patients were studied, mean age 63±15 years, 59% male, 52% diabetic. Overall importance weights (%) were higher for survival (20.6%), pain (20.3) and breathlessness (18.2), than for tiredness (14.4), depression (13.7) or TB (12.8). Pain ranked 1st or 2nd in 15/22, survival 8, breathlessness 6, tiredness 5, depression 4, and TB 3.

Conclusions: There are a variety of difference outcome preferences in this cohort however the majority of patients showed a preference for symptom control, as opposed to survival, and were able to consider increased treatment burden in order to achieve this. Understanding of individual patient preferences for treatment outcome may allow a more informed discussion about changes to therapy, including potential for increased uptake of more intensive therapy.

FR-OR015
Proteomic Analysis of the Plasma in Chronic Kidney Disease Related with Cardiovascular Disease Maria Wanic-Kossowska,1 Magdalena Luczak,1 Dorota Formanowicz,2 Elzbieta Pawlczak,2 Lidia Kozioł,1 *Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznan, Poland, 1Dept of Clinical Biochemistry, Poznan Univ of Medical Sciences; 2Dept of Nephrology, Transplantology and Internal Medicine, Poznan Univ of Medical Sciences.

Background: Atherosclerosis is the most serious complications in chronic kidney disease and it frequently associated with hyponatremia in this setting. It is well known that skeletal muscle plays an important role in the regulation of muscle protein degradation. This study investigated playing a key role in the regulation of muscle protein degradation. This study investigated molecular mechanisms that enhance the formation of plaque in CKD and can overcome muscle wasting, which has important clinical implications in this population.

Methods: We used 2DE and MS methods to study changes in the profiles of plasma protein accumulation during development of CKD. Study involved healthy volunteers and four group of patients: patients in stage 1-2CKD; 3-4CKD and 5CKD and patients with classical CVD with unstable coronary artery disease and after myocardial infarction, but without any classical signs of renal dysfunction. We analyzed three different plasma sets: high-abundant, low-abundant proteins and also low molecular proteins (75kDa) to find differentially expressed proteins. The proteins were identified by MALDI/TOF-TOF mass spectrometry. Differentially expressed proteins were confirmed by selected reaction monitoring (SRM) analysis.

Results: Identified 13 proteins were used to analyze the functional interactions of all identified differential proteins. Created on this basis network revealed that at least three functional nodes are related with CKD: blood coagulation cascade, metabolism of amines and inflammatory processes.

Conclusions: Differential concentration of identified proteins in CKD and CVD indicate that different molecular mechanisms are involved in the development of CKD- and CVD-related atherosclerosis. These results suggest that CKDAs is highly accelerated by the progression of CKD and potentially different pathways play a role in the regulation of muscle protein degradation. This study investigated molecular responses to RE in pre-dialysis CKD.

Methods: 18 patients CKD3b-4 (mean eGFR 23, range 16-36/min/1.73m2; mean age 63, range 45-75 years) were randomised to RE (3 sets 10-12 leg extensions at 70%max, 3/week for 8 weeks, 11=0), or control (usual activity=7). Quadriceps cross-sectional area (CSA) was measured by ultrasonography at baseline (BL) and 8 weeks. Muscle biopsies were obtained at BL and 8 weeks in controls, and BL, 24th post first training session (PRE-RT) and 24th post final training session (POST-RT) in exercisers. Akt phosphorylation, MyoD and MyFb and MuRF1 mRNA expression were analysed by Western blotting and RT-PCR.

Results: No changes were seen in the controls. In exercisers, 8 weeks RE significantly increased quadriceps CSA (P=0.001). After the first RE session, the normal Akt phosphorylation response failed to occur. In contrast, the expected increase was seen after the final RE session (BL vs POST-RT P<0.004). Of the protein breakdown regulators, MuRF1 initially increased in response to RT (BL vs PRE-RT P=0.02). However, after 8 weeks of RE, MyoFb fell below BL (BL vs POST-RT P=0.004).

Conclusions: This study reveals a previously unknown failure of RE-stimulated Akt phosphorylation in CKD, which may be a novel contributor to muscle wasting. However, eight weeks RE restored Akt signalling, suppressed mRNA expression of MyoFb and MuRF1, resulting in significant muscle hypertrophy. These results demonstrate that RE may play an important role in the development of muscle turnover in CKD and can overcome muscle wasting, which has important clinical implications in this population.

FR-OR017
Increased Urine SEMAPHORIN 3A Is Associated with Renal Damage in Hypertensive and Diabetic Patients with Chronic Kidney Disease Ganesan Ramesh,2 Calpurinia Jayakumar,1 Francesca Viazzi,1 Giovanna Leoncini,2 Debora Garneri,1 Roberto Pontremoli,1 *Medicine, Univ of Genoa, Italy; 1Vascular Biology Center, Georgia Regents Univ, Augusta, GA.

Background: Semaphorins are guidance proteins that influence cellular morphology and function, and have been implicated in several pathophysiological processes such as angiogenesis, organogenesis, tumourogenesis, cell migration, cytokine release and immune response, among others. A decrease in SEMA3A is observed in skeletal muscle in CKD and can influence cellular morphology. However, its role in human disease has not been investigated so far.

Methods: To determine the role of sema3A in CKD, we performed a cross-sectional, nested, case-control study on a group of 151 age, gender, and body mass index (BMI) and CKD stage matched hypertensive patients with and without chronic kidney disease (CKD) or diabetes mellitus. SEMA3A was quantified in the urine by ELISA. CKD and its components, i.e., estimated glomerular filtration rate (eGFR) and albuminuria were measured by CKD EPI formula and albumin creatinine ratio (ACR), respectively. Data are expressed as mean ± SD. Statistical analysis was done using Stasview for Windows.

Results: USEMA3A levels were positively correlated with urine albumin creatinine ratio (UACR) (P=0.0038) and serum creatinine (P=0.0031). USEMA3A was significantly higher in patients with both components of renal damage as compared to those with only one and those with normal renal function (P<0.0001 and <0.0001, respectively). In a logistic multiple regression analysis the presence of increased urine USEMA3A levels (i.e. top quartile) entailed a 14 OR (95% CI 3.2-63, P=0.0005) higher risk of combined renal damage and risk of macroalbuminuria or of reduced eGFR even taking into consideration potential confounding factors such as serum uric acid (P<0.0007 and 0.0034, respectively).

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

39A
Conclusions: This study demonstrates that USEMA 3A is significantly associated with renal damage both in diabetic and non diabetic hypertensive patients. USEMA 3A levels appear to be a marker of renal dysfunction, independent of eGFR, albuminuria and serum uric acid.

Funding: NIDDK Support

FR-OR018

Increased TIMP2•IGFBP7 Is Associated with Increased 9 Month Mortality in ICU Patients at Risk for AKI Jay L. Kovenr, Andrew Shaw, Lakshmi S. Chawla, Eric Hoste, Azra Bihorac, Kianoush Banaci-Kashani, Jing Shi, John A. Kellum. On behalf of All Astute Medical Sapphire Investigators.

Background: We recently reported a 728 patient multicenter study (Sapphire) where Insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), were validated for risk stratification for moderate to severe Acute Kidney Injury (AKI, KDIGO stages 2 and 3). We then compared 9-month all cause mortality stratified by these cutoffs using a log rank test. A Cox proportional hazards model was used in which both TIMP2•IGFBP7 and serum creatinine were included as continuous variables.

Results: Baseline TIMP2•IGFBP7 results were available for 715 patients. KDIGO 2/3 observed within 12 hours of study enrollment. We then compared 9-month all cause mortality stratified by these cutoffs using a log rank test. A Cox proportional hazards model was used in which both TIMP2•IGFBP7 and serum creatinine were included as continuous variables.

Conclusion: Our initial analysis of the first prospective CHERUB study, ANG- discrimination for subsequent severe AKI was superior to ANG- when a high negative predictive value of ANG for not progressing to severe persistent AKI, we suggest using ANG as a clinical adjunct to target biomarker testing. We plan to enroll more patients and incorporate biomarkers to validate our results and determine if biomarkers add to the prediction of AKI.

FR-OR020

Insulin-Like Growth Factor-Binding Protein 7, and Tissue Inhibitor of Metalloproteinases-2 Are Significantly Associated with 18 Month Decline in eGFR Kianoush Banaci-Kashani, John A. Kellum. 2Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Critical Care Medicine, Univ of Pittsburgh, School of Medicine, Pittsburgh, PA.

Background: We recently reported Insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) as validated markers for risk stratification for moderate to severe Acute Kidney Injury. We now report the 18-month follow up outcomes of the Mayo Clinic discovery cohort.

Methods: We enrolled 285 critically ill patients without known AKI and followed this cohort for 18 months for mortality and eGFR. Enrollments TIMP2•IGFBP7 was measured by immunoassay and was analyzed with respect to outcomes in a Cox proportional hazards model.

Results: In this cohort of 285 patients 162 (57%) were male, 267 (94%) were Caucasian and median age was 66 years (IQR 56-76). Incidence of moderate to severe AKI (RIFLE I-F) was 53 (19%) and 6 (2%), respectively. Eighty (28%) patients died within 18 months and 105 patients had at least one follow-up serum creatinine value measured between 3 and 18 months after enrollment. Of these patients with follow-up creatinine, 23 (22%) had at least a 25% drop in eGFR compared with baseline. Hazard ratio (HR) for incurring a 25% or greater decline in eGFR for the patients with at least one serum creatinine measured more than three months after enrollment was 1.68 (95% CI, 1.31-2.15, p<0.01) for AKI (KDIGO, 2.52; 95% CI, 1.15-5.75, p=0.03) or without (HR, 2.49; 95% CI, 1.17-5.34, p=0.018) adjustment for enrollment sCr for each unit increment in the enrollment TIMP2•IGFBP7. HR for mortality was in the same direction but did not reach significance with (HR, 1.44; 95% CI 0.97-2.11, p=0.067) or without (HR, 1.42; 95% CI 0.97-2.08, p=0.074) adjustment for enrollment sCr. Discriminative ability of TIMP2•IGFBP7 to detect renal function in 18 month follow up. These results show that TIMP2•IGFBP7 provides valuable information about kidney status in acutely ill hospitalized patients that is relevant to long-term health outcomes.

Funding: Pharmaceutical Company Support - Astute Medical Inc.

FR-OR019

Renal Angina in the Pediatric Intensive Care Unit: The CHERUB Prospective Study Shina Menon, Stuart Goldstein, Rajit K. Basu. Center for Acute Care Nephrology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Delay in recognition of acute kidney injury(AKI) and inability to predict severe AKI delays institution of optimal therapy. We previously showed that fulldiscerning of AKI that occurs before the stem-cell engraftment may be fatal in allogeneic hematopoietic stem cell transplantation. We now report the 18-month follow up outcomes of the Mayo Clinic discovery cohort.

Results: In this cohort of 285 patients 162 (57%) were male, 26 (94%) were Caucasian and median age was 66 years (IQR 56-76). Incidence of moderate to severe AKI (RIFLE I-F) was 53 (19%) and 6 (2%), respectively. Eighty (28%) patients died within 18 months and 105 patients had at least one follow-up serum creatinine value measured between 3 and 18 months after enrollment. Of these patients with follow-up creatinine, 23 (22%) had at least a 25% drop in eGFR compared with baseline. Hazard ratio (HR) for incurring a 25% or greater decline in eGFR for the patients with at least one serum creatinine measured more than three months after enrollment was 1.68 (95% CI, 1.31-2.15, p=0.03) or without (HR, 2.49; 95% CI, 1.17-5.34, p=0.018) adjustment for enrollment sCr for each unit increment in the enrollment TIMP2•IGFBP7. HR for mortality was in the same direction but did not reach significance with (HR, 1.44; 95% CI 0.97-2.11, p=0.067) or without (HR, 1.42; 95% CI 0.97-2.08, p=0.074) adjustment for enrollment sCr. Discriminative ability of TIMP2•IGFBP7 to detect renal function in 18 month follow up. These results show that TIMP2•IGFBP7 provides valuable information about kidney status in acutely ill hospitalized patients that is relevant to long-term health outcomes.

Funding: Pharmaceutical Company Support - Astute Medical Inc.

FR-OR021

Acute Kidney Injury prior to the Stem-Cell Engraftment Is a Harbinger of Short-Term Mortality in Hematopoietic Stem Cell Transplantation Taku Morito, Ken Tsuchiya, Kosaku Witta. 1Renal Div, Dept of Medicine, Tokyo Metropolitan Cancer Center, Komagome Hospital, Bunkyou-ku, Tokyo, Japan; 2Dept IV of Internal Medicine, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan.

Background: AKI occurs before the stem-cell engraftment may be fatal in allogeneic hematopoietic stem cell transplantation (SCT). Prediction of such AKI may contribute to the improvement of prognosis in SCT recipients.

Methods: One-year prospective cohort study was conducted in 94 allogeneic SCT recipients, who had normal kidney function at baseline. Urinary Liver-type fatty acid binding protein (L-FABP) level was measured as a marker of tubular damage before conditioning therapy (baseline), and at days 0 (the morning of SCT). The “AKI prior to the stem-cell engraftment” was defined as the “early AKI” and the subsequently-occurred AKI as the “late AKI”. Cumulative mortality was analyzed by the Kaplan-Meier method. Discriminative ability of L-FABP for emergence of the early AKI was evaluated using AUC-ROC. Multivariate Cox hazards analysis was used to ascertain an association between the “early AKI” and the mortality.

Results: The early and late AKI developed in 23 patients (24.5%) and 41 patients (43.6%), respectively. The cumulative mortality of patients with the early AKI was the highest among the 3 groups: 73.9% in the early AKI; 24.7% in the late AKI; and 21.2% in the non-AKI. The emergence of the early AKI was the significant risk for the 1-year mortality (HR 4.02; 95% CI 1.50-12.0; P = 0.0051). The urine L-FABP level at baseline had good discriminative ability for the early AKI.

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

Underline represents presenting author.

40A
FR-OR022

Development and Standardization of a Furosemide Stress Test to Predict the Severity of Acute Kidney Injury

Eminra Brasha-Mitchell,1 Danielle Davison,1 Jay L. Koyner,2 Andrew Shaw,1 John M. Arthur,3 Divya M. Chalikonda,1 Sharon A. Trevino,4 Paul L. Kimmel,1 James A. Tumlin,4 Michael Senefelt,5 Lakhmir S. Chawla.1
1George Washington Univ; 2Univ of Chicago; 3Duke Univ; 4Medical Univ of South Carolina; 5NIH; 6Univ of Chattanooga.

Background: In the setting of early acute kidney injury (AKI), no test has been shown to definitively predict the progression to more severe stages.

Methods: We investigated the ability of a furosemide stress test (FST) (one-time dose of 1.0 or 1.5 mg/kg depending on prior furosemide-exposure) to predict the development of AKIN Stage-III in 2 cohorts of critically ill subjects with early AKI. Cohort 1 was a retrospective cohort who received a FST in the setting of AKI in critically ill subjects as part of Southern AKI Network. Cohort 2 was a prospective multicenter group of critically ill patients who received the FST in the setting of early AKI.

Results: We studied 77 subjects; 23 from cohort 1 and 54 from cohort 2; 25 (32.4%) met the primary endpoint of progression to AKIN-III. Subjects with progressive AKI had significantly lower urine output following FST in each of the first 6 hours (p<0.001). The area under the receiver operator characteristic curves for the total urine output over the first 2 hours following FST to predict progression to AKIN-III was 0.87 (p<0.001). The ideal-cutoff for predicting AKI progression during the first 2 hours following FST was a urine volume of less than 200mls/100ml/hr with a sensitivity of 87.1% and specificity 84.1%. Furosemide Stress Test Effect on Urine Flow:

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Combined</th>
<th>Non-Progressors</th>
<th>Progressors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour 0 (ml)</td>
<td>253(52.2)</td>
<td>240(48.0)</td>
<td>310.0</td>
</tr>
<tr>
<td>Hour 1 (ml)</td>
<td>196(35.8)</td>
<td>214(42.3)</td>
<td>251(35.2)</td>
</tr>
<tr>
<td>Hour 2 (ml)</td>
<td>251(35.2)</td>
<td>259(46.0)</td>
<td>296(35.8)</td>
</tr>
<tr>
<td>Hour 3 (ml)</td>
<td>329(46.0)</td>
<td>347(66.9)</td>
<td>296(35.8)</td>
</tr>
<tr>
<td>Hour 4 (ml)</td>
<td>89(23.4)</td>
<td>75(17.4)</td>
<td>96(46.6)</td>
</tr>
<tr>
<td>Hour 5 (ml)</td>
<td>265(31.1)</td>
<td>207(24.1)</td>
<td>296(35.8)</td>
</tr>
<tr>
<td>Hour 6 (ml)</td>
<td>75(17.4)</td>
<td>155(17.4)</td>
<td>251(35.2)</td>
</tr>
</tbody>
</table>

Conclusions: The FST in subjects with early AKI serves as a novel assessment of tubular function with robust predictive capacity to identify patients with severe and progressive AKI. Future studies to validate these findings are warranted.

Funding: NIDDK Support

FR-OR023

Plasma Kidney Injury Molecule-1 Is a Sensitive and Specific Biomarker of Kidney Proximal Tubule Injury

Venkata Sabbisetti, Sushrut S. Waikar,1 Daniel J. Antoine,2 Joseph V. Bonventre.1
1Dept of Medicine, Renal Div, Brigham and Women’s Hospital, Harvard Medical School, Boston; 2Dept of Medical & Clinical Pharmacology, Univ of Liverpool, Liverpool, United Kingdom.

Background: Kidney Injury Molecule-1 (KIM-1) is highly upregulated in dedifferentiated proximal tubular cells following kidney injury. The ectodomain of KIM-1 is shed and serves as a urinary biomarker of kidney injury. We report that shed KIM-1 is also leaked into the systemic circulation and serves as a sensitive and specific plasma biomarker of kidney proximal tubule injury.

Methods: Human and rodent plasma KIM-1 assays were developed. Mice were subjected to I/R injury for 10, 20, & 30 min and urine, plasma, and tissue specimens were collected for 14 days. Rats were given saline, 50, or 200 mg/kg of gentamicin i.p daily for 10 days. In humans, KIM-1 and creatinine were evaluated in spot urine and corresponding plasma samples from healthy control (HC), patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), and patients admitted to the surgical ICU. To determine the time course of biomarker changes in prospective studies, plasma and urine samples were collected prior to surgery, at the end of CPB, then at 4h, 12h and then daily for 5 days after CPB. Urine and plasma samples were also collected from individuals with chronic kidney disease (CKD).

Results: Plasma KIM-1 concentration is elevated in both acute and chronic kidney disease and serves as a novel plasma biomarker of kidney injury. To our knowledge, this is the first demonstration of a plasma biomarker with high specificity for kidney proximal tubule injury in rodents and humans.

Funding: Other NIH Support - DK03977, DK072381, DK075941

FR-OR024

Effects of ABT-719 on Incidence of Acute Kidney Injury during Cardiac Surgery Procedures

Samina Khan1, Soren Nielsen,2 Michael Beckert,3 Mark T. Houser,1 Deli Wang.1 1AbbVie; 2Aarhus Univ, Denmark; 3CarBACS, Germany.

Background: Patients undergoing on-pump cardiac surgery are at increased risk for ischemia reperfusion (IR)-induced acute kidney injury (AKI). ABT-719 is a novel melanocortin receptor agonist in development for prevention of IR-induced AKI. We report here the proportion of patients developing postoperative AKI injury by surgical procedure.

Methods: In a double-blind study, patients undergoing on-pump cardiac surgery were randomized to placebo (PBO: n=26), ABT-719 given at either 600μg/kg (n=23), or 800μg/kg (n=26). Each dose was divided into 3 bolus infusions at fixed intervals. AKI was determined according to the AKIN and RIFLE scores.

Results: Baseline characteristics were: mean age, 71yrs; males, 64%; pre-existing kidney disease, 53%. Mean overall bypass duration was 2.0hrs and the majority of patients (53%) underwent combined CABG and valve surgery. ABT-719 (800μg/kg) reduced the incidence of AKI, compared with PBO, for the following surgery types: combined CABG and valve, multiple valve, and CABG with chronic kidney disease. Combined CABG and valve: 2/4 (50%) in the placebo group, 2/2 (100%) in the 800μg/kg group (p=0.10). No significant differences were observed in patients undergoing other cardiac surgeries compared to PBO. However, since the sample size of the study is limited, additional studies are in development to further evaluate ABT-719 in patients undergoing other cardiac surgeries.

Funding: Pharmaceutical Company Support - AbbVie

FR-OR025

Urinary Biomarkers of Acute Kidney Injury and Mortality 3-Years after Cardiac Surgery


Background: The association between urinary biomarkers of acute kidney injury (AKI) and outcomes beyond hospital discharge is unknown.

Methods: 1199 patients that were discharged alive after hospitalization for cardiac surgery in the TRIBE-AKI cohort study were followed prospectively for the occurrence of death. The primary exposures were peak concentrations of five urinary biomarkers on post-operative days 1-3: neutrophil gelatinase-associated lipocalin (NGAL), interleukin (IL)-18, kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), and albumin. Hazard ratios (HRs) of mortality according to tertiles of the five urinary biomarkers were adjusted for pre-operative clinical variables, cardiopulmonary bypass time, and change in serum creatinine from baseline.

Results: During a median follow-up of 3.0 years (IQR 2.2-3.6), 139 (11.6%) participants died (50 per 1000 person-years). Among patients with clinical AKI (serum creatinine change of 50% or 0.3 mg/dL), the upper tertiles of urinary NGAL, IL-18, KIM-1, L-FABP, and albumin were independently associated with a 2.0-3.1-fold higher risk for mortality compared with the lowest tertiles.

Funding: TRIBE-AKI Consortium.

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

Underline represents presenting author.
FR-OR026
The SAFE-T Approach to Collaborative Kidney Biomarker Qualification

Patrick T. Murray,1 Joe F. Keenan,1 Frank Dieterle.2
1SAFE-T Consortium, EKF Diagnostics Ltd, Dublin; 2SAFE-T Consortium, Novartis AG, Basel

METHODS: SAFE-T was established in 2009 with the objective of providing a data submission package to the Health Authorities (FDA & EMA) to allow for the qualification of human kidney biomarkers to monitor drug induced kidney injury. The consortium has performed a first phase exploratory study of a larger list of candidate biomarkers through a number of healthy volunteer and drug induced kidney injury (DIKI) cohorts. Following statistical assessment of these exploratory studies SAFE-T will dismiss certain candidates that do not meet performance criteria and then perform a larger confirmatory DIKI study, the results of which are intended to serve as a convincing submission package for the qualification of a number of key kidney markers with the health authorities.

RESULTS: SAFE-T has established a candidate shortlist of 22 kidney biomarkers assembled from an extensive literature search of 50 biomarkers which were graded using a number of variables (including clinical publications, preclinical evidence, Marker stability, IP, etc.) and which have been validated at 3 testing sites (the top 30 markers using dual technology i.e. both microtitre ELISA and Luminex). A healthy volunteer cohort of samples has already been assessed to establish marker variation and normative ranges. Clinical samples from three clinical studies have been collected and assessed: 1. Cisplatin Nephrotoxicity; 2. Acute Glomerulonephritis (GN); 3. Contrast Media. The quality of evidence across studies was rated (GRADE).

CONCLUSIONS: The quality of evidence among studies was variable. There was strong evidence to determine the accuracy of plasma iothalamate clearance. There was insufficient evidence (limited scientific evidence) as was plasma clearance of DTPA (limited scientific evidence). Endogenous creatinine clearance was an inaccurate method (strong scientific evidence) as was plasma clearance of DTPA (limited scientific evidence). There was insufficient scientific evidence to determine the accuracy of plasma iothalamate clearance. Accurate methods to measure GFR are renal clearances of iothalamate and 125I-EDTA and plasma clearances of 131I-EDTA and iothalamate. Endogenous creatinine clearance is an inaccurate method. The conclusions are supported by moderately strong to strong scientific evidence.

Funding: Government Support - Non-U.S.

FR-OR029
Relevance of Correction for Day-To-Day Variation in Cystatin C Measurement

Priya Vart,1 Stephan J.L. Bakker,2 Hiddo Jan Lambers Avarius,1 Daniël de Zeeuw,1 Sijmen A. Reijneveld,2 Ute Bültmann,3 Ron T. Gansevoort,2 1Health Sciences; 2Nephrology; 3Clinical Pharmacology, UMC Groningen

Background: For epidemiological research it is important to obtain the most reliable measurement of filtration markers to estimate GFR. Despite standard laboratory quality control day-to-day variation in cystatin C (cysC) measurements can be observed. We investigated whether correction for day-to-day variation might help in obtaining more optimal cystC based GFR estimates.

Methods: Plasma samples of the PREVEND study (a general population-based observational cohort study, N=8,592 subjects) were used to re-measure cysC (Gentian assay) over a period of 243 days (March 2010 to October 2012). Each measurement day two independent plasma pools were used as control samples. Two reviewers assessed the quality of each sample. Two proficiency testing samples were assayed against the international reference standard for cysC. Second, using these control samples, we calculated for each measurement day a correction factor to adjust individual cysC values for day-to-day variation in cystatin C measurement. Estimated GFR with the cystC-CKD-EPI equation.

Results: Coefficient of variation of cysC in control samples was 6.9%. Mean SD of GFR using non-corrected cystatin C (GFRcorr) was 92.8±19.3 and using corrected cystatin C (GFRcorrcysC) 94.9±19.0 ml/min/1.73m2. Subjects were categorized in 6 strata of GFRcorrcysC as reference: ≤120, 90–119, 75–89, 60–74, 45–59 and ≤45 ml/min/1.73m2. Use of GFRcorrcysC was more accurate to predict cardiovascular risk compared to GFRcorr, measured either in eGFR (p=0.001). Importantly, eGFRcorrcysC had a better association with incident cardiovascular events (n=789, follow-up 3.2±2.7 years) than eGFRcorr (NRI 0.102, p=0.006).

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

Underline represents presenting author.

42A
Conclusions: In the absence of a gold standard measurement of GFR, these epidemiological data suggest that correction for day-to-day variation in cystatin C measurements improves GFR estimation using cystatin C.

Methods: We measured iohexol clearance in a non CKD-population of 570 participants of the Berlin Initiative Study (BIS) with a mean age of 78.5 yrs and compared the most recent 7 creatinine and/or cystatin C-based estimating equations to our measured GFR (mgGFR). For iohexol clearance measurement blood samples were taken after 30, 60, 90, 120, 150, 180, 240, and 300 min (5h) after injection of 5 ml of iohexol. All comparisons were done separately for male and female patients and dependent on age.

Results: Compared to the mgGFR (red line) the MDRD overestimates GFR by appr. 10-15 ml/min/1.73m² in all age groups, followed by the CKD-EPI equation and the new combined CKD-EPI(crea/cysC) equation. The CKD-EPI(crea/cysC) equation performs closer to the gold standard. The BIS-equations are the closest to the mgGFR. The zig-zag pattern of lines beyond the age of 85 in females might be due to the small numbers in that age group (n=34). Overall the bias was largest for the MDRD equation (mean 11.2 ± 11.4 SD) followed by the CKD-EPI equation (mean 8.9 ± 10.1 SD) and CKD-EPI(crea/cysC) (mean 7.4 ± 9.2 SD). The BIS1(crea), BIS1(crea/cysC) and BIS3(crea) and the CKD-EPI(crea/cysC) showed lowest bias (mean -0.9, 0.1, 0.5, 4.8, SD = 9.2, 8.1, 8.9, 10.7, respectively).

Background: GFR declines with age, leading to a high prevalence of CKD in the elderly. Causes of this decline are not well understood due in part to absence of reliable information about GFR in a representative elderly population and its associations with midlife factors.
FR-OR035

A Comparison of Slopes in Measured and Estimated GFRs: The CRIC Study

Background: This study compared the slopes in measured GFR (mGFR) and three estimated GFRs (eGFRs) from CRIC, MDRD and CKD-EPI equations.

Methods: Included were 1009 CRIC participants with \(>2\) mGFRs. Linear regression models estimated the slopes. Spearman correlations were calculated among the slopes. The slope difference of CRIC eGFR vs mGFR was regressed on baseline covariates.

Results: Mean length of follow up was 3.5 years (range=1.6-8.9). The Spearman correlations were >0.9 among the three eGFR slopes, and 0.59, 0.53, and 0.53 between mGFR and CRIC, MDRD, CKD-EPI eGFR slopes. Mean slope difference between CRIC eGFR and mGFR was 0.56 (SD=3.84, median=0.41, IQR: -1.33 to 2.37) ml/min/1.73m2/year. Model estimates which were the eGFR versus mGFR slope difference per unit change in the predictor were shown in Table.

FR-OR034

Chronic Kidney Disease Diagnosis and Referral Patterns by International Classification of Diseases-9 Codes
Anja A. Oommen, Lynn E. Schlanger, James L. Bailey, Jeff M. Sands, Janice P. Lea. Nephrology, Emory Univ School of Medicine, Atlanta, GA.

Background: There are an estimated 20 million persons with CKD in the U.S., which is associated with significant morbidity and mortality. Patients at high risk for CKD require screening including those with diabetes, hypertension, family history of CKD, and African Americans. The estimated glomerular filtration rate (eGFR) reporting has become standard practice in most labs to help identify persons with CKD stage 3-5. Despite having access to eGFR values < 60ml/min/1.73m2 lower per 1-y older age, the figure shows the relationships of estimated GFRs (eGFRs) from CRIC, MDRD and CKD-EPI equations.

Methods: We measured GFR (mGFR) using plasma clearance of iohexol in 805 people participating in a community based prospective cohort study, Age, Gene/Environment Susceptibility Reykjavik Study (AGES-RS). We examined the associations of mGFR with susceptibility to risk factors for cardiovascular disease, inflammation, insulin sensitivity, creatinine generation, and poor agreement between baseline eGFR and mGFR.

Conclusions: Elderly patients have low levels of GFR, suggesting decline in GFR may be secondary to pathological processes rather than aging. The strong associations of higher levels of SBP and DBP at midlife even less than 140/90 with lower mGFR in late life suggest possible mechanisms for GFR related decline and may provide some directions for prevention of CKD in the elderly.

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

FR-OR042

National Impact of Cystatin C on Safe and Appropriate Utilization of Metformin among Patients with Type 2 Diabetes
Delphine S. Tuot,1 Michael Shlipak,1 Jerry Yee,2 Rajiv Saran,3 Neil R. Powe. 1 Univ of California, San Francisco, San Francisco, CA; 2 Henry Ford Hospital, Detroit, MI; 3 Univ of Michigan.

Background: Metformin may be underused among persons with diabetes (DM) and chronic kidney disease (CKD) because of concerns of side effects at low glomerular filtration rates (GFR). eGFR=Cr cystatin C correlates better with measured GFR than other measures and may be a more reliable measure on which to base medication dosing. We examined the potential impact of eGFR<Cr-cys on guiding safe and appropriate utilization of metformin among US adults with DM.

Methods: Self-reported metformin use was assessed among 397 diabetic adults using 1999-2002 National Health and Nutrition Examination Survey data. DM was defined by self-report or a glycosylated hemoglobin \(>6.5\%)g/dL. eGFR<Cr was measured by the 4-variable MDRD equation; eGFR<Cr-cys by the CKD-EPI 2012 equation. We used proportions to reclassify (1) the percentage of diabetics with eGFR<Cr <45ml/min on metformin who could presumably safely be on metformin because a eGFR<Cr-cys >45ml/min and (2) the percentage of diabetics with eGFR<Cr <45ml/min on metformin, who should presumably not be on metformin because of an eGFR<Cr-cys <45ml/min. Results are weighted to the US population.

Results: Overall, 28% of patients with DM reported a metformin prescription, of whom 97% had an eGFR<Cr <60ml/min. Nearly 16% of patients with DM and eGFR<Cr <45ml/min not on metformin could safely be on metformin (Table 1) and 23% of persons with DM and eGFR<Cr >45ml/min on metformin should use the drug with caution based on eGFR<Cr-cys <45ml/min (Table 2).

Conclusions: eGFR<Cr-cys may help clinicians better identify individuals for whom metformin prescription is safe and appropriate. Prospective studies should further clarify the role of eGFR<Cr-cys for evaluation of safety and efficacy of medication dosing among CKD patients.

Funding: NIDDK Support, Other U.S. Government Support

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

44A
FR-OR037
GFR Decline as an Endpoint for Clinical Trials in CKD: Report of an NKF-FDA Workshop Andrew S. Levey,1 Josef Coresh,2 Aliza M. Thompson,3 Edmund J. Lewis,4 Dick de Zeeuw,5 Alfred K. Cheung,6 Kerry Willis,7 Norman Stockbridge,1 1Tufts Medical Center; 2Johns Hopkins Univ; 3Food and Drug Administration; 4Rush Univ Medical Center; 5Univ Medical Center Groningen; 6Univ of Utah; 7National Kidney Foundation.

Background: The FDA accepts halving of GFR, assessed as doubling of serum creatinine (Scr) level, as a surrogate end point for development of kidney failure in clinical trials of kidney disease progression. A Scr doubling is generally a late event in CKD and takes a long time to develop. There is great interest in considering alternative endpoints for clinical trials to shorten their duration and to extend their application to earlier stages of CKD. However, there is uncertainty about the associations of lesser declines in GFR with subsequent development of kidney failure. The NKF and FDA sponsored a scientific workshop to exam critically data that might new definitions of GFR decline as endpoints in clinical trials of CKD-related therapies. The anticipated outcome of the workshop was the identification of new definitions of GFR decline with sufficiently strong associations with important clinical outcomes of CKD so that they can be used as endpoints in CKD clinical trials.

Results: Summary of performance of alternative time-to-event endpoints for 2-5 year trial

<table>
<thead>
<tr>
<th>GFR decline</th>
<th>Baseline GFR High</th>
<th>Baseline GFR medium</th>
<th>Baseline GFR low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>40% decline</td>
<td>40% decline</td>
<td>30% decline</td>
</tr>
<tr>
<td>Stage 3</td>
<td>30% decline</td>
<td>30% decline</td>
<td>40% decline</td>
</tr>
<tr>
<td>Stage 4</td>
<td>30% decline</td>
<td>40% decline</td>
<td>40% decline</td>
</tr>
</tbody>
</table>

GFR: Glomerular filtration rate; CI: Confidence interval.

Conclusions: Based on a series of meta-analyses of 21 cohorts and 43 clinical trials and simulations of trial designs and analytic methods, the workshop concluded that a confirmed decline in eGFR of <30 or >40% may be an acceptable surrogate endpoint (acceptable type 1 error and power improved) in some circumstances, based on baseline GFR, magnitude of acute effects, duration of follow-up.

Funding: Private Foundation Support

FR-OR038
Lower Creatinine Clearance Is Associated with Reduced Walking Speed and Muscle Atrophy among Older Adults Babace Koshelravavan,1 Cassianne Robinson-Cohen,1 Ian H. de Boer,2 Ann M. O’Hare,3 Jonathan Himmelfarb,4 Kushang V. Patel,5 Bryan R. Kestenbaum.6 1Nephrology, Univ of Washington, Seattle, WA; 2Anesthesiology & Pain Medicine, Center for Pain Research on Impact, Measurement & Effectiveness, Seattle, WA.

Background: CKD promotes malnutrition and inflammation which may lead to loss of skeletal muscle and reduced physical performance. Associations of kidney function with human skeletal muscle structure and longitudinal measures of physical performance are unknown.

Methods: We tested associations of 24hr creatinine clearance (CrCl) with physical function in the InCHIANTI study, a community-based cohort of adults ≥65yrs. We included 826 participants without stroke or disability who completed a 24hr urine collection. Linear regression was used to assess cross-sectional associations of CrCl with gait speed over 7 and 400 meters, and knee extension strength. We adjusted for age, sex, wt, study site, smoking, education, diabetes, and CAD. We tested associations of CrCl with muscle and fat areas of the calf muscle by CT. Mixed effects models to estimate associations of baseline CrCl with gait performance measures across 7 yrs.

Results: Mean age was 74 ±17yrs. Mean CrCl was 79 ±25 ml/min with 206 participants with CrCl<60 ml/min. In cross-sectional analysis each 10ml/min lower CrCl was associated with an adjusted mean difference of -0.01 ml/min (95% CI: -0.04, -0.003; P=0.002) in usual gait speed and -0.009ml/min (95% CI: -0.015, -0.004; P=0.004) in 400m gait speed. No difference was seen with knee strength at baseline (P=0.8). Each 10ml/min lower CrCl was associated with an adjusted mean difference of -0.32 ml/min (95% CI: -0.58, -0.20; P=0.03) in calf muscle area and -0.16 mg/cm² (95% CI: -0.27, -0.05; P=0.005) in muscle mass. In longitudinal analysis each 10ml/min lower CrCl was associated with an adjusted difference of -0.025g/year in knee mass in 95% CI: -0.04, -0.01; (P=0.001) but no difference in gait speed.

Conclusions: Lower CrCl is associated with slower 7m usual gait speed and 400m gait speed and diminished calf muscle area and muscle density. Knee extension strength declined more rapidly among those with lower CrCl.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging support for InCHIANTI

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

FR-OR039
Effects of Aging on Renal Arteriolar Hyalnosis in Autopsies: The Hisayama Study Toshihiro Ninomiya,1 Michiaki Kubo,2 Masaharu Nagata,3 Yoshinoda Oda,4 Takaharu Kitazono,5 Yutaka Kiyohara.4 1Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; 2Laboratory for Genotyping Development, RIKEN Yokohama Institute, Yokohama, Japan; 3Dept of Anatomic Pathology, Kyushu Univ, Fukuoka, Japan; 4Dept of Environment Medical, Kyushu Univ, Fukuoka, Japan.

Background: There were limited studies addressing the effect of aging on renal arteriolar hyalnosis in autopsies. By examining a large autopsy sample, this study aimed to identify the associations of arteriolar hyalinosis with aging in autopsies. The advanced renal arteriolar hyalnosis was determined based on the 95 percentile values of arteriolar hyalinosis index among subjects who had no clinical signs of kidney disease. The risk estimates were computed using a logistic regression analysis.

Results: Aging was significantly associated with the likelihood of advanced renal arteriolar hyalnosis after adjusting for other cardiovascular risk factors, being 1.00 (reference) 1.66 (95% confidence interval, 0.60-4.60), 2.03 (0.79-5.24), and 5.31 (1.21-21.79) for 40-59, 60-69, 70-79, and ≥80 years. In the analysis stratified by hypertensive status, however, the multivariate-adjusted odds ratios of the presence of advanced renal arteriolar hyalnosis increased significantly with aging in hypertensives, whereas there was no evidence of the association in nonhypertensives: 1.00 (reference), 2.23 (0.64-7.72,) and 1.97 (0.54-7.19) for 40-69, 70-79, and ≥80 years in nonhypertensives: 3.37 (1.18-9.61), 4.35 (1.62-11.71), and 7.33 (2.75-19.49) in hypertensives. In the multivariate analysis, age, smoking, hypertension, glucose intolerance, and proteinuria were significant risk factors for the presence of advanced renal arteriolar hyalnosis, where hypertension had the greatest odds ratio.

Conclusions: Our findings suggest that aging is a significant risk factor for renal arteriolar hyalinization, but its magnitude of effect is less than that of hypertension.

Funding: Supported by the Ministry of Health, Labor, and Welfare of Japan.

FR-OR040
Incidence of Dementia Based on Dialysis Modality Dawn F. Wolfgram,1 Qian Xiang,2 Aniko Szabo.3 1Medicine, Medical College of Wisconsin and Zahloky VA Medical Center, Milwaukee, WI; 2Biostatistics, Medical College of Wisconsin, Milwaukee, WI.

Background: Dementia prevalence is increasing in our ESRD population. Although this increase reflects their overall higher risk of vascular disease, dementia increases substantially after initiation of dialysis. This suggests that hemodialysis itself, with its rapid fluctuations in blood pressure and osmolality, contributes to initial cognitive changes. Currently, there is no data on the incidence of dementia in the peritoneal dialysis (PD) population. Since PD lacks the fluctuations seen in HD, we hypothesize that that person on PD would be less likely to develop dementia than those on HD.

Methods: Using linked Medicare - United States Renal Data System data, we identified persons who initiated dialysis during 2006-2008 and did not have a dementia diagnosis code during the two years preceding dialysis initiation. We followed this cohort for up to 3 years to identify new dementia diagnoses. We estimated cumulative dementia incidence rates overall and for persons receiving HD vs PD using Nelson-Aalen estimators, censoring for mortality, and at December 31, 2008. We used Cox proportional hazards models to determine the independent effect of initial dialysis modality.

Results: We identified 144,244 eligible patients; PD was the initial modality in 6.2%. The overall mortality was 62.3% in 3 years. The cumulative incidence of dementia at 3 years was 6.1% overall; 6.8% and 3.5%, respectively, among those whose first modality was HD and PD. In bivariate analyses, African American race, older age, female sex, and hypertension or diabetes as primary ESRD cause were associated with increased risk for dementia. After adjusting for potential confounders, persons initiating dialysis with PD remained significantly less likely to develop dementia (HR 0.60, 95% CI 0.53-0.68).

Conclusions: Initial modality of PD is associated with lower risk of incident dementia than HD. Analysis taking into account further risk factor adjustment and time on dialysis modality is ongoing. These results suggest a need for more research regarding the potential risks of intradialytic events, including fluctuations in BP and osmolality.

Funding: None

FR-OR041
Cognitive Impairment in Moderate Chronic Kidney Disease: The Brain In Kidney Disease (BRINK) Study Anne M. Murray,1,2 Yelena Slinin,2 Sarah L. Pederson,1 Elizabeth Amiot,3 David Tupper.1 1Hennepin County Medical Center, Minneapolis, MN; 2Univ of MN; 3MMRF.

Background: In the longitudinal BRink In Kidney disease (BRINK) study we are characterizing burden of cognitive impairment (CI) in 350 CKD and 100 non-CKD subjects. We describe the frequency of domain-specific CI in CKD and non-CKD cohorts after one year of recruitment.

Methods: Pts with CKD Stages 3b-5 (eGFR > 60 ml/min; dialysis pts exclude/ a-d) and age, and race, and education-matched controls (eGFR ≥ 60 ml/min) were recruited from three Minneapolis urban clinics. Domain- specific neuropsychological testing was performed at baseline using the following tests: 1) 3MS (Modified Mini-Mental State Exam) for global cognition, 2) Hopkins Verbal Learning Test-Revised (HVLT-R, Immediate and Delayed, verbal memory), 3) Controlled Oral Word Association Test (COWAT, semantic memory-language), 4) Color Trails 1 and 2 (executive function) (CTT2), 5) Symbol-Digit-
FR-OR042

Dizziness and Vestibular Disorders Are Associated with Falls in Chronic Kidney Disease (CKD)  
Premila Bhat,1,2 Ashok Valluri,2

Background: CKD is associated with increased risk of falls and fracture but the factors contributing to fall risk in CKD are not fully known. We hypothesize that vestibular disorders, including disorders of balance and dizziness, contribute to fall risk in CKD. To examine this association cross-sectional analysis of the continuous National Health and Nutrition Examination Survey (NHANES) was conducted.

Methods: Subjects ≥40 years of age and enrolled in NHANES 2001-2004 (n=21,161) were included. Screening for problems with dizziness, balance, or falls and results of a modified Romberg test were ascertained from the NHANES Balance Questionnaire and Exam. Uni- and multivariate logistic regression were used to compare the prevalence of balance associated symptoms or Romberg test failure across CKD categories. Continuous and categorical data are presented as means±SD and percents (%), respectively.

Results: Of the 4,878 subjects, 48.9% were female, 16.8% black, mean age was 60.7±13.4 yrs, mean BMI 28.2±5.3, 42.2% with HTN, 13.0% DM. Prevalence of CKD was: Stages 1-2 (eGFR≥60), 88.5%; 3A (45≤eGFR<60), 7.8%; 3B (30≤eGFR<45), 2.5%; and 4-5 (eGFR<30), 1.2%. Of 23.3% who reported dizziness, balance or falling problems, 24.2% reported falls. Compared to those with eGFR≥60, for CKD Stage 3A, 3B, and 4-5 unadjusted OR’s for balance symptoms were 1.818 (95%CI: 1.452, 2.277), 2.475 (95%CI:1.709, 3.584), and 3.069 (95%CI: 1.829, 5.348), respectively. The relationship between advanced CKD (Stages 3B and 4-5) and balance symptoms was seen even after adjustment for age, gender, race, DM, and BMI, with OR’s 1.706 (95%CI: 1.151, 2.530) and 2.141 (95%CI:1.204, 3.808), respectively. Failure to pass level 2 or 3 Romberg exam remained predictive of falls after adjustment for CKD (level 2 OR=1.839, 95%CI: 1.570, 2.141; level 3 OR=2.530, 95%CI: 1.546, 2.421).

Conclusions: Problems with balance and dizziness are common in CKD. There is a graded relationship between CKD stage and balance symptoms. Among those with CKD, falls are associated with failure to pass sequential Romberg tests, suggesting that the Romberg test can identify individuals with CKD at high risk for falls.

Funding: Clinical Revenue Support

FR-OR043

Starting Dialysis at Age 75 Years or Older – Outcomes Data to Help in Shared Decision Making  
Bioerg Thorsteinsdottir,1 Hanna L. W. Larson,2 LaTonya J. Hickson,1 Molly A. Fectey,1 Amy W. Williams,1 1Medicine, Mayo Clinic, Rochester, MN; 2Univ of San Diego, San Diego, CA.

Background: The intensity of medical care for the oldest old has escalated beyond population growth in the past decades driven by powerful moral and technological imperatives to treat. Many elderly patients and their families feel that they have no choice but to start renal replacement therapy (RRT) with several expressing regret of having initiated therapy. High HD withdrawal rates have been found in this group. Shared decision making regarding RRT in the elderly is hampered by the lack of evidence to guide practice in this age group.

Methods: Review of the medical record for all patients 75 years and older, initiating any form of RRT at Mayo Clinic Jan 1, 2007 - Dec 31, 2011.

Results: Of 390 patients, 66% were male, 94% were Caucasian, and mean age was 81.3 years (Interquartile range [IQR] 77.5-84.4); 40% had diabetes, and 27% had congestive heart failure. The mean Charlson comorbidity index was 7.9 (IQR 6-10). The majority, 290 (74%), started RRT in hospital. 147 (57%) began with continuous RRT in the ICU. Of 210 hospital-initiated patients admitted from independent living, only 70 (33%) were discharged home. Mean follow up was 17 months (range 0-74). Early mortality was high with 104 (27%) dying in less than 30 days and 140 (36%) dying in less than 90 days. The 6-month survival rate was 58% and 12 month survival 49% (Figure 1). Among hospital starters, 110 of 290 (38%) died during the index hospitalization.

Conclusions: This cohort study of elderly incident RRT patients suggests that most initiate RRT in the hospital following an illness or an event. Loss of independent living is frequently observed following hospitalization. Early and overall mortality is high. Patient awareness of these outcomes may allow for better informed discussions at time of RRT consideration.

Funding: Other NIH Support - NIA, Private Foundation Support

FR-OR044

Determinants of Outcome of Conservatively Managed CKD Stage 5 Patients: Single Centre Review  
Muhammad Nauman Hashmi, Mohammed Awais Hameed, Arvind Ponnusamy, Vijay Sundaram Thanaraj, Ajay Prabhakar Dhaygude. Renal Medicine, Royal Preston Hospital, Preston, United Kingdom.

Background: Conservative treatment has become a recognized modality of treatment in end stage renal disease (ESRD) in selected group of chronic kidney disease (CKD) patients. These patients are managed in a multidisciplinary setting. However, there is lack of data regarding outcome of these patients.

Methods: This is a retrospective analysis of conservatively managed patients CKD stage 5 (Total number 119) patients followed up in a single centre from January 2005 till December 2010. Residual renal function (eGFR), laboratory parameters (calcium, phosphate, albumin & haemoglobin) were recorded from the time of decision to manage conservatively. These parameters were co-related.

Results: Mean age of the study population was 85.5 years. The most common co-morbidity was hypertension. Mean haemoglobin at baseline was 11.3g/dl, calcium 2.30mmol/l, phosphate 1.31mmol/l and albumin 39 g/l. Median overall survival was 816 days.

The number of patients died were 87. Haemoglobin >10 g/dl at presentation was associated with greater survival (p<0.001). Median survival of patients with haemoglobin >10 g/dl was 1116.5 days compared to 705.3 days for those with haemoglobin <10 g/dl.

Conclusions: Other parameters did not predict outcome. Interestingly, other parameters did not predict outcome.

Funding: Clinical Revenue Support

Underline represents presenting author.
Non-Dialysis Management in the Elderly: Survival, Symptom Control and Quality of Life

**Background:** Decisions concerning appropriateness of dialysis in the elderly require knowledge of expected survival and whether reasonable life can be maintained without dialysis. We compared prospectively symptom control, Quality of Life (QOL) and survival between ESKD patients managed without dialysis (NFD) and those planned for dialysis (Pre-Dx).

**Methods:** In a single centre prospective observational study over 4 years 290 Pre-Dx patients had usual nephrology care and 135 NFD patients also received Renal Supportive Care (RSC) adding the skills of a Palliative Medicine team. Patients were recommended for a NFD pathway based on co-morbidity, frailty, poor functional status or nutrition and their nephrologist’s view that survival would be poor. Symptoms were measured using the validated MSAS survey and QOL using the SF-36 survey.

**Results:** NFD patients were older than the Pre-Dx group (median 83 vs. 69 yrs, p<0.001); median eGFR at 1st clinic visit was 16/ml/min in both. 126(43%) of Pre-Dx patients had stable or improved symptoms over the 1st 6 months and 52%(12/23) vs. 45%(23/52) at 12 months. Physical QOL was better in both groups at 6 and 12 months in 51%(20/39) and 52%(11/21) of NFD and 57% (59/104 and 31/54) of Pre-Dx patients.

**Conclusions:** As expected, elderly patients carefully selected for dialysis survive longer than those treated conservatively. However, a RSC service utilising the skills of palliative medicine ensures symptom control and QOL without dialysis to the level of those receiving usual nephrology care including dialysis. These data support a role for palliative (supportive) care and can assist nephrologists counselling elderly patients regarding appropriateness and likely outcomes if dialysis is not employed.

**Funding:** Pharmaceutical Company Support - Amgen Australia

FR-OR047

Dignity and Quality of Life in End Stage Renal Disease Patients, Close to the End of Life

**Background:** Maintaining dignity of patients in end-of-life (EOL) situations has been a foundation of palliative care. An empirical model of dignity (Chochinov et al, 2002), has been used to explore dignity in EOL cancer populations, but no work has yet sought to identify sources of dignity related distress in the End Stage Renal Disease (ESRD) population.

**Methods:** Entry criteria: ESRD patients on dialysis >3 months and between 65 and 80 years of age and their caregivers were consented. Demographics were collected and the disposition of the patient followed for up to two years. Various instruments measuring psychological and existential distress including the Patient Dignity Inventory (PDI), Structured Interview for Symptoms and Concerns. (SISC) and KDQOL, were administered at the onset of the study and 3 months later.

**Results:** 103 patients on dialysis median of 1-3 years from two sites in Canada were enrolled. Sixty percent were male, 52% diabetic, mean age 72.5 years. Eighty-two percent had never had counseling or treatment for an emotional problem. SISC indicated 18.8% patients felt some loss of dignity; 51.6% some degree of suffering, 50.5% feelings of hopelessness. 53.5% endorsed one of more items of the PDI. However more malignant expressions of distress such as; desire for death (9.9%) and thoughts of suicide (14.9%) were less frequent, comparable to terminal ill cancer populations.

**Conclusions:** Suffering and existential distress appears to be quite prominent in this patient population. However, more severe expressions of marked distress are less common. Further research must explore the full experiential landscape of distress, in order to determine appropriate therapeutic approaches.

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

FR-OR048

Phospholipase A, Receptor Antibody Levels Predict Clinical Outcome and Therapeutic Response in Patients with Primary Membranous Nephropathy

**Background:** The prediction of clinical outcome and the decision for an immunosuppressive treatment in patients with Membranous Nephropathy (MN) currently relies on prolonged follow-up measurements of proteinuria. Yet, changes in proteinuria do not necessarily reflect the activity of immunologic disease. A marker which would reflect immunologic and clinical activity in real time and predict clinical outcome could substantially improve the care of patients with MN. Phospholipase A, Receptor antibody (PLA2-R, Ab) levels may serve as such a biomarker.

**Methods:** The correlation of PLAR-R, Ab levels with proteinuria and their predictive value for clinical response was analyzed in a prospective multicenter study including 133 patients with primary MN. The patients were followed for up to 24 months. PLAR-R, Ab levels were assessed at the time of inclusion in the study and at 3 months intervals.

**Results:** During the time of observation 101 patients were treated with immunosuppressants, 32 patients received supportive care only. Following standard immunosuppression PLAR-R, Ab level fell mildly (81% in 3 months), while the decrease in proteinuria was protracted (39% after 3 months). Immunosuppressive regimens (calcineurin inhibitors, alkylating agents or rituximab) did not show differences in the efficacy to reduce PLAR-R, Ab levels. In patients with spontaneous remission of proteinuria, PLAR-R, Ab levels fell (from 197±279 U/ml at study start to 7.6±2 U/ml at 15 months) but remained high in patients who did not show a reduction in proteinuria (from 193±184 U/ml at study start to 98.88±8 U/ml at 15 months). At the time of inclusion in the study there was a significant difference in the PLAR-R, Ab levels between patients who experienced remission of proteinuria after 12 months and those with no remission of proteinuria (Remission: 179±207 U/ml; No remission: 311±297 U/ml).

**Conclusions:** PLAR-R, Ab levels reflect clinical disease activity and predict clinical response in patients with primary MN. PLAR-R, Ab are reliable real time markers of disease activity in patients with primary MN and may affect clinical outcome.

FR-OR049

Measurement of AntiPLA2R Antibodies Predicts Relapse Rate after Immunosuppressive Therapy in Patients with Idiopathic Membranous Nephropathy

**Background:** Antibodies against the phospholipase A2 receptor (PLA2R-ab) are present in 70% of patients with idiopathic membranous nephropathy (IMN). During immunosuppressive therapy a decrease of PLA2R-ab precedes remission of proteinuria. The clinical value of repeated PLA2R-ab measurements is unknown. Aim of this study is to evaluate if PLA2R-ab levels at the end of immunosuppressive treatment predict relapse rate in IMN.

**Funding:**"
Methods: We evaluated patients with iMN, and positive PLAR2-ab, who were treated with immunosuppression, and developed a remission. PLAR2-ab levels were measured with ELISA (Kanigicherla et al, 2013, KJ) in serum samples collected at baseline and at the end of treatment.

Results: In total 26 patients were included (18 male). Treatment consisted of cyclophosphamide (n=11), MMF (n=8), or ACTH (n=7). At the start of treatment, the median eGFR was 59 ml/min/1.73m² (IQR 49-74), serum albumin 25 g/l (IQR 19-30) and PLAR2-ab 201 U/l (IQR 122-314). At the end of therapy, 27% of patients still were PLAR2-ab positive. During follow-up 35% of all patients developed a relapse of proteinuria (> 3.5 g/day with ≥ 50% increase from lowest level during remission) within 5 years after therapy. The risk of relapse in patients with PLAR2-ab positivity at end of treatment was significantly higher when compared to patients in whom PLAR2-ab had disappeared (relapse rate 21% versus 71%, p < 0.01).

Conclusions: PLAR2-ab remained elevated in a significant number of patients with iMN treated with immunosuppressive therapy. The persistence of antibodies was associated with a higher relapse rate. Our observations suggest that measurement of PLAR2-ab may guide duration of therapy in patients with iMN.

FR-OR505
Changes in Plasma Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR) Levels Correlate with Naïve T-Regulatory and Monocyte Subset Populations in Nephrotic Children with Focal Segmental Glomerulosclerosis (FSGS) following Rituximab Therapy

Woo Song Yeo,1 Chang Yien Chan,1 Changli Wei,1 Jochen Reiser,2 Subhra K. Biswas,1 Hui Kim Yap,1 1Pediatrics, National Univ of Singapore, Singapore; 2Internal Medicine, Rush Univ, Chicago, IL; 1Singapore Immunology Network, A*STAR, Singapore.

Background: Recent studies suggest suPAR as the plausible circulating factor in FSGS. In recent years, rituximab has been used in patients with nephrotic syndrome who have failed therapy with conventional immunosuppressants. This study aimed to examine the effect of rituximab in children with FSGS on plasma suPAR levels and identify the source of suPAR by correlating suPAR trends with various immunological subsets.

Methods: Eleven nephrotic children with FSGS were given 2-weekly doses of rituximab at a dose of 375 mg/m² for 1-4 doses. Urinary/blood biochemistry and immunological subsets (Th, B, NK, cells, and monocytes) with corresponding plasma suPAR levels were monitored throughout the study. Statistical analysis was done using Mann-Whitney U test and Spearman's correlation.

Results: Five (45%) patients achieved complete response defined as urine protein:creatinine ratio of <0.02 g/mmol and ability to wean off at least 2 immunosuppressants. This study aimed to examine the efficacy of action of rituximab in FSGS patients who failed therapy due to steroid resistance. Five (45%) patients achieved complete response defined as urine protein:creatinine ratio of <0.02 g/mmol and ability to wean off at least 2 immunosuppressants. Complete responders showed a negative correlation between complete responders and suPAR levels (r=-0.85, p<0.001), as well as mean change in monocyte subsets (CD14dimCD16+ and CD14+CD16+) (ΔMNCs) (r=0.65, p=0.042). ΔMNCs also demonstrated a significant negative correlation with ΔMNCs (r=-0.75, p=0.013).

Conclusions: Our study suggested that the efficacy of action of rituximab in FSGS may be mediated via decrease in plasma suPAR levels, and this may be related to monocyte subset changes, regulated by naïve T-regulatory cells.

Funding: Government Support - Non-U.S.

FR-OR52
Solute Urokinase Receptor (suPAR) Is Not a Clinical Marker for Focal Segmental Glomerulosclerosis

Biorn Meijers,1 Ruben Poesen,1 Markus Stoor,2 Kathleen Claes,3 Dirk R. Kuypers,2 Pieter Evenepoel,3 Nephrology, Univ Hospitals Leuven, Belgium; 2Gambro Dialysatoren GmbH, Hechingen, Germany.

Background: Solute urokinase receptor (suPAR) promotes proteinuria and induces glomerular focal segmental glomerulosclerosis (FSGS)-like lesions in mice. Furthermore, a serum suPAR concentration cut-off of 3000 pg/mL has been proposed as clinical biomarker for FSGS patients. Interestingly, several studies in patients with glomerulopathy demonstrated an inverse correlation between the eGFR and suPAR concentrations. As patients with FSGS present at different eGFR, we studied the relationship between eGFR and suPAR in a large cohort of non-FSGS patients.

Methods: We measured suPAR concentrations in patients with chronic kidney disease (CKD) from the Leuven mild-to-moderate CKD study (Clinical trials protocol NCT00414623) using the human suPAR enzyme-linked immunosorbent assay (ELISA, R&D systems). Variables determining suPAR concentrations were identified using multivariate regression analysis.

Results: We determined suPAR concentrations in 486 patients with known non-FSGS CKD (controls), and in 18 patients with biopsy-proven FSGS (cases: 6 active disease, 2 partial remission and 10 complete remission). In multivariate analyses, eGFR was the strongest determinant of suPAR concentrations (P<0.0001, R²=0.46). suPAR concentrations exceeded the proposed cut-off for FSGS of 3000 pg/mL in 17%, 39% and 88% in patients with eGFR of less than 30, 45-60 and 30-45 ml/min/1.73 m², respectively. In patients with eGFR of less than 30, suPAR concentrations exceeded the proposed cut-off in 95% of patients. suPAR levels of patients with biopsy-proven FSGS were interspersed with non-FSGS controls and for any given eGFR did not discriminate FSGS cases from non-FSGS controls.

Conclusions: This study does not support an absolute cut-off of suPAR concentration as biomarker for FSGS. Our data moreover question the validity of relative, i.e. eGFR-dependent, suPAR cut-off values.

FR-OR53
Randomized Controlled Trial of Low-Dose Intravenous Cyclophosphamide versus Oral Mycophenolate Mofetil in Treatment of Lupus Nephritis

Aay Goyal,1 Manish Rathi,1 Vivekanand Jha,2 Aman Sharma,2 Kusum Joshi,3 Ritambhara Nanda,1 Vinay Sakhuja,1 1Nephrology, PGIMER, Chandigarh, India; 2Internal Medicine, PGIMER, Chandigarh, India; 3Pathology, PGIMER, Chandigarh, India.

Background: Several recent controlled trials establish Mycophenolate Mofetil (MMF) as one of the first-choice drugs for inducing a remission in lupus nephritis. However, in most of these trials MMF was compared with either oral or high dose monthly pulses of intravenous cyclophosphamide (CYC). The current study was aimed at comparing the efficacy and safety of MMF with low-dose intravenous CYC (Euro-Lupus regimen) in these patients.

Methods: The study was an open label, prospective, randomized, two-arm study which included patients who had a kidney biopsy diagnosis of lupus nephritis (Class III/ IV). Out of 94 patients who were screened for inclusion, 53 patients were randomized to receive either low dose intravenous CYC (6 fortnightly pulses at a fixed dose of 500 mg) or MMF (target dosage 3g/day) as induction treatment for a period of 24 weeks in addition to steroids. The primary end point was a pre-specified decrease in proteinuria and
stabilization or improvement in serum creatinine. Secondary end points included complete renal remission, systemic disease activity (by Safety of Exogenous Estrogens in Lupus Erythematosus National Assessment/Systemic Lupus Erythematosus Disease Activity Index) and adverse events.

Results: At the end of 24 weeks, both groups had similar response rates. In the intention-to-treat analysis, 19 of the 26 patients (73.1%) who received CYC and 19 of the 27 patients receiving MMF (70.4%) showed a response (primary end point) (95% CI, 0.34–3.78%; p=0.83). Complete remission was achieved in 13 of the 26 patients (50.0%) and 13 of the 27 patients (48.1%), respectively (p=0.89). Gastro-intestinal symptoms and infections occurred in significantly lesser number of patients in CYC group as compared to MMF group. Four patients (1 in CYC group and 3 in MMF group) died during the study period.

Conclusions: MMF had similar efficacy in comparison to low dose intravenous CYC in terms of response and remission rates, however, it was associated with more adverse events.

FR-OR054
Long Term Follow Up of Patients Who Received Repeat Dose Rituximab as Maintenance Therapy for ANCA Associated Vasculitis (AAV)

Vasculitis and Lupus Clinic, Addenbrooke’s Hospital, Cambridge, United Kingdom.

Background: Rituximab (RTX) is an established induction agent in AAV. We previously showed that repeat dose RTX for two years is a potential maintenance strategy. Relapse risk after repeat dose RTX discontinuation is not known.

Methods: We report long term follow up of patients who received a two year repeat dose RTX regimen for relapsing/refractory AAV (1g x 2, then 1g/6 months x 4). Results: Sixty-nine patients completed the two year RTX course, during the treatment course 9 (13%) relapsed. Median time post-treatment follow-up was 22.7 months (IQR 12.5-38.6). 25 relapsed after a median of 30.6 months (95%CI 18.4-42.7). For relapse treatment, 20 received RTX and five other agents. By 6 months, 21/25 (88%) had regained remission. 54/69 were ANCA negative at the end of the RTX course. 12 (22%) became ANCA positive during follow up, of which 9 (75%) relapsed a median of 1.6 months (0.5-4.6) after 15 remained ANCA positive after the RTX course, of which 3 (20%) relapsed. Thus, 12/25 (48%) had detectable ANCA at relapse. Switch of ANCA to positive conferred an 11.81 fold increased risk of relapse compared to those whom maintain their ANCA status (p=0.001). Of 56 patients (81%) with available B-cell counts, 42 (75%) had B-cell return a median of 11 months (IQR 9-13) after the RTX course. 17/25 (68%) had detectable B cells at relapse, and in 11/17 (65%) B cells had returned in the 6 months preceding relapse. The patients experiencing B-cell return within 12 months had a significant shorter relapse free survival compared to the ones whose B-cell returned after 12 months.

Conclusions: Following a two year RTX course, relapse risk was lower than that seen following a single RTX course for relapsing GPA. A switch from ANCA negativity to positivity and earlier B cell return were relapse predictors.

FR-OR055
Rituximab and Cyclophosphamide Decreases Dialysis and Death Rates in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

Background: Current evidence for use of rituximab (RTX) in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis (AAV) has not shown improvement in hard outcomes including dialysis or death.

Methods: 100 patients with AAV (1991-2011) who received RTX, cyclophosphamide (CYC) and corticosteroids without RTX for treatment. End-stage renal disease (ESRD) at onset was excluded. Comparisons were done by Fisher’s exact test for categorical and Kruskal-Wallis test for continuous variables. Multivariable Cox Regression was used. Incidence per person-year of follow-up was calculated.

Results: 166 RTX courses were given to 100 patients who had previously or concurrently received CYC. 4 patients had RTX at induction, 18 for resistance to CYC, 123 for relapse and 21 for remission maintenance. Incidence of infection was higher in patients treated with CYC alone than patients also treated with RTX (0.29 95% CI [0.19, 0.21]; 0.13 95% CI [0.12, 0.15], respectively, p=0.001); likewise severe infection (0.24 95% CI [0.21, 0.28]; 0.17 95% CI [0.13, 0.22], respectively p=0.0150). Those treated with RTX and CYC were less likely to reach death or dialysis than those treated with CYC alone which remained significant controlling for age, MPO/P3 ANCA positivity, lung or upper respiratory involvement and entry creatinine.

Conclusions: Compared to the ones whose B-cell returned after 12 months.

FR-OR056
Genetic Analysis of the Coagulation Pathway in Atypical Hemolytic Uremic Syndrome

Background: Atypical Hemolytic Uremic Syndrome (aHUS) is a complement-driven disease. Approximately 40% of patients carry single mutations in CHI, C3, CPI, CFB or CD46; multiple mutations are identified in 3% of patients. We hypothesized that additional genetic risk factors for aHUS could be identified by screening all genes in the coagulation pathway. We used targeted genomic enrichment and massively parallel sequencing (TGE=MPSS) to screen all coding exons of the 85 genes that comprise the coagulation and complement pathways.

Methods: 47 patients with sporadic aHUS patients were included in this study. TGE was performed using an RNA-bait panel and MPSS of captured libraries was completed on a HiSeq2000 and a MiSeq. Data were analyzed using a local installation of the open-source Galaxy software running on a high-performance computing cluster at the University of Iowa.

Results: Mean total reads per sample approximated 9,000,000, with >97% mapping to the reference genome and >50% mapping to targeted regions. Average coverage-per-targeted-base was larger than 1600 reads; 99% of targeted regions had 30x coverage. Of the 9,966 variants identified, 9,424 (94.56%) passed quality control. After filtering for frequency and predicted functionality, 25 novel and 101 non-synonymous variants (nsRVs) remained. 55 of these variants were known or predicted to be deleterious and were carried by 32 patients. 27 of these 55 variants were found in previously reported aHUS genes, 16 were found in other complement-related genes, and 16 were found in coagulation pathway genes. The greatest number of deleterious variants was found in C5H and the second greatest number was found in PLG. Rare variants in CFB (rs143259927, Fisher Exact P = 0.001) and PLAU (rs357744193, Fisher Exact P = 0.01) were also significantly correlated with the disease.

Conclusions: As expected, most deleterious variants (39 of 55) were found in complement genes implicated in the pathogenesis of aHUS. However, variants in coagulation pathway genes, especially in antithrombotic genes PLAU, PLG, PROC and ADAMTS13, were also found in aHUS patients implicating this pathway in the pathogenesis of aHUS.

Funding: NIDDK Support

FR-OR057
Eculizumab (ECU) Inhibits Thrombotic Microangiopathy (TMA) and Improves Renal Function in Adult Atypical Hemolytic Uremic Syndrome (aHUS) Patients (Pts)

Background: Eculizumab (ECU) is approved for the treatment of aHUS. Here, we report safety and efficacy results of ECU in adult pts from the largest prospective study performed in aHUS.

Funding: NIDDK Support
Results: 41 pts enrolled and 38 (93%) received 26 wks of treatment. 30 pts (73%) were newly diagnosed (median duration to treatment initiation of 2 weeks). Six pts had no PE/PI during the current clinical manifestation. At wk 26, 30 pts (73%) achieved the primary endpoint.

Conclusions: We demonstrate increased renal oxygen utilization in the CLP rats despite lower GFR and reabsorptive load leading to hypoxia. We also demonstrate dissociation between excess oxygen consumption and ATP generation in CLP mitochondria, which can explain the inefficiency in oxygen utilization. We are investigating alterations in mitochondrial dynamics which could explain mitochondrial dysfunction and tubular injury, and the role of HIF-1a pathway in ameliorating mitochondrial dysfunction and consequently global renal function.

Funding: NIDDK Support

FR-OR059
Even Delayed Therapy with the Mitochondria-Targeted Antioxidant Mito-TEMPO Ameliorates Sepsis-Induced Acute Kidney Injury
Naeem K. Patil, Lee Ann MacMillan-Crow, Philip R. Mayeux, Univ of Arkansas for Medical Sciences, Little Rock, AR.

Background: Sepsis is characterized by severe systemic inflammatory response to a microbial infection. Acute kidney injury (AKI) is a frequently encountered complication of sepsis and leads to a high mortality rate ~70%. Human and animal studies suggest that mitochondrial dysfunction plays an important role in sepsis induced multi-organ failure, but the importance of mitochondrial dysfunction in renal injury during sepsis has not been well studied.

Methods: We used a clinically relevant cecal ligation and puncture (CLP) murine model of sepsis to assess renal mitochondrial function. High resolution respirometry was used to measure mitochondrial complex respiration. Intravital video microscopy was used to study oxidant generation and renal microcirculation.

Results: As early as 4h after CLP, the activity of manganese superoxide dismutase (MnSOD) was decreased by 50% and inhibition was sustained through 36h. This was associated with increased mitochondrial superoxide levels, implying compromised mitochondrial antioxidant defense. CLP also caused a time-dependent decrease in renal mitochondrial complex I and II/III respiration and a reduction in renal ATP levels. Thus, we hypothesized that a mitochondrial specific antioxidant Mito-TEMPO (MT) could protect renal mitochondria and attenuate sepsis-induced AKI. Dose-response studies with 3, 10 and 30mg/kg ip showed that 10mg/kg was the most efficacious dose that decreased renal mitochondrial superoxide levels after CLP. Thus, this dose was used in a clinically relevant delayed dosing paradigm. MT given at 6h post CLP decreased mitochondrial superoxide levels, protected complex I and II respiration, restored MnSOD activity and improved renal microcirculation by 18h. Importantly, delayed therapy with MT significantly increased the 96h survival rate from 40% in untreated septic mice to ~83%.

Conclusions: Mitochondrial dysfunction is a critical event in sepsis induced AKI and even delayed therapy with mitochondria-targeted antioxidant MT represents a promising approach to treat septic AKI. Supported by NIH DK075991 (PRM) and AHA 12PRE12040174 (NKP).

Funding: NIDDK Support, Private Foundation Support

FR-OR060
Enhanced Glycolytic Activity and Mitochondrial Dysfunction in a Mouse Model of Sepsis-Induced Acute Kidney Injury
Joshua Andrew Smith, Prabhleen Singh, Koji Aoyama, Joanna Thomas, Medicine, UCSD & VASDHS, San Diego, CA.

Background: Sepsis-associated AKI is frequently observed and has poor prognosis. The lack of complete understanding of its pathogenesis is a significant barrier to progress and fresh insights into its pathogenesis are critically needed.

Methods: We examined renal oxygen delivery and consumption and mitochondrial function in the cecal ligation and puncture (CLP) model of sepsis in rats. RBF, GFR, and kidney oxygen consumption (QO2) were measured at 6 and 24 hours post CLP or sham surgery. Mitochondrial QO2, ATP generation, HIF1alpha expression and response were measured in renal cortex at 6 and 24 hours post-CLP. We used a clinically relevant cecal ligation and puncture (CLP) murine model of sepsis to assess renal mitochondrial function. High resolution respirometry was used to measure mitochondrial complex respiration. Intravital video microscopy was used to study oxidant generation and renal microcirculation.

Results: As early as 4h after CLP, the activity of manganese superoxide dismutase (MnSOD) was decreased by 50% and inhibition was sustained through 36h. This was associated with increased mitochondrial superoxide levels, implying compromised mitochondrial antioxidant defense. CLP also caused a time-dependent decrease in renal mitochondrial complex I and II/III respiration and a reduction in renal ATP levels. Thus, we hypothesized that a mitochondrial specific antioxidant Mito-TEMPO (MT) could protect renal mitochondria and attenuate sepsis-induced AKI. Dose-response studies with 3, 10 and 30mg/kg ip showed that 10mg/kg was the most efficacious dose that decreased renal mitochondrial superoxide levels after CLP. Thus, this dose was used in a clinically relevant delayed dosing paradigm. MT given at 6h post CLP decreased mitochondrial superoxide levels, protected complex I and II respiration, restored MnSOD activity and improved renal microcirculation by 18h. Importantly, delayed therapy with MT significantly increased the 96h survival rate from 40% in untreated septic mice to ~83%.

Conclusions: Mitochondrial dysfunction is a critical event in sepsis induced AKI and even delayed therapy with mitochondria-targeted antioxidant MT represents a promising approach to treat septic AKI. Supported by NIH DK075991 (PRM) and AHA 12PRE12040174 (NKP).

Funding: NIDDK Support, Private Foundation Support

FR-OR058
Mitochondrial Dysfunction in Sepsis-Associated Acute Kidney Injury
Prabhleen Singh, Koji Aoyama, Joanna Thomas, Medicine, UCSD & VASDHS, San Diego, CA.

Background: Sepsis-associated AKI is frequently observed and has poor prognosis. The lack of complete understanding of its pathogenesis is a significant barrier to progress and fresh insights into its pathogenesis are critically needed.

Methods: We examined renal oxygen delivery and consumption and mitochondrial function in the cecal ligation and puncture (CLP) model of sepsis in rats. RBF, GFR, and kidney oxygen consumption (QO2) were measured at 6 and 24 hours post CLP or sham surgery. Mitochondrial QO2, ATP generation, HIF1alpha expression and response were measured in renal cortex at 6 and 24 hours post-CLP. We used a clinically relevant cecal ligation and puncture (CLP) murine model of sepsis to assess renal mitochondrial function. High resolution respirometry was used to measure mitochondrial complex respiration. Intravital video microscopy was used to study oxidant generation and renal microcirculation.

Results: As early as 4h after CLP, the activity of manganese superoxide dismutase (MnSOD) was decreased by 50% and inhibition was sustained through 36h. This was associated with increased mitochondrial superoxide levels, implying compromised mitochondrial antioxidant defense. CLP also caused a time-dependent decrease in renal mitochondrial complex I and II/III respiration and a reduction in renal ATP levels. Thus, we hypothesized that a mitochondrial specific antioxidant Mito-TEMPO (MT) could protect renal mitochondria and attenuate sepsis-induced AKI. Dose-response studies with 3, 10 and 30mg/kg ip showed that 10mg/kg was the most efficacious dose that decreased renal mitochondrial superoxide levels after CLP. Thus, this dose was used in a clinically relevant delayed dosing paradigm. MT given at 6h post CLP decreased mitochondrial superoxide levels, protected complex I and II respiration, restored MnSOD activity and improved renal microcirculation by 18h. Importantly, delayed therapy with MT significantly increased the 96h survival rate from 40% in untreated septic mice to ~83%.

Conclusions: Mitochondrial dysfunction is a critical event in sepsis induced AKI and even delayed therapy with mitochondria-targeted antioxidant MT represents a promising approach to treat septic AKI. Supported by NIH DK075991 (PRM) and AHA 12PRE12040174 (NKP).

Funding: NIDDK Support, Private Foundation Support

FR-OR060
Enhanced Glycolytic Activity and Mitochondrial Dysfunction in a Mouse Model of Sepsis-Induced Acute Kidney Injury
Joshua Andrew Smith, L. Jay Stallons, Rick G. Schnellmann, Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.

Background: Sepsis is a common cause of acute kidney injury (AKI), accounting for approximately half of AKI cases in the ICU. Recent evidence indicates that sepsis-induced mitochondrial dysfunction is a critical event in sepsis induced AKI. We hypothesized that glycolysis would be enhanced and mitochondrial dysfunction would occur.

Methods: Male C57BL/6 mice were treated with lipopolysaccharide (LPS, 10 mg/kg, i.p.) and kidneys harvested (3, 6, and 18 h post-LPS). Renal function was determined by measuring blood urea nitrogen (BUN) and urine output. Mitochondrial electron transport chain and glycolytic mRNAs and proteins in the renal cortex were assessed by qRT-PCR and immunoblot analysis. Standard biochemical assays were used to determine renal cortical hexokinase (HK), phosphofructokinase (PFK), and pyruvate kinase (PK) activities.

Results: LPS administration resulted in AKI with increased BUN and reduced urine output at 18 h post-LPS. Transcript levels of mitochondrial markers (PGC-1a, ATP5b, NDUF5, and COX1) were reduced >50% 18 h post-LPS treatment. Expression of HK2 mRNA increased (~2-fold) in these mice, while expression of other glycolysis-related mRNAs remained unchanged (glut1, pklk, pkm, and ldha) or decreased (pfkm, pgk1, and pdk1). Immunoblot analysis revealed no changes in protein levels of glycolytic enzymes (hkg1, hkg2, pfk, pkp, pmk1/2, and ldha). However, the 3-fold increase in HK activity was observed 3 h after LPS exposure and was maintained over 18 h.

Conclusions: Renal hexokinase activity rapidly increases in conjunction with the loss of mitochondrial function following LPS exposure. These findings suggest that glycolysis may be induced to maintain ATP levels and renal function in sepsis-induced AKI.

Funding: Other NIH Support - 5R01GM084147-04, Veterans Affairs Support
**FR-OR061**

**Muc1 Is Protective in a Mouse Model of Acute Kidney Injury**  
Rebecca P. Hughey,1 Sheldon Bastacky,2 Kenneth R. Hallows,2 Nuria M. Pastor-Soler,2 Timothy A. Sutton.2  
1Dept of Medicine, Renal- Electrolyte Div, Univ of Pittsburgh School of Medicine, Pittsburgh, PA; 2Dept of Medicine, Div of Nephrology, Indiana Univ School of Medicine, Indianapolis, IN; 2Div of Anatomic Pathology, Dept of Pathology, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.

**Background:** Ischemia-reperfusion injury (IRI) due to hypotension or sepsis is the most common cause of acute kidney injury (AKI). Human MUC1 is an apical transmembrane protein expressed in the distal tubules and collecting ducts of the adult kidney. MUC1 is induced by hypoxia and directly interacts with both HIF-1 and β-catenin in the nucleus where MUC1 transactivates these protective pathways and modulates metabolic adaptations and promotes cell survival.

**Methods:** To assess the function of Muc1 during AKI, we used a model of IRI in Muc1 knockout (KO) and congenic control C7BL/6 mice. Both renal pedicles of mice were clamped for 19 min prior to recovery periods of 0, 4, 24 and 72 h when blood and kidneys were recovered.

**Results:** Profiles of serum creatinine and BUN were significantly higher in the profile from Muc1 KO than control mice consistent with increased kidney damage and delayed recovery of kidney function in the absence of Muc1. This difference was readily apparent in several cancer cell lines. Immunoblot analysis of kidney extracts revealed a significant increase in Muc1 levels consistent with its induction by hypoxia. We observed Muc1-dependent changes in glycolytic enzymes (e.g., LDHA) and kinases (e.g., PDK1 and PKM2) involved in the hypoxia-induced switch of glucose metabolism from oxidative to glycolytic, consistent with Muc1 transactivation of the HIF-1 pathway. This was supported by finding an accentuated and prolonged activation of AMPK in the kidneys of Muc1 KO mice after IRI when compared to controls, reflecting energy stress. As PKM2 also transactivates the β-catenin pathway we discovered significant Muc1-dependent increases in β-catenin and its downstream target consistent with a role for Muc1 in cell survival.

**Conclusions:** Altogether the data indicate that Muc1 is required for both efficient adaptation of glucose metabolism in response to IRI to avoid energy stress and for promoting tubule survival and recovery.

**Funding:** NIDDK Support, Other NIH Support - DCl, Inc.

---

**FR-OR062**

**Increasing GMP-Dependent Protein Kinase I Activity Attenuates Cisplatin-Induced Kidney Injury through Protection of Mitochlondrion Function**  
Shuxia Wang. Nutritional Sciences, Univ of Kentucky, Lexington, KY.

**Background:** Cisplatin is widely used to treat malignancies. However, its major limitation is the development of dose-dependent nephrotoxicity. The precise mechanisms of cisplatin-induced kidney damage remain unclear, and the renoprotective agents during cisplatin treatment are still lacking.

**Methods:** Both in vitro proximal tubular cell culture and in vivo ischemia-reperfusion-induced acute kidney injury mouse model were utilized. In addition, genetic as well as pharmacological approach was used to increase GMP-dependent protein kinase activity in mice and the development of acute kidney injury in these mice was determined.

**Results:** We demonstrated that the expression and activity of GMP-dependent protein kinase (GK) in proximal tubular cells was significantly increased in cisplatin-treated mice as well as in the kidney tissues from cisplatin treated mice in vivo. Increasing PKG activity by both pharmacological and genetic approaches attenuated cisplatin-induced kidney cell apoptosis in vitro. This was accompanied by decreased Bax/Bcl2 ratio, caspase 3 activity, and cytokine levels. Cisplatin-induced mitochondrial membrane potential loss in the tubular cells was also prevented by increased PKG activity. All of these data suggest a protective effect of PKG on mitochondria function in renal tubular cells. Importantly, increasing PKG activity pharmacologically or genetically diminished cisplatin-induced tubular damage and preserved renal function during cisplatin treatment in vivo. Mitochondria structural and functional damage in the kidney from cisplatin treated mice was inhibited by increased PKG activity. In addition, increasing PKG activity enhanced cisplatin induced cell death in several cell lines.

**Conclusions:** These results suggest that increasing PKG activity may be a novel option for renoprotection during cisplatin-based chemotherapy.

**Funding:** NIDDK Support, Veterans Affairs Support

---

**FR-OR063**

**Conditional Proximal Tubule Mitofusin 2 Knockout (cPT-MFN2 KO) Accelerates Renal Recovery and Improves Survival after Ischemia**  
Zhiying Yang, Jonathan M. Gall, Ramon G. Bonegio, Andrea Havasi, John H. Schwartz, Steven C. Borkan. Renal Section, Boston Univ Medical Center; Boston, MA.

**Background:** Elimination of MFN 2, a major mitochondrial elongation protein, sensitizes proximal tubule (PT) cells to Bax-mediated death after in vitro stress. To assess its role in the intact kidney, the effect of cPT-MFN2 KO was evaluated after renal ischemia in vivo.

**Methods:** cPT-MFN2 KO mice were generated by crossing MFN2 floxed mice (MFN2flx) with animals harboring a testosterone activated, PT-specific KAP2-Cre. These mice were supplemented with exogenous testosterone to enhance conditional PT MFN2 knockout prior to ischemia induced by bilateral renal pedicle occlusion. Testosterone treated parental line mice served as control. MFN2KO in cultured cells was achieved by exposing primary PT cells harvested from MFN2flx mice to Cre expressing adenovirus.

**Results:** Compared to control, testosterone exposure in MFN2flx-MFN2 KO mice selectively decreased PT MFN2 expression and resulted in short, punctate mitochondria in renal cortical PT cells. After transient renal ischemia induced AKI, only 28% of testosterone-treated control mice survived (n=18). In contrast, 86% of cPT-MFN2-KO animals survived (n=20; P<0.001). Enhanced survival in cPT-MFN2 KO mice was associated with a significantly lower peak BUN on days 1-2 post injury. Although histologic injury score did not differ between groups, cPT-MFN2-KO mice exhibited a four-fold increase in cell proliferation restricted to the renal cortex, the region targeted by the conditional MFN2 KO (P<0.05). Preliminary studies in primary PT cells suggest that MFN2 KO enhances proliferation by increasing RAS-dependent, ERK-1/2 activation. MFN2 binds p21 RAS, linking cell MFN2 to ERK-1/2 mediated PT cell proliferation.

**Conclusions:** These results support the hypothesis that MFN2 KO enhances survival by simultaneously increasing the removal of damaged PT cells, apoptosis and accelerating repair of injured tubular epithelium after ischemia AKI.

**Funding:** NIDDK Support

---

**FR-OR064**

**Activation of AMP-Activated Protein Kinase Contributes to Cisplatin-Induced Acute Kidney Injury**  
Yanlin Wang, Xiaogao Jin. Dept of Medicine, Div of Nephrology, Baylor College of Medicine, Houston, TX.

**Background:** Cisplatin, a commonly used anti-cancer drug, has been shown to induce acute kidney injury, which limits its clinical use in cancer treatment. Emerging evidence has suggested that AMP-activated protein kinase (AMPK), which functions as a cellular energy sensor, is activated by various cellular stresses. However, the potential role of AMPK in cisplatin-induced acute kidney injury has not been studied.

**Methods:** We used mouse renal proximal tubular epithelial cells to examine the role of AMPK signaling in cisplatin-induced apoptosis in vitro and we treated mice with Compound C, a selective AMPK inhibitor, to determine the role of AMPK in cisplatin-induced acute kidney injury in vivo.

**Results:** Our results demonstrated that cisplatin activated AMPK (Thr172 phosphorylation) in cultured renal tubular epithelial cell in a dose- and time-dependent manner, which led to p53 phosphorylation, Bax induction, caspase 3 activation, and apoptosis. Compound C, a selective AMPK inhibitor, abolished cisplatin-induced AMPK activation and p53 phosphorylation and apoptosis. Furthermore, silence of AMPK expression by siRNA attenuated cisplatin-induced apoptosis through inhibiting p53 phosphorylation, Bax induction, and Caspase 3 activation. Conversely, AICAR, a selective AMPK activator, dose-dependently induced p53 phosphorylation and subsequent Bax induction and apoptosis. AMPK is activated in the kidney in cisplatin treated mice. Cisplatin-induced renal dysfunction and tubular epithelial cell apoptosis in vivo were attenuated by treatment with Compound C.

**Conclusions:** Our results indicate that AMPK signaling plays a pivotal role in the development of cisplatin-induced renal injury through regulation of P53-Bax apoptosis pathway. These findings suggest that inhibition of AMPK signaling could be a novel target for the prevention and treatment of acute kidney injury.

**Funding:** NIDDK Support

---

**FR-OR065**

**Preconditioning Mouse Proximal Tubular Cells with Pharmacologic Activators of AMP-Activated Protein Kinase Ameliorates Apoptosis Induced by Subsequent Metabolic Stress**  
Wifred Lieberth,1 Lei Jiang,1 Jerrold S. Levine.2 1Medicine, Stony Brook Medical Center, Stony Brook, NY; 2Medicine, Univ of Chicago at Illinois, Chicago, IL.

**Background:** We have previously reported that AMP-activated protein kinase (AMPK) is activated when mouse proximal tubular (MPT) cells are subjected to metabolic stress, and plays a role in ameliorating stress-induced apoptosis of these cells (Lieberth et al.: AJP, 301:F1177, 2011). We now test the hypothesis that preconditioning MPT cells with pharmacologic activators of AMPK, can reduce apoptosis induced by subsequent metabolic stress. We also compare the efficacy of two novel AMPK activators (A768662 and RSV A314) with that of AICAR, an AMPK activator used for many years to elucidate the functions of AMPK.

**Methods:** MPT cells were preconditioned with AICAR, A-768662, or RSV A314. After preconditioning, the cells were subjected to metabolic stress by inhibiting mitochondrial function using antimycin A.

**Results:** Preconditioning MPT cells with AMPK activators was found to: 1) increase the expression of Glul and hexokinase II; 2) stimulate lactate production; 3) reduced the fall in cell ATP levels induced by metabolic stress and 4) ameliorate stress-induced apoptosis of MPT cells. All these effects of preconditioning were substantially greater with A768662 and RSV A314 than with AICAR.

**Conclusions:** Preconditioning MPT cells with AMPK activators substantially ameliorates apoptosis induced by subsequent metabolic stress. This beneficial effect of preconditioning appears due to the stimulation of glycolysis, and to a consequent conservation of cell energy stores during metabolic stress. Furthermore, A768662 and RSV A314 are more effective preconditioning agents than AICAR.

**Funding:** Veterans Affairs Support

---

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

---

51A
Deleterious Role of the Polyol Pathway and Fructokinase Activation in the Proximal Tubule in Mice Undergoing Ischemic Acute Kidney Injury

Miguel A. Lanasa, Ana Andres-Hernando, Cristina Ciccheri, Shinchiro Inaba, Sarah Faubel, Richard J. Johnson. Medicine, Div of Renal Disease and Hypertension, Univ of Colorado Denver, Aurora, CO.

Background: Despite important discoveries in the pathophysiology of acute kidney injury, no clinically applicable treatment to accelerate kidney recovery has emerged and new targets are needed. Our published data show that the metabolism of dietary fructose by fructokinase (KHK) results in ATP depletion and the generation of uric acid and oxidants causing acute tubulointerstitial injury. Here we show that besides dietary intake, fructose is endogenously produced from glucose by the polyol pathway in the renal cortex of mice undergoing ischemic acute kidney injury (IAKI). The aim of this study is to determine the specific role of this endogenous fructose and its metabolism by KHK in IAKI.

Methods: iAKI was induced by renal pedicle clamping in wild type (WT) or KHK knockout (KHK-KO) mice. Sham operation referred to renal pedicle exposure without clamping. iAKI was assessed by determination of parameters of renal function (serum creatinine [sCr], BUN levels, and serum and renal levels of the pro-inflammatory cytokine IL6. Furthermore, KHK-KO mice undergoing iAKI had improved renal function compared to WT mice with lower serum creatinine and BUN levels, reduced NGAL levels and improved proximal tubule histology.

Results: Our data demonstrate that fructose generated and metabolized by KHK in proximal tubules during IAKI may have a deleterious role in the pathogenesis of this condition. Therefore, fructokinase (KHK) is a novel potential target for the prevention and treatment of IAKI.

Funding: NIDDK Support

Hypoxia-Inducible Factor-2 in Endothelial Cells Mediates Protection and Recovery from Ischemic Kidney Injury

Pinelopi P. Kapitsinou,1 Hideto Sano,1 Timothy A. Sutton,2 Volker H. Haase.1 Nephrology, Vanderbilt Univ, Nashville, TN; 2Nephrology, Indiana Univ, Indianapolis, IN.

Background: Key mediators of cellular adaption to hypoxia are hypoxia-inducible factor (HIF)-1 and -2, which are regulated by the prolyl hydroxylases (PHDs). Although we know about their cell type-specific expression of AQP2 mainly via Gs/cAMP/PKA signaling. Tankyrase, members of the tumour suppressor family, are known to mediate tankyrases and their prolyl hydroxylases (PHDs). Therefore, we investigated whether HIF-2α in endothelial cells (EC), Vcadherin (Cdh5)-Cre transgenic mice were crossed to mice carrying conditional HIF-1α and/or HIF-2 α alleles. Systemic HIF activation was induced by a prolyl-hydroxylase-inhibitor (PHI), while EC specific activation was achieved by crossing transgenic mice to PHD2 floxed mice. IRi was induced by unilateral/hilar arterial renal clamping.

Results: While at 2hrs and day 1 post IRI, Hif1Hif2-/- showed similar injury to controls, at day3 they demonstrated impaired recovery as shown by higher morphologic injury score, an 1.6-fold increase in CD45 + area in Hif1Hif2-/- at day3 post IRI, which correlated with increased urine osmolality significantly in the first few hours after a single injection.

Conclusions: By HTS screening and subsequent assays, we identified one compound that stimulates AQP2 expression, which induces membrane accumulation, and stimulates urine concentration in a VP-dependent manner. These data show that our chemical screening is effective in identifying novel and unsuspected strategies for the potential treatment of water balance disorders. Its mechanism of action is now under investigation.

Funding: NIDDK Support

Tankyrase/β-Catenin Signaling: A Novel Regulatory Signaling Pathway for Vasopressin-Induced AQP2 Expression in Kidney Collecting Duct Cells

Hyun Jun Jung, Eunjung Kim, Tae-Hwan Kwon. Biochemistry and Cell Biology, School of Medicine, Kyungpook National Univ, Taegu, Korea.

Background: Water channel aquaporin-2 (AQP2) mediates arginine vasopressin (AVP)-induced water reabsorption in the kidney collecting ducts. AVP increases the expression of AQP2 mainly via Gsα/cAMP/PKA signaling. Tankyrases, members of the PARF family, are know to mediate Wnt/ß-catenin-signaling-induced transcription of Wnt-targeting genes. We aimed to examine as to whether tankyrases/ß-catenin signaling play a role in AVP-induced AQP2 expression in kidney collecting ducts.

Funding: NIDDK Support

Modulation of cAMP Signaling, AQP2 Phosphorylation and Osmotic Water Permeability in Response to DDAVP or FK under Tolvaptan Treatment in Renal Cells

Grazia Tamma,1 Annarita Di Mise,1 Marianna Ranieri,1 Peter M.T. Deen,2 Maria Svelto,3 Giovanna Valenti.1 1Dept of Biosciences, Biotechnologies and Biopharmaceutics, Univ of Bari, Bari, Italy; 2Dept of Physiology, Univ, Niijmegen, Netherlands.

Background: The vasopressin receptor antagonist tolvaptan has emerged as tool in the management of hyponatremia. However, no direct evidence that the aquaretic effect of tolvaptan is based on impairment of vasopressin stimulated AQP2 phosphorylation and targeting to the plasma membrane has been provided. Methods: MDCK stably expressing hAQP2 or rat kidney slices were exposed to DDAVP or forskolin (FK) stimulation in the presence or in the absence of tolvaptan (10nM). The effect of these treatments on cAMP levels, AQP2 phosphorylation and osmotic water permeability was analyzed.

Results: In MDCK cells, DDAVP treatment significantly increased cAMP levels and AQP2 phosphorylation. DDAVP pretreatment with tolvaptan significantly reduced both effects. Surprisingly, tolvaptan pretreatment strongly reduced the increase in p256AQP2 elicited by FK, a direct activator of adenylyl cyclase. Similar results were obtained in rat kidney slices. In line, tolvaptan prevented the increase in the osmotic water permeability stimulated by DDAVP or FK in MDCK. We therefore analyzed whether tolvaptan had, per se, a cellular effect. Calibration of cellular calcium in MDCK cells revealed that tolvaptan caused a significant increase in intracellular calcium (tolvaptan 64.0±2.6 m; n= 32±1.7 nm). Since p256AQP2 can be de-phosphorylated by PKA, a calcium dependent serine/threonine phosphatase, rat kidney slices were pretreated with tolvaptan and exposed

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

FR-OR067

High Throughput Screening for Novel Drugs to Treat Nephrogenic Diabetes Insipidus by Stimulating Vasopressin-Independent Aquaporin-2 Membrane Trafficking

Nagohiro Nomura, Paula Nunes, Richard Bouley, Stanley Shaw, Hua Ann Jenny Lu, Dennis Brown. Program in Membrane Biology, Massachusetts General Hospital, Boston, MA.

Background: Nephrogenic diabetes insipidus (NDI) is characterized by loss of urine concentration with no response to vasopressin (VP). In most cases, NDI is caused by loss of plasma membrane accumulation of AQP2 in kidney principal cells due to VP signaling through the VP receptor (V2R). The amount of AQP2 on the plasma membrane is increased by VP, and is determined by a balance of exocytosis and endocytosis. To find novel therapeutic approaches for NDI treatment, we performed high throughput screening (HTS) for chemicals that stimulate AQP2 expression independently of VP/V2R signaling.

Methods: HTS was performed with an exocytosis assay using LLCP51 cells expressing soluble secreted YFP (sYFP) and AQP2. We evaluated exocytosis of AQP2 by quantifying fluorescent sYFP in the medium, and then tested whether identified compounds also induced AQP2 membrane accumulation in other cell lines, including MDCK cells and rat kidney slices in vitro. Positive compounds were injected intraperitoneally into VP-deficient Brattleboro rats, and urine volume and osmolality were measured over 24 h.

Results: We screened 4000 compounds and identified 34 candidate exocytosis enhancers. Finally, 20 "novel" AQP2 enhancers were tested further. Three compounds increased AQP2 membrane accumulation in LLC-PK1 cells and two were also effective in MDCK cells and rat kidney slices. Then we treated Brattleboro rats with each compound. One of them, AG490, a JAK2 kinase and EGFR inhibitor, decreased urine volume and increased urine osmolality significantly in the first few hours after a single injection.

Conclusions: By HTS screening and subsequent assays, we identified one compound that stimulates AQP2 expression, which induces membrane accumulation, and stimulates urine concentration in a VP-independent manner. These data show that our chemical screening is effective in identifying novel and unsuspected strategies for the potential treatment of water balance disorders. Its mechanism of action is now under investigation.

Funding: NIDDK Support

FR-OR068

Deleterious Role of the Polyol Pathway and Fructokinase Activation in the Proximal Tubule in Mice Undergoing Ischemic Acute Kidney Injury

Miguel A. Lanasa, Ana Andres-Hernando, Cristina Ciccheri, Shinchiro Inaba, Sarah Faubel, Richard J. Johnson. Medicine, Div of Renal Disease and Hypertension, Univ of Colorado Denver, Aurora, CO.

Background: Despite important discoveries in the pathophysiology of acute kidney injury, no clinically applicable treatment to accelerate kidney recovery has emerged and new targets are needed. Our published data show that the metabolism of dietary fructose by fructokinase (KHK) results in ATP depletion and the generation of uric acid and oxidants causing acute tubulointerstitial injury. Here we show that besides dietary intake, fructose is endogenously produced from glucose by the polyol pathway in the renal cortex of mice undergoing ischemic acute kidney injury (IAKI). The aim of this study is to determine the specific role of this endogenous fructose and its metabolism by KHK in IAKI.

Methods: iAKI was induced by renal pedicle clamping in wild type (WT) or KHK knockout (KHK-KO) mice. Sham operation referred to renal pedicle exposure without clamping. iAKI was assessed by determination of parameters of renal function (serum creatinine [sCr], BUN levels, and serum and renal levels of the pro-inflammatory cytokine IL6. Furthermore, KHK-KO mice undergoing iAKI had improved renal function compared to WT mice with lower serum creatinine and BUN levels, reduced NGAL levels and improved proximal tubule histology.

Results: Our data demonstrate that fructose generated and metabolized by KHK in proximal tubules during IAKI may have a deleterious role in the pathogenesis of this condition. Therefore, fructokinase (KHK) is a novel potential target for the prevention and treatment of IAKI.

Funding: NIDDK Support
to FK in the presence or absence of calcium (5 mM) a specific inhibitor of PKA. Under these conditions tolvaptan failed to prevent FK-induced increase in p256AQP2 suggesting that tolvaptan, actuates PKA.

Conclusions: Tolvaptan prevents vasopression induced increase in p256AQP2, AQ2P trafficking and increase in osmotic water permeability. Moreover tolvaptan increases basal intracellular calcium, which might have relevant consequences in modulating p256AQP2 levels and therefore the clinical response to the drug.

Funding: Government Support - Non-U.S.

FR-OR071

Aquaporin2 (AQP2) Expression and Phosphorylation in Rats with Severe Salt Wasting and Volume Depletion. Kayvan A. Zahedi, Sharon L. Barone, 1 Manooshar Soleimani. 2

Background: Concomitant ablation of Na-Ci co-transporter (NCC) and pendrin leads to salt wasting, profuse diuresis and severe volume depletion. The carbonic anhydrase inhibitor acetazolamide (ACTZ) inhibits salt absorption in the proximal tubule and down regulates salt wasting, profuse diuresis and severe volume depletion. The carbonic anhydrase inhibitor (CAI) increases fractional renal glucose excretion (FGE) to ~55% in euglycemic mice (Vallon et al 2010). Western blot analyses of kidney extracts from the vehicle and ACTZ/HCTZ treated animals revealed that the levels of total AQP2 and Ser256p-AQP2 were significantly increased in ACTZ/HCTZ treated animals.

Results: Therefore, we examined the expression of AQP2 in vehicle and ACTZ/HCTZ treated rats. Despite severe volume depletion, the latter alterations point to impaired water reabsorption. In urine output in ACTZ/HCTZ treated animals that display severe salt wasting and volume depletion. We propose that the increase in AQP2 in urine output in ACTZ/HCTZ treated animals that display severe salt wasting and volume depletion is due to AQ2P dysfunction.

Conclusions: ACTZ/HCTZ treated animals have reduced levels of total and surface bound/cycling AQ2P (p-AQP2, Ser256p-AQP2) while their cytosolic AQP2 levels are significantly reduced. The inability to conserve water in ACTZ/HCTZ treated animals in the face of volume depletion mimics the situation in NCC/pendrin dko mice and is due to reduced expression of AQP2, its diminished surface expression and impairment of water salvage mechanism. Despite being considered mild agents individually, we propose that the combination of ACTZ and HCTZ is a powerful diuretic regimen.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR072

Abolished Renal Aquaporin Reabsorption in Euglycemic Mice Lacking SGLT1 and SGLT2. Volker Vallon,1 Maria Gerasimova, 1 David R. Powell, 2 Hermann Koepsell,3 Timo M. Riegler. 4

Background: Gene knockdown of the sodium-glucose cotransporter (SGLT2) (Sglt2-/-) increases fractional renal glucose excretion (FGE) to ~55% in euglycemic mice (Vallon 2011), whereas deletion of SGLT1 (Sglt1-/-) increases FGE to ~3% (Gorboud 2012). To further define the role of SGLT1 or of a possible non SGLT1/SGLT2 glucose transporter for renal glucose reabsorption, we generated and characterized mice lacking both SGLT2 and SGLT1 (Sglt2-/-/s). Methods: All mice were fed a glucose-free diet to prevent glucose/galactose salvaging and subsequent diabetes due to complete absence of SGLT2. Food and fluid intake were determined in regular cages. Plasma glucose and urinary glucose to creatinine ratios (UCGR) were determined in non-fasted mice. Renal 17-23 invitro clearance studies with precise determination of GFR/filtered and excreted glucose were performed under terminal anesthesia in Sglt2-/-/s to determine FGE. *P<0.05 vs WT.

Results: Absolute urinary glucose concentrations and UCGR were increased in Sglt2-/-/s compared with wild-type mice (WT) (402±34* vs 1.0±0.1mM; 4906±573* vs. 4±1 μmol/gcreatinine). Plasma glucose levels and therefore the clinical response to the drug.

Funding: Government Support - Non-U.S.

FR-OR073


Background: EF3 ubiquitin-protein ligases confer the specificity to ubiquitylation by recognizing target substrates. Ubiquitylation by HECT E3 ligase, NEDD4, has gained interests as a central mechanism for understanding the regulation of the epithelial sodium channel (ENaC) in the kidney. Although NEDD4 is most abundantly expressed in the kidney, the functionality of collecting ducts, most studies on NEDD4-mediated ubiquitylation to date are focused on NEDD4-specific substrate protein ENaC mainly expressed in the cortical collecting ducts. Herein, we aimed to identify novel substrate proteins of NEDD4 in rat kidney inner medulla.

Methods: All three WW domains-containing fragment protein of rat NEDD4 was made for substrate binding. Interactions between the WW domains and the rat kidney inner medullary homogenates were induced with post-chemical crosslinking (Sulfo- SMCC) and these were subjected to LC-MS/MS analysis. In vitro ubiquitylation assay showed that S100A11 was monoubiquitylated by NEDD4. When in vitro ubiquitylation reactions were carried out with increasing calcium concentrations, significant decreases in NEDD4-mediated monoubiquitylation of S100A11 as well as NEDD4 auto-ubiquitylation were detected.

Conclusions: We demonstrated that S100A11, an EF hand calcium binding protein, is a novel substrate protein for NEDD4-mediated ubiquitylation, which is affected by calcium levels. Further studies are needed to examine the role of monoubiquitylation of S100A11 by NEDD4 in translocation of S100A11 to the plasma membrane or to the nucleus for the regulation of water channel protein AQ2P and osmotic water permeability in the collecting ducts.

Funding: Government Support - Non-U.S.

FR-OR074

Protein Kinase C (PKC) Increases UT-A1 Urea Transporter Glycan Sialylation, Membrane Expression and Urea Transport Activity Xuechen Li,1 Janet D. Klein,2 Jeff M. Sands, 2 Guangping Chen. 1Physiology, Emory Univ, Atlanta, GA; 2Renal Medicine, Emory Univ, Atlanta, GA.

Background: UT-A1 urea transporter was initially identified as a vasopressin-regulated urea transporter and plays an important role in the urine concentration mechanism. However, accumulating evidence demonstrates that protein kinase C (PKC) also regulates urea permeability in the inner medullary collecting duct (IMCD). PKC particularly mediates hypertonicity-stimulated urea transport in kidney. In this study, we investigated the role of PKC in UT-A1 protein membrane expression and glycosylation structure change.

Methods: UT-A1 MDCK cells, HEK293 cells and rat kidney IMCD suspension were used for PKC activator PDBu treatment or PKC alpha gene (pcDNA3-PKC alpha) transfection. Crude cell membrane from PKC alpha knockout mouse was isolated by sucrose gradient ultracentrifuge. Cell surface UT-A1 was measured by flow cytometry and the glycans structure change of UT-A1 was examined using sugar-specific binding lectins.

Results: Treatment with 2 μM of the PKC activator PDBu significantly increases UT-A1 protein abundance in UT-A1 MDCK cells. Interestingly, activation of PKC by PKC alpha gene markedly increases UT-A1 glycans acidic. Consistently, activation of PKC increases UT-A1 sialylation from kidney inner medulla (IM). Functionally, increased UT-A1 sialylation has enhanced urea transport activity when the UT-A1 MDCK cells were incubated with 2 mM saltic acid for 24 h. To exclude the possible non-specific effect of the PKC activator, the PKC alpha gene was transcribed into UT-A1 HEK293 cells. Cell surface sialylation assay showed that PKC alpha directly increased UT-A1 membrane expression and the increased UT-A1 is highly sialylated as judged by SNA lectin pulldown assay. A PKC alpha knockout mouse has impaired urine concentrating ability. We examined UT-A1 gene glycosylation change and found that the UT-A1 sialylation is impaired from PKC alpha knockout mouse.


Funding: NIDDK Support

FR-OR075

Transgenic Mice That Express UT-A1 but Lack UT-A3 Have Increased AQP3 and Normal Urine Concentrating Ability. Janet D. Klein,2 Abinash Mishry, Patricia A. Molina, 1 Priya Datta, 1 Richard T. Rogers, 1 Mitsi A. Bloom 2 Jeff M. Sands. 2

Background: Mice lacking the inner medullary collecting duct (IMCD) urea transporters, UT-A1 and UT-A3, are unable to concentrate their urine. To determine whether this defect results from the absence of UT-A1 (located intracellularly and at the apical membrane), UT-A3 (active at the basolateral membrane), or both, we made a mouse transgenic UT-A1 but not UT-A3 (UT-A1+/A3-/). Since AQP3 has been reported to transport urea across the basolateral membrane, we assessed AQP3 levels and cellular location in the UT-A1+/A3- mice.

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

53A
Methods: We generated a UT-A1 gene that could not be spliced to produce UT-A3, behind its original UT-A promoter. We introduced this transgene into UT-A1/A3 knock-out (KO) mice to yield a mouse expressing only UT-A1 (UT-A1+/+ A3-/-). Western blot and immunohistochemistry were used to assess transport and channel proteins in the UT-A1+/+A3-/- mice.

Results: Western blot demonstrated 1) UT-A1 protein in inner medulla (IM) of UT-A1+/+ A3-/- and wild-type (WT) mice, but not in UT-A1/A3 KO mice and 2) UT-A3 absent from both mice. UT-A1 protein was not detected in extra-renal tissues from UT-A1+/+ A3-/- mice. Immunohistochemistry showed negative UT-A3 staining and positive UT-A1 staining present only in the IM of the UT-A1+/+ A3-/- mice. Basal urine osmolalities in WT (2844 mOsm) and UT-A1+/+A3-/- mice (2508 mOsm) increased upon overnight water restriction to 4469 mOsm in WT and 3656 mOsm in UT-A1+/+A3-/- mice. Both WT and UT-A1+/+A3-/- urine osmolalities were significantly higher than in UT-A1/A3 KO (basal: 920 mOsm; dehydrated: 1365 mOsm) mice. AQP5 was increased 61.13% (n=11, p<0.05), but its basolateral location was unchanged in the UT-A1+/+A3-/- mice compared with WT mice.

Conclusions: Mice expressing UT-A1, but not UT-A3, are able to concentrate their urine to similar levels as WT mice. This suggests that UT-A3 may not be essential for urine concentration. The increase in AQP5 suggests a potential role moving urea across the basolateral membrane to compensate for the lack of UT-A3.

Funding: NIDDK Support

FR-OR076

A Small Molecule Screen Identifies Selective Inhibitors of Urea Transporter UT-A1 Cristina Esteva-Font,1 Puay Wah Phuan,1 Marc O. Anderson,2 Alan S. Verkman.3 1Depts of Medicine and Physiology, Univ of California San Diego, San Diego, CA; 2Dept of Chemistry and Biochemistry, San Francisco State Univ, San Francisco, CA.

Background: Urea transporter (UT) proteins, including UT-A in kidney tubule epithelia and UT-B in vasa recta microvessels, facilitate urine concentrating function. UT-A1/A3 double knock-out mice have reduced urine-concentrating ability. We previously identified small-molecule UT-A inhibitors with low nanomolar potency using an enzyme-based screening assay. UT-A is of greater importance in urinary concentration, with UT-A1 as the principal target. The goal of this study is to identify UT-A1 inhibitors for application as diuretics ('urearetics') with a novel mechanism of action.

Methods: A robust screen for UT-A1 inhibitors was developed in MDCK cells expressing UT-A1, aquaporin-1, and fluorescent chloride sensor YFP-H148Q/V163S. Changes in cell volume alter intracellular chloride concentration, producing a near-instantaneous change in YFP-H148Q/V163S fluorescence. Creation of an inwardly directed chloride gradient produces rapid cell shrinking due to osmotic water efflux (decreased fluorescence), followed by UT-A1-dependent cell swelling due to water and urea entry (increased fluorescence).

Results: Screening of 100,000 synthetic small molecules yielded 3 UT-A1 inhibitors of four chemical classes with low micromolar IC50. The compounds fully and reversibly inhibited UT-A1-facilitated urea transport. Structure-activity analysis of analogs of the active compounds revealed compounds with high UT-A1 selectivity and compounds with comparable potency for UT-A1 and UT-B inhibition. Docking computations based on a homology model of UT-A1 suggested binding modes of the inhibitors into the hydrophobic channel region. Optimization of in vivo inhibitor pharmacology and testing in rodent models is in progress.

Conclusions: Small-molecule UT-A1 selective and non-selective inhibitors were identified with high-throughput screening. UT-A1 inhibitors may be useful as diuretics that may be effective in high-vasoressin, fluid-retaining conditions in which conventional salt transport-blocking diuretics have limited efficacy.

FR-OR077

Urea Transport in the Collecting Duct, Regulated by an Endothelin/ Nitric Oxide Signaling Pathway, Is Required for Sodium Reabsorption Richard T. Rogers, Sara K. Redd, Seongun M. Hong, Mitsi A. Blount. Dept of Medicine - Renal Div, Emory Univ, Atlanta, GA.

Background: Through several regulatory mechanisms, the kidney modulates fluid homeostasis. Nitric oxide (NO) production in the collecting duct regulates sodium and water reabsorption to stabilize blood volume by regulating transmural proton efflux and secretion of proton in the collecting duct urea transporters. Urea and NaCl gradient is produced rapidly by the collecting duct endothelial (ET-1) and NO signaling pathways to transport urea and fluid. Here, we investigate the importance of NO signaling and ET-1 on urea transport in the collecting duct.

Methods: We collected serum and 24-h urine samples then harvested renal medullary tissue from UT-A1/A3 KO mice and corresponding control littermates (WT). Samples were subjected to ELISA, qRT-PCR, Western, and electrolyte analysis accordingly. Blood pressure was measured in UT-A1/A3 KO and WT mice via tail cuff following 4 days of training.

Results: In corroboration with previous reports, urinary nitrate/nitrite levels were increased 3-fold in UT-A1/A3 KO mice. Investigation of nitric oxide synthase (NOS) mRNA expression levels revealed that NOS2 and NOS3 expression were unchanged in UT-A1/A3 KO medulla compared to WT; however, NOS1 expression was increased 40-fold in inner medulla of UT-A1/A3 KO mice. Because collecting duct endothelin (ET-1) / NO signaling pathways modulate pressure-natriuresis, we investigated this pathway in the inner medullary collecting ducts of UT-A1/A3 KO mice. We found that serum aldosterone levels and mineralocorticoid receptor protein expression, regulators of ET-1 concentration, were increased and endothelin type-B (ETB) receptor protein expression, the target of ET-1, was also increased in UT-A1/A3 KO mice compared to WT. Urinary sodium excretion in UT-A1/A3 KO was increased 57% and blood pressure was slightly lower in these mice compared to WT in accordance with the natriuretic and antihypertensive effects of ET-1 and NO.

Conclusions: Renal handling of sodium and water has always been linked processes in regulation of blood volume. The present studies suggest that urea handling in the collecting duct, acting through endothelin-simulation of NOS1, also regulates sodium reabsorption.

Funding: NIDDK Support, Private Foundation Support

FR-OR078

Nephrology Curriculum Moving Forward in the Era of Team Based Learning Rupal Mehta, James J. Paparelo. Nephrology, Northwestern Univ, Feinberg School of Medicine, Chicago, IL.

Background: Team Based Learning (TBL) is an approach to medical education that focuses on active learning and application of knowledge in group collaboration. There are few studies to date that show correlations between how students perform on their TBL exercises to their own standardized final exam scores.

Methods: After being given preparation material, 162 first year medical students were given 10 acid base and 9 renal pathology questions as the individual readiness assurance test (IRAT). In groups of 10-12, students were then given the same questions as the group readiness assurance test (GRAT), followed by application to more complex clinical scenarios. The final exam given 2 weeks later consisted of 109 questions, 78 of which were related to the TBL material.

Results: The preliminary data suggests an improvement between IRAT and final examination scores with the average percentile on the IRAT score of 66% compared to 80.21% on the final exam. The average acid base physiology percentage was 64% vs 70% on the renal pathology component. This does not prove causation but shows that TBL can be a complement of teaching nephrology.

Conclusions: TBL is an effective teaching tool in medical education. Ongoing steps include analyzing individual scores on the 78 questions testing TBL material and compare this to the 31 questions taught by other methods. This has the ability to show that TBL can be more successful than standard models. We are looking to identify subsets of students who benefited the most by TBL with qualifiers such as baseline IRAT score percentile or gender. These groups can then be the focus of TBL exercises. Students identified the renal curriculum as ideal for the TBL model and this will broaden its use at Northwestern University. Team based learning is a rapidly growing educational strategy and the implementation will likely be seen throughout many levels of training.

FR-OR079

Palliative Care Training during Fellowship: National Survey of Second-Year U.S. Nephrology Fellows Sara A. Combs,1 Stacey Culp,3 Jean L. Holley,2,4 Alvin H. Moss.3 1Univ of Colorado, Aurora, CO; 2Carle Physicians Group, Urbana, IL; 3West Virginia Univ, Morgantown, WV; 4Univ of Illinois, Urbana-Champaign, IL.

Background: Dialysis patients have a high symptom burden and a limited life expectancy. Nephrologists are responsible for their care.

Methods: In 2013 we surveyed US second-year nephrology trainees to assess their attitudes toward and the quality of teaching in palliative care received during fellowship and their perceived preparedness to care for patients at end of life (EOL). 326 trainees were surveyed with a 64% response rate. These responses were compared to results from a similar fellows’ survey in 2003.

Results: More fellows thought it was moderately to very important to learn to provide care to dying patients (95% in 2013, 54% in 2003, p<0.001). 99% of fellows in both surveys believed physicians have a responsibility to help patients at the EOL. On a 10-point scale in which 0 is “no teaching” and 10 is “a lot of teaching”, fellows reported more teaching in teams than with a physician (mean 9.0 ± 1.4) than a patient at the EOL (mean 4.5 ± 2.5) and with distal RTA (mean 6.5 ± 2.3), all p<0.001. On a similar 10-point scale for preparedness, fellows’ self-assessments in managing a patient at the EOL (mean 6.1 ± 2.5) and with distal RTA (mean 7.3 ± 2.0) were also lower than managing a patient on hemodialysis (mean 8.9 ± 1.2), all p<0.001. Ranking of quality of teaching during fellowship in all areas (mean 4.1 ± 0.8 on a scale of 0-5 where 0 is poor and 5 is excellent) and specific to EOL care (mean 2.4 ± 1.1) did not change between 2003 and 2013, but knowledge of annual gross mortality rate for dialysis patients was worse in 2013, only 57.4% answered correctly (p=0.048). 86% reported that no palliative care rotation was offered during fellowship. To an open-ended question about what would most improve fellows’ EOL care education, the most common response was a required palliative medicine rotation during fellowship.

Conclusions: The amount of teaching specific to palliative care has not improved over the last decade, but fellows increasingly believe that they should learn how to provide this care during fellowship.

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

54A
Use of Simulated Patients for Teaching Core Communication Skills to Nephrology Trainees Robert A. Cohen,1 Jane O. Schell,2 ’Dept of Medicine Nephrology Div, Beth Israel Deaconess Medical Center (BIDMC)/Harvard Medical School, Boston, MA; 1Section of Palliative Care and Section Renal-Electrolyte, Univ of Pittsburgh School of Medicine/UPMC, Pittsburgh, PA.

Background: Nephrologists face challenging conversations with patients about dialysis decision-making and end of life. Yet minimal training of nephrology fellows for how to engage in these discussions occurs. Other specialties have employed simulated patients to assist fellows in practicing communication skills for delivering bad news and discussing end of life transitions. We present a communication workshop for nephrology fellows using standardized patients to teach and practice key communication skills.

Methods: First-year nephrology fellows from the BIDMC, Brigham and Women’s Hospital, and Massachusetts General Hospital and UPMC participated in a full-day interactive communication skills workshop for delivering serious news and promoting discussions about dialysis decision-making and end of life. This consisted of didactics followed by practice sessions. Simulated patients role-played cases giving each fellow an opportunity to practice newly learned skills. Faculty facilitated sessions, providing formative feedback. Surveys were completed prior to and at end of each workshop. Fellows’ perceptions of preparedness for engaging in these discussions were rated on a Likert scale prior to and after the workshop.

Results: Nineteen fellows (9 females; 10 males) participated at two sites (13 in Boston and 6 in Pittsburgh). Each fellow had an opportunity to participate in facilitated role play with simulated patients at least once during the workshop. Perception of preparedness for engaging in these conversations increased for all fellows following the workshop.

Conclusions: Using nephrology specific cases, we report the use of simulated patients for teaching nephrology fellows communication skills for addressing dialysis decision-making and end of life issues. Simulated patients provide a novel approach to communication education in nephrology training. Future efforts include increasing the number and location of such workshops in an effort to train more nephrology fellows in core communication skills.

Funding: Clinical Revenue Support

Conclusion: This study demonstrated the feasibility of iChoose Kidney to improve shared decision-making about treatment options for AA ESRD patients. A future randomized trial will assess clinical effectiveness and acceptability.

Funding: Other NHI Support - National Center for Advancing Translation Sciences (NCATS)

Successful Development of Worldwide Nephrology through the ISN Sister Renal Centre Programme Matthew O. Brook,2 Paul N. Harden,1,2 ’International Society of Nephrology, Brussels, Belgium; 2Oxford Kidney Unit, Oxford, United Kingdom.

Background: The International Society of Nephrology (ISN) sister renal centre (SRC) programme seeks to advance nephrology by linking emerging centres (EC) in the developing world with supporting centres (SC) in the developed world.

Methods: Of 34 active links in 2012, 26 (76%) responded to a survey investigating each links focus for development and success.

Results: ECs were distributed throughout 4 continents and 19 countries whilst SCs originated from 11 countries. Developing general clinical nephrology (16/34 links), haemodialysis (12/34) and acute kidney injury (11/34) services were the most prolific areas of activity although significant diversity was evident. The most improved aspects of nephrology were identified as general clinical nephrology (13/21 responding links), Haemodialysis (12/21) and transplantation services (9/21) (Figure).

Conclusion: The SRC programme provides a template that may be adopted by other specialties for substantial and sustained improvement in healthcare tailored to the demands and resources of the emerging unit.

Funding: None

Conclusion: The SRC link between Oxford, U.K. and Minsk, Belarus is a good example of sustained success.

Methods: A new paediatric programme contributed to a >20 fold increase in transplantation in Belarus. The Minsk team have since used their experience to support the first ever paediatric transplants in Khazakstan and living donor transplants in Krygykstan.

Conclusion: The SRC programme provides a template that may be adopted by other specialties for substantial and sustained improvement in healthcare tailored to the demands and resources of the emerging unit.

Funding: None

Conclusion: The SRC programme provides a template that may be adopted by other specialties for substantial and sustained improvement in healthcare tailored to the demands and resources of the emerging unit.

Funding: None

Conclusion: The SRC programme provides a template that may be adopted by other specialties for substantial and sustained improvement in healthcare tailored to the demands and resources of the emerging unit.

Funding: None
Conclusions: To our knowledge this is the first educational social media campaign performed of this magnitude in medicine. The campaign was successful in drawing many people to interact and learn about nephrology. Traffic to the originating blog was the highest in it’s history by a wide margin. Use of interactive campaigns are possible and deserve formal study. Such interactive games could spark interest in nephrology, at a time when interest is declining.

FR-OR084
Two Novel Educational Interventions to Navigate the Challenges of CKD Care

Background: There is a scarcity of translational research in CKD that incorporates educational tools. We are 1 of 5 NIDDK R34 grants whose focus is improving outcomes for CKD patients through T2 research. We describe the development of two interventions, a CKD Patient Navigator program and a CKD specific enhanced personal health record (PHR).

Methods: To accomplish our specific aims, we assembled key members from our multidisciplinary CKD Team and enlisted new members from information technology and data management. Creation of the CKD Navigator Program encompassed three phases: hiring, training, and implementing. We hired a navigator who could provide “individual guidance, support, education, coordination of care, and other assistance to patients”. For training, there were three key areas a) Harold Freeman Patient Navigator Institute b) CKD education and c) electronic health record (EHR) training. For implementation, we defined barriers of care, ensured randomization, and created EHR templates for which pertinent study data could be extracted. Enhanced PHR creation was a multi-step process. We selected educational materials specific to CKD Stage 3b/4 patients, developed a user guide for potential participants who may not be familiar with our PHR, and pilot tested including verifying our ability to collect PHR use data among participants.

Results: We created a CKD Patient Navigator program adapting the use of patient navigators successfully employed in other fields with the well-established chronic care model. We developed an EHR-based enhanced PHR that allows for CKD stage-specific education disseminated electronically and utilized many publicly available NKFDEP and NKF education materials. We’re performing an RCT to determine the effect of these interventions alone and in combination on CKD outcomes. Recruitment is underway and we have enrolled over half of our target population (n=208) and await future analyses.

Conclusions: CKD research that uses novel educational approaches is pressing and will require technology, stakeholders, and a multidisciplinary team to translate frameworks into adaptable interventions.

Funding: NIDDK Support, Other NIH Support - S.D.N. was supported by National Center for Research Resources, Multidisciplinary Clinical Research Career Development Program Grant RR024990

FR-OR085
Changes in Endothelial and Smooth Muscle Cells Morphology by Patient-Specific Disturbed Flow Patterns Derived from Autologous Arteriovenous Fistulae
Andrea Remuzzi,1,2 Bogdan Ene-Iordache,1 Marco Franzoni,1 Irene Cattaneo,1 1IRCCS - Mario Negri Institute, Bergamo, Italy; 2Univ of Bergamo, Dalmine, Italy.

Background: Radial-cephalic arteriovenous fistula (AVF) is the first choice for haemodialysis access. AVF surgery has significant early failure rates due to vessel stenosis or AVF failure. We investigated whether WSS acting on EC in regions of disturbed flow develops in A VF, may in and A VF failure. We investigated whether WSS acting on EC in regions of disturbed flow develop in the venous site in side-to-end AVF importantly affect EC and SMC function. These results confirm that disturbed flow conditions acting on EC may be responsible for IH and AVF stenosis.

Conclusions: Our data demonstrate that exposure of EC to oscillating WSS that develop in the venous site in side-to-end AVF importantly affect EC and SMC function. These results confirm that disturbed flow conditions acting on EC may be responsible for IH and AVF stenosis.

Funding: Not applicable

FR-OR086
Pancreatic Elastase (PRT-201) Improves Radiocephalic Arteriovenous Fistula (AVF) Maturation and Patency
Bradley S. Dixon,1 Robert J. Hye,2 Michael R. Jaff,3 Pamela Gustafson,4 Francesca Lindow,5 Marco D. Wong,5 Laura M. Dember,5 Steven K. Burke,5 1’U Iowa; ‘Kaiser Permanente; ‘UPenn; ‘Mass General; ‘Protein Therapeutics.

Background: Over 50% of AVFs lose primary unassisted patency within one year of creation. A pilot study suggested PRT-201 is safe and may prolong AVF patency.

Methods: We conducted a randomized double-blind, placebo controlled trial of PRT-201 on primary unassisted patency (time from AVF creation to thrombosis or an intervention to maintain patency) of a new AVF. Secondary outcomes included secondary patency (time from AVF creation to fistula abandonment), and unassisted maturation assessed by duplex ultrasound (blood flow ≥ 500 mL/min and vein lumen diameter ≥ 4 mm).

Results: 169 patients were randomized and 151 patients treated with PRT-201 (10 μg, n=51 or 30 μg, n=49) or placebo (n=51) applied topically to the exposed artery and vein immediately following surgery. Primary unassisted patency at one year was 47% in placebo compared to 59% for PRT-201 (10 μg and 30 μg dose groups combined; p=0.11). In a Cox model adjusting for baseline covariates, the hazard ratio for time to primary unassisted patency loss was 0.76 (95% CI 0.43-1.35; p=0.35) for 10 μg and 0.59 (95% CI 0.32-1.10; p=0.10) for 30 μg. Unassisted maturation at 12 weeks was 67% for placebo compared to 87% (p=0.03) for 10 μg and 92% (p=0.01) for 30 μg. Stratifying by AVF location (Table 1), 30 μg PRT-201 significantly improved primary unassisted patency and unassisted maturation in radiocephalic but not brachiocephalic AVFs.

Conclusions: PRT-201 improved primary unassisted patency and unassisted maturation in radiocephalic AVFs.

Funding: Pharmaceutical Company Support - Proteon Therapeutics

FR-OR087
Genotype Polymorphisms of Dimethylarginine Dimethyl Aminohydrolase 1 (DDAH1) Predict Restenosis of Vascular Access after Angioplasty in Hemodialysis Patients
Chih-Ching Lin. Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

Background: Elevated plasma asymmetric dimethylarginine (ADMA) has been reported to be associated with restenosis after percutaneous transluminal angioplasty (PTA) of AVF in hemodialysis (HD) patients. Dimethylarginine dimethylaminohydrolase 1 (DDAH1) is the major enzyme eliminating ADMA, but the effect of genetic variations in DDAH1 on the outcome of vascular access after PTA in HD patients remained unknown.

Methods: We assessed the association between polymorphisms in DDAH1 and vascular access outcome in 473 maintenance HD patients, who were prospectively followed up for one year after PTA for vascular access dysfunction. Eleven single nucleotide polymorphisms (SNPs) in endothelial function related genes were analyzed and plasma ADMA levels were determined at baseline.

Results: After adjustment of demographic, access, and risk factors, individuals with high baseline plasma ADMA (>400 pmol/L) levels had higher rates of re-intervention at 3 and 6 months after PTA (three months, 56% vs. 36%, p=0.08; six months:74% vs. 53%, p=0.05). DDAH1 rs233112 was significantly associated with increased levels of plasma ADMA levels. Compared with individuals with rs233112 AA genotypes, individuals with rs233112 GA or GG genotypes had higher risks for re-intervention (58% vs. 45%, p=0.003) after
Conclusions: Our results provide the first evidence that rs233112 GG+GA genotypes of DDAH1 gene predict early and frequent restenosis of vascular accesses after PTA in HD patients.

Funding: Government Support - Non-U.S.

FR-OR088
The Impact of Arterial Micro-Calciﬁcation of Vascular Access on Early Access Failure in Hemodialysis Patients  Su Jin Choi,1 Yu-Seon Yun,2 Young Soo Kim,3 Sunae Yoon,3 Young Ok Kim.3 Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Korea; 2Gyeonggi Province Geriatric Hospital of Dongducheon.

Background: Vascular calcification is common in hemodialysis (HD) patients, and it is a signiﬁcant predictor for cardiovascular mortality in HD patients. Also, vascular access calcification identiﬁed by plain radiography was reported as a risk factor for cardiovascular mortality in HD patients. But the relationship between arterial micro-calciﬁcation (AMiC) by pathologic study and patency of vascular access has been rarely reported. The aim of this study was to determine the impact of AMiC of vascular access on access patency in HD patients.

Methods: One-hundred six HD patients (Mean age; 59.6 ± 12.9 years, Male/Female; 66/40, Percent of diabetes mellitus; 73%) receiving vascular access operation were included in this study. During the operation, we obtained partial arterial specimen and performed pathologic examination by von Kossa stain to identify AMiC. We investigated early access failure (complete obstruction of blood ﬂow or severe stenosis requiring radiologic intervention or surgical correction of AVF within 1 year after the operation) between the patients with AMiC and those without AMiC.

Results: Mean duration of follow-up was 42.5 ± 33.8 months and the incidence of AMiC was 38.7% (n=41). The form of vascular calcification is arterial medial calciﬁcation. Early access failure was occurred in 45 patients (42.5%), and mean time between the operation and access failure was 4.1 ± 3.1 months (range, 1 to 12 months). The access failure was associated with older age (62.7 ± 11.8, 57.3 ± 13.2, p-value = 0.032) and low BMI (23.3 ± 2.9, 24.5 ± 3.5, p-value = 0.043). The early AVF failure rate was higher in patients with AMiC than those without AMiC (56.1%, n=23/41, vs. 33.8%, n=22/65, p-value = 0.024). Diabetes, cardiovascular disease and cardiovascular death were not related to access patency. Kaplan-Meier analysis showed that the presence of AMiC signiﬁcantly increased the risk for the access failure (Log rank = 4.98, p-value = 0.026).

Conclusions: This study demonstrates that AMiC of the vascular access is associated with early access failure in HD patients.

FR-OR089
Liposomal Delivery of Prednisolone Improves Outward Remodeling in Murine Arteriovenous Fistulas  ChunYu Wong,1 Carolien Rothuizen,1 Josbert Metselaar,1 Floris Veerbeck,2 Erik Stroes,2 Anton Jan Van Zonneveld,1 Ton J. Rabelink,1 Paul Quax,1 Joris I. Rotmans.1 Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Korea; 2Gyeonggi Province Geriatric Hospital of Dongducheon.

Background: Arteriovenous ﬁstulas (AVFs) have a 1-year primary patency of only 60%, mainly as a result of maturation failure that is caused by insuﬃcient outward remodeling (OR) and intimal hyperplasia (IH). The exact pathophysiology remains unknown, but the locally augmented inﬂammatory response is thought to play a role. Corticosteroids (CS) are powerful inhibitors of inﬂammation but result in adverse side eﬀects when given systematically at a higher dose. In this study we evaluated the eﬀect of CS combined with a targeted delivery method using liposomes in a murine AVF model.

Methods: AVFs between the jugular vein and common carotid artery were created in an end-to-side manner in C57Bl6 mice. Subsequently, the animals were injected i.v. (dose 10 mg/kg) with either liposomal prednisolone phosphate (LPP), empty liposomal vehicle, prednisolone phosphate or PBS at days 0,2,5 and 10 after surgery. At 14 days, the labeled liposomes were visualized in mice in vivo by near infrared fluorescent imaging whereupon the animals were sacriﬁced for histomorphometric and immunohistochemical analysis.

Results: Liposomes accumulated in the anastomotic area of the AVF. Treatment with LPP resulted in a 27% increase in venous circumference and 47% increase in lumen (p<0.01-p<0.003) when compared to the PBS group. No signiﬁcant diﬀerence in intimal hyperplasia development and arteriovenous ﬁstula (AVF) non-maturation have yet to be performed in vascular access. The objective of this study was to evaluate gene expression changes from vein specimens from subjects without chronic kidney disease, advanced chronic kidney disease (CKD) receiving new vascular access, advanced CKD subjects receiving new vascular access. The early AVF failure rate was higher in patients with AMiC and those without AMiC.

Conclusions: Liposomal CS targeting proved to be an eﬀective and selective method to ameliorate venous remodeling in AVFs by increasing the luminal area that was caused by augmented OR, rather than the reduction of IH formation. Treatment with liposomal prednisolone phosphate could be a valuable strategy to reduce the peri-anastomotic inﬂammatory response and improve maturation of AVFs.

Funding: Private Foundation Support

FR-OR090
Genomics of Arteriovenous Fistula Maturation  Timmy C. Lee,1 Jing Chen,1 Prabir Roy-Chaudhury,1 Begotha Campos,1 Mario Medvedovic,1 Internal Medicine, Univ of Cincinnati, Cincinnati, OH; 2Medicine, Univ of Alabama at Birmingham, Birmingham, AL

Background: Studies that evaluate the progressive eﬀects of vascular injury and biological mechanisms leading to venous neointima hyperplasia development and arteriovenous ﬁstula (AVF) non-maturation have yet to be performed in vascular access. The objective of this study was to evaluate gene expression changes from vein specimens from subjects without chronic kidney disease, advanced chronic kidney disease (CKD) receiving new vascular access, advanced CKD subjects receiving new vascular access, advanced CKD subjects receiving new vascular access. The early AVF failure rate was higher in patients with AMiC and those without AMiC.

Methods: Vein samples were isolated for RNA from non-CKD deceased donors (n=2), advanced CKD subjects receiving new vascular access (n=2), subjects at the time of second stage basilic vein transposition (n=2), and stenotic early AVF failure (n=2).

Conclusions: We performed diﬀerential gene expression analysis using high throughput RNA-seq to compare gene expression at these various time points. We also performed qRT-PCR for selected genes of interests.

Results: We found signiﬁcant and progressive increases in expression of genes regulating cellular proliferation, cell adhesion, chemokine and cytokine signaling, and extracellular matrix production with increased vascular injury to the vein. qRT-PCR for monocyte chemoattractant protein-1 (MCP-1), showed signiﬁcantly progressive gene expression from non-CKD vein to stenotic AVF (p<0.005) (see ﬁgure).

Conclusions: Our results show signiﬁcant and progressive increases in gene expression in pathways regulating inﬂammation, oxidative stress, and endothelial function from the non-CKD period to the time of venous stenosis. Future studies are needed to evaluate in greater detail the eﬀect of diﬀerent vascular injuries (uremia and hemodynamics) at diﬀerent time points in the natural history of AVF maturation.

FR-OR091
Notch/FPS-1 Signaling Contributes to CKD-Induced Neointima Formation in AV Fistula  Yuhno Cheng,1 William E. Mitch,1 Yun Yang,1 Anlin Liang,1 1Dept of Medicine/Nephrology, Baylor College of Medicine; 2Dept of Medicine/Nephrology, Baylor College of Medicine; 3Dept of Medicine/Nephrology, Baylor College of Medicine.

Background: Functional arteriovenous ﬁstulas (AVF) are critical for hemodialysis patients but neointima formation causes 60% of AVFs to fail in 2 years. The migration and proliferation of smooth muscle cells (SMCs) are the major resources of neointima formation. Fibroblast speciﬁc protein 1 (FSP-1) regulates cell migration and could be associated with CKD-induced AVF failure. Methods: AVFs were created in WT and FSP-1 KO mice with or without CKD, the neointima formation in AVFs was evaluated. The expression of FSP-1 and the underlying mechanism were investigated in cultured SMCs.

Results: FSP-1 expression was signiﬁcantly increased in neointima area of AVFs from patient and CKD mice compared with that of WT mice. SMCs treated with FSP-1 showed enhanced potential of migration and proliferation. FSP-1 promoter contains RBP-Jk-bound (a downstream transcription factor of Notch) consensus sites. Notch ligand, Jagged 1, increased FSP-1 expression and its promoter activity. Deletion of the RBP-Jk-binding sites inhibited Jagged 1-induced FSP-1 promoter luciferase activity. Moreover, CHIP and electrophoretic mobility shift assay (EMSA) analysis showed that Jagged 1 stimulated direct interactions of RBP-Jk with FSP-1 promoter sequences. Knockout of RBP-Jk in SMCs ablated these interactions. Similar responses were detected by using Notch inhibitor, DAPT. FSP-1-mediated migration and proliferation in SMCs were also suppressed by Notch inhibitor and by RBP-Jk knock out. Finally, AVFs created in mice with KO FSP-1 suppressed CKD-induced neointima formation. In these mice, neointima formation was ~ 40% below that in wild type, uremic mice.

Funding: NIH/NEI, National Institute of Diabetes and Digestive and Kidney Diseases (DK60066 to W.E. Mitch).
Conclusions: Thus, uremia enhances FSP-1 expression through activation of Notch/RBP-Jk signaling in SMCs and causes migration and proliferation of neighboring SMCs which accelerates neointima formation and AVF failure. FSP-1 could become a therapeutic target for suppressing neointima in AVFs.

Funding: NIDDK Support

FR-OR092
Preclinical Dataset Supports Initiation of Clinical Trials for Bioengineered Vascular Access Grafts
Shannon L. M. Dahl,1 Jeffrey Lawson,2 Heather L. Prichard,3 Robert J. Manson,3 William Tente,1 Alan P. Kypson,2 Shawn Michael Gage,2 Juliana Blum,1 Laura E. Niklason,4 *Huamcyte, Inc.; 5Duke Univ; 6East Carolina Univ; 7Yale Univ.

Background: End stage renal disease (ESRD) patients who require hemodialysis access would benefit from an alternative to synthetic grafts, which have high rates of thrombosis and venous intimal hyperplasia. Our bioengineered vascular graft is comprised of human extracellular matrix and is similar in strength to native human vein and artery. This acellular graft may be stored in a regular refrigerator, making it readily available for off-the-shelf surgical use. This graft is currently in clinical studies for evaluation of safety and efficacy for use as hemodialysis vascular access in patients with ESRD.

Methods: Banked smooth muscle cells were cultured in bioreactors in vitro to produce bioengineered tissue grafts, and a decellularization process was subsequently employed to remove cellular antigens and render grafts non-immunogenic. Canine-derived grafts were implanted as carotid artery bypass grafts in dogs, which provided directional guidance for evaluation of human grafts. Human-derived grafts were implanted as arteriovenous fistulas in baboons. Evaluations included patency, durability, cannulation, immunogenicity, intimal hyperplasia, and remodeling.

Results: The mechanical integrity of these acellular grafts was retained throughout 1-year of refrigeration. Canine studies demonstrated long-term (1-year) safety and function of engineered tissues. Baboon studies showed that bioengineered grafts were safe, well tolerated, and functioned as intended. No significant intimal hyperplasia was observed in the grafts after 12-months in any recipient. Histologic analysis demonstrated evidence of host vascular cell migration into the graft.

Conclusions: These bioengineered grafts demonstrated high patency, could be cannulated repeatedly, and did not show significant intimal hyperplasia. These preclinical results support the evaluation of the grafts to provide dialysis access in patients with end stage renal disease.

FR-OR093
Tauridine-Citrate-Hepatin Lock Solution Significantly Improves Hemodialysis Patients with Tunneled Catheters
Javier Donate,1 Néstor Fontserè,2 Celia Cardozo,1 Mercedes Muñoz,4 Alex Soriano,5 Mercedes Pons,4 Josep Mensa,1 Josep M. Campistol,1 Francisco Maduell,1 Juan F. Navarro-Gonzalez,1,6 *Research Unit, HUNSC, S/C Tenerife; 7Hepatology, Hosp. Clinic, Barcelona; 8Infectious Diseases, Hosp. Clinic, Barcelona; 9Clinical Analysis, HUNSC, S/C Tenerife; 10CETIRSA, Barcelona; 11Hepatology, HUNSC, S/C Tenerife.

Background: The tauridine-citrate-hepatin lock solution (TCHLS) effectively eradicated thrush in tunneled catheter biofilms and helped to maintain catheter lumen sterility. We aimed to evaluate the potential beneficial effect of this solution on the inflammatory profile of hemodialysis (HD) patients.

Methods: Thirty-one chronic patients, 18 males and 13 female, with a mean age of 72 years, and a mean time on HD of 82 months, were included in the study. All patients were on maintenance HD with tunneled catheters locked with a heparin filling were subsequently converted to a TCHLS. Serum concentration of inflammatory parameters [high-sensitive C-reactive protein (hsCRP), tumor necrosis factor-alpha (TNFa), interleukin (IL)-6 and IL-10], as well as mRNA expression levels of TNFa, IL6 and IL10 in peripheral blood mononuclear cells (PBMC) were analysed at baseline and after 6 months of TCHLS.

Results: Serum concentrations of hsCRP and IL-6 experienced a significant reduction (2.1±0.5 and 14.8±3.9 vs 1.5±0.4 and 10.6±2.7, respectively, p<0.01), whereas serum TNFa and IL10 did not change. Regarding inflammatory cytokine expression in PBMC, after 6 months of TCHLS, mRNA levels of IL-6 and TNFa significantly decreased by 20% and 19%, respectively (p<0.05), without changes in the expression levels of IL-10.

Conclusions: The use of TCHLS in maintenance HD patients with tunneled catheters resulted in the alteration of the inflammatory profile, with a significant decrease in the serum levels of hsCRP and IL-6, as well as in the mRNA gene expression levels of TNFa and IL-6 in PBMC.

FR-OR094
Safety of Small Bore Tunneled Central Venous Catheters in Chronic Kidney Disease Population
Gauri Bhutani,1 Mireille El Ters,2 Joe L. Klunder,3 Sandra J. Taler,1 Andrew Stockland,2 Marie C. Hogan,1 *Nephrology & Hypertension, Mayo Clinic; 2Interventional Radiology, Mayo Clinic, Rochester.

Background: There is accumulating evidence that peripherally inserted central venous catheters (PICCs) are associated with high rates of venous thrombosis, remnant vascular injury and in the dialysis population, subsequent lack of functioning AV fistulas. Data from our center demonstrated improved rates of PICC use of 30% in the chronic hemodialysis population. A potential strategy to reduce vascular injury to arm veins may be to employ central neck veins for venous access.

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

FR-OR095
Poly cystic Kidney Disease without Apparent Family History (AFH)
Yashisha Kalatharan1 Alessia C. Borgo,2 Young-Hwan Hwang,1 Kaorong Wang,1 Jamie L. Sundbäk,1 Christina M. Heyer,1 Peter C. Harris,1 York P. Pei,1 *Div of Nephrology, Univ Health Network, Toronto, Canada; 2Dept of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: The absence of a positive family history in 15-20% of patients poses a diagnostic challenge for autosomal dominant polycystic kidney disease (ADPKD) and may be due to multiple causes.

Methods: In the Toronto Genetic Epidemiology Study of PKD (TGESP), 220 unrelated probands prospectively underwent renal function and imaging testing as well as a comprehensive PKD1 and PKD2 mutation screen. From this cohort, we identified all cases without AFH, examined their parental medical records, and performed renal imaging in any available parents of unknown disease status. From these results, we re-classified our cases into: (i) de novo disease (DND); (ii) positive family history (FHI) in retrospect; and (iii) indeterminate family history (IFH).

Results: We found that 53/230 (24%) of the TGESP probands did not have AFH. Among this patient subgroup, 26/53 (49%) had DND, 4/53 (8%) had a FHI in retrospect, and 23/53 (43%) had an IFH. Their re-classified family history and mutation types are shown below:

<table>
<thead>
<tr>
<th>Type of Mutation</th>
<th>De Novo Disease (n=26)</th>
<th>Positive Family History in Retrospect (n=4)</th>
<th>Indeterminate Family History (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKD1</td>
<td>16/26 (62%)</td>
<td>2/4 (50%)</td>
<td>1/23 (4%)</td>
</tr>
<tr>
<td>PKD2</td>
<td>10/26 (39%)</td>
<td>2/4 (50%)</td>
<td>2/23 (9%)</td>
</tr>
<tr>
<td>No mutation found (NMD)</td>
<td>0/26 (0%)</td>
<td>0/4 (0%)</td>
<td>1/23 (4%)</td>
</tr>
<tr>
<td>% patients column percent of n</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Among the cases with de novo disease, we found one family (with two affected siblings and unaffected parents) suggestive of germline mosaic and 5 others with asymptomatic PKD1 and PKD2 mutation screen of the latter patients by Sanger sequencing was negative in all but one case (with a PKD1 frameshift mutation affecting the proband and her daughter).

Conclusions: PKD patients without AFH comprise a heterogeneous group resulting from de novo mutations, germline and/or somatic mosaicism, mild disease from both hypomorphic PKD1 and PKD2 mutations, and unavailable parental medical records. Additionally, in ~1/3 of the cases, no pathogenic mutations could be found despite a comprehensive screen of both PKD1 and PKD2.

FR-OR096
Identification of Mosaic Mutations in Mild, Mutation Negative ADPKD Patients Using Next-Generation Sequencing
Katharina Hopp,1 Sandro Rossetti,2 Maria V. Irazabal,3 Bina M. Paul,1 Jamie L. Sundbäk,1 Christina M. Heyer,1 Peter C. Harris,1 *Mayo Clinic; 2Cardio-Renal Dept Otsuka Pharma.

Background: In ~10% of ADPKD patients no PKD1/PKD2 mutation is detected by conventional Sanger sequencing, and even if such testing is targeted not the strongest. The majority of these patients have mild disease and often a negative family history. An explanation consistent with these findings is mosaicism, which has rarely been described in ADPKD but might often be undetected since it is difficult to identify by Sanger sequencing.

Methods: We have combined imaging, family, and sequencing analysis to identify ~80 mild, mutation negative ADPKD patients with a negative/uncertain family history. Using next-generating sequencing we developed a protocol to deep sequence (>5000x) the PKD1/PKD2 loci that reliably detects variants at the >3% level. This protocol takes into account equal read start site, additional allele call, and vicinity mismatch penalties, For Rev read balance scores, and common false positive filters gathered from next-generation sequencing data of >200 ADPKD samples.

Results: A total of 70 STCCs were placed in 62 adult patients under ultrasound guidance by interventional radiologists.

Number of lumens | 63 lines (7 unknown) | 1 to 3 (1 = 44.4% ; 2 = 52.4% ; 3 =3.2% )
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 patients</td>
<td>21 to 84 (mean = 56.5)</td>
</tr>
</tbody>
</table>
| Site of placement| 7 lines (1 unknown)   | Right External Jugular = 9 (13.4%)  
|                  |                       | All Internal Jugular = 20 (29.3%)   
|                  |                       | Others = 4 (6%)               |

93 % lines were inpatient and for 72%, the indication was antibiotic administration (n=35). No placement complications were noted. Indwelling days ranged from 1 - 175 (mean 32). Follow up ranged from 4 - 1165 (mean 255) days. 69% of patients receiving these 35 STCCs had CKD, renal transplant or ESRD. There were no observed superficial deep venous thrombosis sequelae.

Conclusions: We have observed a zero incidence of venous thrombosis over 918 indwelling days with STCCs. This is significantly lower than the 20 - 30% rate reported for PICCs in the current literature. STCCs may be a safer option in CKD patients in order to protect their arm veins for future dialysis access.
Results: In the first test run of 8 ADPKD probands we detected two promising variants, PKD1 c.700T>G, p.Y233D (6.6%, read depth 791x) and PKD1 c.1268C>T, p.R4228X (7.4%, read depth 3601x). The first variant scored as highly likely pathogenic in the ADPKD Mutation Database and was found in a proband with only ~25 small cysts at 76 years of age and an unclear family history. The second variant was found in a patient with negative family history, who was diagnosed at 34 years with a few renal cysts and now at 73 years has a TKV of 1.417ml and serum creatinine of 1.3mg/dl. This variant was confirmed by allele specific PCR and Sanger sequencing, where the c.1268C>T peak could be seen just above the background level.

Conclusions: We hypothesize that mosaicism explains a significant portion of ADPKD mutation negative patients with mild disease and the incidence is likely underestimated due to the lack of a protocol that allows reliable detection of these variants. Here, we have developed such a protocol using next-generation sequencing technologies and have shown its efficacy in an initial test run.

Funding: NIDDK Support, Private Foundation Support

FR-OR097
Prediction of GFR Endpoints in Early Autosomal Dominant Polycystic Kidney Disease

Michel Mrug, Sylvie Mrug, Doug Landsittel, Vicente E. Torres, Kyoungtae Ty Bae, Peter C. Harris, Lisa M. Guay-Woodford, Michael F. Flessner, William M. Bennett, Jared J. Grantham, Arlene B. Chapman, AL Birmingham, U Pittsburgh, Mayo Clinic; Children’s Nat Med Ctr; NIH; Legacy Good Samaritan Hosp; Kansas U; Emory U.

Background: There are no reliable formulas for predicting renal function over time in early autosomal dominant polycystic kidney disease (ADPKD).

Methods: We developed multivariable logistic models for reaching progression endpoints of CKD stage 3a and 3b and GFR decline by 30% and 50%. We developed the models and assessed their utility (with 10-fold cross-validation) using data collected by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP), a prospective, observational, longitudinal, multicenter study of 241 ADPKD adults with preserved renal function. Demographic, physical, laboratory and imaging data were collected at baseline and during follow up visits.

Results: After a mean follow-up of 8.7 years, mean iothalamate clearance (GFR) decreased from 97.8 to 74.0 ml/min/1.73m². Baseline GFR alone was a poor predictor of GFR outcomes. However, prediction of the GFR endpoints has improved when ten baseline variables were used in multivariable models. GFR outcomes were significantly predicted by baseline age, BMI, hypertension, GFR, serum calcium and alkaline phosphatase, hemoglobin, white blood cell count, urinary MCP-1 and total kidney volume (TKV).

Predicting the development of CKD stages 3a and 3b or GFR decline by 30% and 50% within 8.7 yrs using ROC analyses demonstrated an area under the curve (AUC) of 0.92, 0.93, 0.87 and 0.86, respectively for multivariable models. Similar AUCs were obtained using 10-fold cross-validation. The GFR-based modeling was repeated with MDRD-GFR, yielding similar outcomes.

Conclusions: Multivariable logistic models using routine clinical data predicted mild-moderate GFR decline endpoints in patients with early ADPKD. Such models may also facilitate the development of ADPKD therapies by informing selection of study participants with the highest risk for reaching FDA favored end-points.

Funding: NIDDK Support

FR-OR098
A New Algorithm to Predict Renal Outcome in Autosomal Dominant Polycystic Kidney Disease

Emilie Corec-Le Gall, Mary-yonne Hourmant, Marie-Pascale Morin, Regine Perrichot, Christophe Charasse, Pascale Sihoian, Marie-Pierre Audrezet, Claude Ferec, Yannick Le Meur. CHRU BREST; France; INSERM 1078, CHRU Brest; CHU Nantes; CHU Rennes; CH Quimper; CH Vannes; CH Saint-Brieuc.

Background: As targeted therapies are under development in Autosomal Dominant Polycystic Kidney Disease (ADPKD), the selection of patients who should be treated is crucial. Herein, we present a new prognostic model to target patients at risk of poor renal outcome.

Methods: In a population of 1017 patients from 755 pedigrees, we studied the in

Results: The association of hypertension and at least one urologic complication (macroscopic hematuria, cysts infection or flank pain) before 35 yrs (group g1) is associated with the poorest renal outcome (median age at ESRD=48 yrs, HR=3.8), the presence of either hypertension or urologic complication (g2) is of intermediate severity (54.4 yrs, HR=1.9), while patients without these characteristics (g3) have the best renal outcome.

Conclusions: Based on the integration of simple clinical features with molecular genetic data, this algorithm might contribute to the development of a tailored approach of the therapeutic decision in ADPKD patients.

Funding: Government Support - Non-U.S.

FR-OR099
Novel Imaging Classification to Predict Functional Disease Progression in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Maria V. Irazabal, Laurenzo J. Rangel, Eric J. Bergstrahl, Amber J. Harmon, Marie C. Hogan, Ziad El-Zoghby, Peter C. Harris, Bernard F. King, Vicente E. Torres. Mayo Clinic, Rochester, MN.

Background: CRISP showed that height adjusted total kidney volume (HTKV) measured by stereology (TKVs) predicts eGFR decline in ADPKD. TKV can be used (1) as outcome measure in clinical trials and (2) for selection of patients more likely to exhibit treatment effect in a trial or benefit from an effective treatment. High precision but time consuming TKVs is essential for (1), but not for (2). Also, TKV and renal function correlate poorly in some patients. Our goal was to develop and validate a fast method to measure HTKV that can be used for (2).

Methods: 590 ADPKD patients with CT/MR images and ≥3 eGFR measurements 26 months apart were classified as Atypical (class 1) or Typical (class 2) using pre-specified criteria (Figure 1 A). Class 2 patients were randomly partitioned into development and validation sets. TKV was calculated by stereology and ellipsoid formula (TKVe). Patients from the development set were subclassified (a-e) by age and HTKV. A longitudinal mixed effects regression model was used to model eGFR decline.

Results: Figure 1 A shows baseline characteristics. TKVe correlated well with TKVs (R²=0.98) without systematic bias (95% CI: -20.7%, 19.6%) (Figure 1 B). HTKV predicted eGFR decline in class 2 patients (p<0.0001), but not in class 1 (p=0.07). In the development set, patient subclasses showed significant differences in eGFR decline, with an average predicted error of -13.3 mL/min/1.73m² for the validation set (Figure 1C).

Conclusions: TKVe by CT/ MR is an excellent predictor of TKVs and a fast way of estimating TKV for classifying class 2 ADPKD patients. The classification provides a practical tool for selecting the most appropriate patients for clinical trials and identifying patients with progressive disease likely to benefit from therapy.
FR-OR100
A Novel Agent That Inhibits Disease Progression in Models of Autosomal Dominant Polycystic Kidney Disease (ADPKD)  
Sorin V. Fedeles,1 Bogdan I. Fedeles,2 Seung H. Lee,1 Stefan Somlo.1 1Internal Medicine, Yale School of Medicine, New Haven, CT; 2Biological Engineering, MIT, Cambridge, MA.

Background: ADPKD is a common monogenic cause of end-stage kidney disease for which no effective therapy exists. We examined the role of the novel antitumor agent 11β (Fedeles, et al., J Biol Chem, 286:33910) in ADPKD. 11β has been shown to induce apoptosis in prostate cancer cells in vitro and to prevent growth of xenograft tumors in nude mice.

Methods: We used the orthologous Pkd1 model, Pkd1<sup>fl/ox</sup>:Pkhd1-Cre. Mice were given daily intraperitoneal injections of 11β from P10 to P24. We determined kidney to body weight (KW/BW) ratio, cystic index, BUN, apoptosis, and proliferation at P24 in treated and control animals.

Results: 11β administration resulted in a decrease in KW/BW ratio as compared to vehicle injected controls (6.3+/−0.4 vs 15.1+/−2;***p<0.001); the body weight of treated animals was not statistically lower than controls. These changes were accompanied by a decrease in th cystic index (50%+/−1.1 vs. 70%+/−1.2;***p<0.001) and a decrease in BUN levels (41+/−1.4 vs. 76+/−1.5;***p<0.001). 11β specifically increased apoptosis as assessed by the cell-titer blue viability assay in cultured Pkd1 null cells compared to control (***p<0.001). The in vivo apoptotic index by TUNEL staining also showed significant decrease in treated mice (**p<0.001). Importantly, the effect of the drug was specific in vivo, as the vast majority of apoptotic cells stained positive were of collecting duct origin where the Cre is active; proximal tubule cells did not exhibit increased apoptosis. Interestingly, 11β did not have a statistically significant effect on the proliferation of Pkd1 null cells in vivo, as measured by Ki67 staining.

Conclusions: Our data show that 11β is a potent and specific inducer of apoptosis of Pkd1 null cells both in vitro and in vivo. In previous work 11β has been shown to have a pleiotropic effect on several cellular signaling pathways including mTOR, the unfolded protein response (UPR), and MAP kinase. Further studies are needed to elucidate the role of 11β in the apoptotic response seen on a Pkd1 knockout background.

Funding: NIDDK Support

FR-OR101
Inhibition of DNMT1 Delays Cyst Growth in Autosomal Dominant Polycystic Kidney Disease  
Xia Zhou,1,2 James P. Calvet,2,3 Xiaogang Li.1,2,3 1Dept of Internal Medicine; 2Kidney Institute; 3Dept of Biochemistry and Molecular Biology, Univ of Kansas Medical Center, Kansas City, KS.

Background: Aberrant expression of DNA (cytosine-5)-methyltransferases (DNMTs) leads to promoter hypermethylation and the transcriptional silencing of a variety of tumor suppressor genes. Epigenetic alterations that result in dysregulated intracellular signaling pathways are proposed to promote cyst formation in ADPKD animal models. However, it is unknown whether DNMTs have a role in renal cyst formation.

Methods: To functionally test the role of DNMTs in renal cyst growth in vivo, Pkd1 conditional knockout mice were treated with the DNMT inhibitor 5-azacytidine. To investigate how DNMTs might regulate cystic renal epithelial cell proliferation and apoptosis, cystic cells were treated with either DNMT1 siRNA or the inhibitor 5-azacytidine.

Results: We found that DNMT1 mRNA was upregulated in Pkd1<sup>fl/ox</sup>:Ksp-Cre mice vs Pkd1<sup>fl/lox</sup> wild-type mice. Administration of 5-azacytidine to Pkd1<sup>fl/ox</sup>:Ksp-Cre mice resulted in a significant delay in cyst growth in vivo. Knockdown of DNMT1 with siRNA or inhibition with 5-azacytidine in Pkd1<sup>fl/ox</sup> mutant renal epithelial cells 1) decreased cystic epithelial cell proliferation as analyzed by the MTT assay, and induced G1 phase arrest as detected by FACS; and 2) decreased expression of Cyclin D1, phospho-Stat3, EGFR, and phospho-ERK, which were aberrantly upregulated and contribute to cystic epithelial cell proliferation in ADPKD. These results suggest that DNMT1 regulates cystic epithelial cell proliferation through these pathways. We also found that treatment with 5-azacytidine 1) induced cystic epithelial cell apoptosis as analyzed by Annexin V and PI double staining and TUNEL assay; and 2) increased the expression of p53, Bax and cleaved PARP, which suggested that the p53-Bax signaling pathway was involved in 5-azacytidine induced cystic renal epithelial cell death.

Conclusions: Inhibition of DNMT1 produces a potent anti-proliferative and pro-apoptotic effect in cystic renal epithelia and delays cyst formation in vivo, which suggests that targeting DNMT1 may function as a potential therapeutic strategy in ADPKD.

Funding: NIDDK Support

FR-OR102
Lanreotide Halts Polycystic Liver and Kidney Growth in Patients with Autosomal Dominant Polycystic Kidney Disease  
Tom JG Gevers,1 Jeroen C. Hol,1 René Monshouwer,1 Helena Dekker,1 Jack F. Wetzelis,2 Joost P.H. Drenth.1 1Gastroenterology and Hepatology, Radboud Univ Nijmegen Medical Centre, Netherlands; 2Nephrology, Radboud Univ Nijmegen Medical Centre, Netherlands; 3Radiation Oncology, Radboud Univ Nijmegen Medical Centre, Netherlands; 4Radiology, Radboud Univ Nijmegen Medical Centre, Netherlands.

Background: We showed that the somatostatin analogue lanreotide reduced liver volume in patients with polycystic livers. However, this trial included patients with autosomal dominant polycystic kidney disease (ADPKD) and with isolated polycystic liver disease (PCLD). The aim of the present study was to assess the efficacy of lanreotide treatment in ADPKD patients with symptomatic polycystic liver disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: This open-label clinical trial evaluated the effect of 6 months of lanreotide 120 mg subcutaneously every 4 weeks. Exclusion criteria were eGFR (MDRD) < 30 ml/min/1.73m², use of oral contraceptives and PCLD. The primary outcome was change in liver volume determined by computed tomography-volumetry. Secondary outcomes were changes in total kidney volume, eGFR and symptom relief. The severity of gastro-intestinal symptoms was measured with a 7-points scale questionnaire, and were dichotomized for absence or presence.

Results: We included 43 ADPKD patients with polycystic liver disease (84% female, mean age 51 years, eGFR 63 ml/min/1.73m²). Median liver volumes decreased from 4859 ml to 4595 ml (-3.2%, p<0.01), the reduction did not improve eGFR.

Conclusions: Lanreotide reduces polycystic liver and kidney volumes and decreases symptoms in ADPKD patients with polycystic livers. Previous treatment with somatostatin analogues does not impair efficacy.

Funding: Pharmaceutical Company Support - Received an unrestricted grant from Ipsen Pharmaceuticals

FR-OR103

Clinical Outcomes in ADPKD: Results from the TEMPO 3:4 Trial
Frank S. Czerwiec,1 Arlene B. Chapman,2 Olivier Devuyst,3 Ron T. Gansevoort,4 Frank E. Torres.7
1Otsuka, USA; 2Boston, USA; 3Kansas City; 4Rotterdam, Netherlands; 5Mitaka, Japan; 6Boston, USA; 7Rochester, USA.

Background: ADPKD is a hereditary disease of progressive kidney destruction by cysts associated with systemic complications. The effect of tolvaptan (T) on systemic aspects of ADPKD was prospectively assessed in the TEMPO trial.

Methods: Clinical outcomes related to ADPKD were collected at each study visit and were analyzed by incidence and time to multiple events as a 13- (systemic) and 9-item (kidney) composite and the 4 most frequently observed events.

Results: Tolvaptan (T) subjects had less ADPKD-related outcomes in both disease composites (p<0.05). Of the most common events renal pain, hematuria, and UTI occurred less often with T (p<0.05).

For each of these events, T subjects reported less medical resource use (healthcare visits and/or medical procedures) and lost productivity due to the event. All 9 kidney-related events occurred less often with T.

FR-OR104

Effect of Tolvaptan on Urine Osmolality Versus Outcome in ADPKD: Results from the TEMPO 3:4 Trial
Olivier Devuyst,1 Arlene B. Chapman,2 Ron T. Gansevoort,2 Jared J. Grantham,3 Eiji Higashihara,4 Ronald D. Perrone,4 Vicente E. Torres,5 Holly Krasa,1 John Ouyang,4 Susan E. Shoaf,6 Xiaofeng Wang,1 Frank S. Czerwiec,7 Zürich, Switzerland; 8Atlanta, USA; 9Groningen, Netherlands; 10Kensington, City; 11Tokyo, Japan; 12Boston, USA; 13Rochester, USA; 14Otsuka PDC.

Background: The TEMPO 3:4 trial indicated that the vasopressin V2-receptor (V2R) antagonist tolvaptan (T) slowed the increase in total kidney volume (TKV) and the decline in kidney function (eGFR) over 3 years in ADPKD patients with preserved eGFR. We investigated whether this beneficial effect could be predicted by changes in urine osmolality (Uosm).

Methods: Post-hoc, exploratory analyses of a prospective, blinded RCT. Trough morning spot urine samples were collected at baseline (BL), and months (M) 12, 24 and 36. By protocol, water intake was encouraged and use of diuretics discouraged.

Results: Baseline Uosm was similar in placebo (N=333) and T (N=668) subjects (515 vs 497 mOsm/kg, respectively). It correlated with age, eGFR, and TKV. Placebo treated subjects had mean changes from BL Uosm ranging between -26 and -85 mOsm/kg over M36, reflecting increased water intake. A lower average Uosm during the trial was associated with a lesser increase in TKV. T treatment significantly reduced Uosm vs. placebo (by 249 mOsm/kg at week 3 and by 190 mOsm/kg at M36), with no loss of effect over time. T subjects with a greater suppression in Uosm had a 2-fold reduction in the occurrence of clinical progression events (severe renal pain and worsening kidney function) vs. those with less Uosm suppression (12.1% vs. 23.3%, highest vs. lowest quartile of Uosm change vs. baseline, respectively), as confirmed by Kaplan-Meier analysis. T subjects with the greatest mean changes from BL Uosm were more likely to achieve no change in renal function.

Conclusions: These data in T treated patients (i) support the link between vasopressin V2R signalling and progression in ADPKD; (ii) suggest that monitoring Uosm could guide T titration and maintenance; and (iii) indicate that greater renoprotective effect may be achieved when Uosm is reduced by 300 mOsm/kg.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceuticals
Mortality and Length of Stay Increase with Acute Kidney Injury (AKI) Severity Stage in Critically Ill Children  

Scott M. Sutherland,1 John James Byrnes,2 Manish Kothari,2 Pablo Garcia,2 Stuart Goldstein,2 Pediatrics, Stanford Univ, Stanford, CA; 1SRU International, Menlo Park, CA; 4Center for Acute Care Nephrology, Cincinnati Children’s Hospital, Cincinnati, OH.

Background: Recently, standardized AKI definitions have been developed (pRIFLE, AKIN, and KDIGO). These consensus definitions do not have been correlated with outcomes in pediatric patients on a large scale.

Methods: Pediatric data including age, height, and serial serum creatinine values were extracted anonymously from the electronic medical record. Mortality rates and length of stay (LOS) distributions were calculated for each stage of each definition. Likelihood ratios were calculated to assess the mortality risk associated with incremental AKI severity stages.

Results: 2365 intensive care unit (ICU) hospitalizations were analyzed. The median age was 6.0 (IQR 2.0-14.0) AKI rates varied between the pRIFLE (39%), AKIN (30%), and KDIGO (35%) definitions; across all three, AKI severity stage was associated with increased mortality rates and LOS (Figure 1). Compared to patients without AKI, patients with AKI experienced a greater likelihood of death; more severe AKI was associated with a greater mortality risk (Table 1, all p-values < 0.001).

Table 1: Likelihood Ratio (LR) of Death by AKI Severity Stage

<table>
<thead>
<tr>
<th>AKI Definition</th>
<th>Stage 1 vs. No AKI</th>
<th>Stage 2 vs. No AKI</th>
<th>Stage 3 vs. No AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>pRIFLE</td>
<td>2.1</td>
<td>3.8</td>
<td>2.4</td>
</tr>
<tr>
<td>AKIN</td>
<td>0.7</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>KDIGO</td>
<td>1.2</td>
<td>6.6</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Figure 1: Mortality Rates and Median LOS by AKI Severity Stage

Conclusions: Within a large pediatric ICU cohort, AKI was significantly associated with poorer outcomes. Mortality rates and LOS increased incrementally as AKI severity increased. All three AKI definitions demonstrated strong outcome association. Further analysis is required to determine which definition is optimal.

Microalbuminuria in Children with Chronic Kidney Disease  


Background: Children are generally screened for proteinuria by measurement of urine protein/creatinine ratio (Up/c). By this screening method those with microalbuminuria (urine albumin:creatinine between 30 and 300 mg/g) are classified as having clinically insignificant proteinuria. We sought to examine microalbuminuria, in the absence of elevated Up/c, as a potential marker for lower GFR in children with CKD.

Methods: We used data collected in the Chronic Kidney Disease in Children (CKiD) study. Linear regression was used to quantify the association of initial spot urine protein/creatinine ratio (Up/c). By this screening method those with microalbuminuria (urine albumin:creatinine > 300 mg/g) were extracted anonymously from the electronic medical record. Mortality rates and length of stay (LOS) distributions were calculated for each stage of each definition. Likelihood ratios were calculated to assess the mortality risk associated with incremental AKI severity stages.

Results: 2365 intensive care unit (ICU) hospitalizations were analyzed. The median age was 6.0 (IQR 2.0-14.0) AKI rates varied between the pRIFLE (39%), AKIN (30%), and KDIGO (35%) definitions; across all three, AKI severity stage was associated with increased mortality rates and LOS (Figure 1). Compared to patients without AKI, patients with AKI experienced a greater likelihood of death; more severe AKI was associated with a greater mortality risk (Table 1, all p-values < 0.001).

Table 1: Likelihood Ratio (LR) of Death by AKI Severity Stage

<table>
<thead>
<tr>
<th>AKI Definition</th>
<th>Stage 1 vs. No AKI</th>
<th>Stage 2 vs. No AKI</th>
<th>Stage 3 vs. No AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>pRIFLE</td>
<td>2.1</td>
<td>3.8</td>
<td>2.4</td>
</tr>
<tr>
<td>AKIN</td>
<td>0.7</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>KDIGO</td>
<td>1.2</td>
<td>6.6</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Figure 1: Mortality Rates and Median LOS by AKI Severity Stage

Conclusions: Within a large pediatric ICU cohort, AKI was significantly associated with poorer outcomes. Mortality rates and LOS increased incrementally as AKI severity increased. All three AKI definitions demonstrated strong outcome association. Further analysis is required to determine which definition is optimal.
remained untreated. Treatment was started either prophylactically (P) at time of induction or with a two-week delay (D). Animals were sacrificed after 4 wk or observed open-ended.

**Results:** The 125kbp promoter of NPHS1, the gene which encodes nephrin, has been shown to have renal specificity. We developed a novel AA V2/9-MNP-GFP vector as a tool to direct kidney specific gene expression and potential therapy. Our goal was to characterize GFP expression in mice after systemic tail vein injection with the AA V2/9-MNP-GFP vector.

**Methods:** We designed an AA V2/9-MNP-GFP vector with the 1.25kb nephrin promoter to drive GFP gene expression. A CMV promoter (AAV2/9-CMV-GFP) was used as the positive control vector and saline as a negative control. Eight-week-old female C57 mice were injected with 3x10^11 viral particles of each vector. GFP expression within the kidneys by immuno- 

**Results:** AA V2/9-MNP-GFP transfected mice showed 6 fold higher viral copy numbers than CMV controls with a trend similar to the other tissues. Renal GFP RNA expression was 5 fold higher in the AAV2/9-CMV-GFP transfected controls compared to the AAV2/9-MNP-GFP mice. AAV9-MNP-GFP livers showed GFP RNA expression but no protein expression. GFP RNA expression was absent in brain and heart of AAV9-MNP-GFP mice. AAV2/9-MNP-GFP transfected mice demonstrated sustained glomerular GFP protein expression within the kidneys by immunofluorescence with no protein expression in the liver, brain and heart.

**Conclusions:** The AAV2/9 vector utilizing the 1.25kbp nephrin promoter provides a safe, viable tool for renal directed gene therapy in mice. These experiments provide a novel method for the investigation and potential therapy for congenital renal diseases in mice.

**Funding:** Private Foundation Support

**FR-OR112**

**Chronic Epithelial Kidney Injury Molecule-1 Expression in Mice Causes Inflammation, Fibrosis and Kidney Failure**

**Benjamin D. Humphreys, Venkata Sabbisetti, Fengfu Xu, Ivica Grgic, Said Movahedi Naini, Ningning Wang, Guochun Chen, Sheng Xiao, Dhruti D. Patel, Joel M. Henderson, Takaharu Ichimura, Shou Mou, Savuth Soeung, Andrew P. McMahon, Joseph V. Bonventre. Renal Div; Brigham and Women's Hospital, Boston, MA.

**Background:** Acute kidney injury predisposes to future CKD and ESRD but the molecular details underlying this clinical association are unknown. We report that chronic expression of Kidney Injury Molecule-1 (KIM-1), an epithelial phosphatidylserine receptor, expressed during acute injury and in fibrotic renal disease, promotes kidney fibrosis.

**Methods:** We generated a transgenic mouse line for conditional overexpression of KIM-1 in a cell specific manner. The KIM-1 conditional mouse line was crossed with a tubular Cre driver and we examined kidney phenotype over time. We also evaluated susceptibility to unilateral ureteral obstruction (UUO) induced fibrosis in mice with a targeted deletion of the murin domain of KIM-1, a KIM-1 polyepitope with markedly diminished phosphocytotic function.

**Results:** Mice with transgenic overexpression of KIM-1 in tubule epithelia, but no other cell type, developed spontaneous and progressive interstitial kidney inflammation with fibrosis leading to renal failure. Mice developed anemia, proteinuria, hyperphosphatemia, hypertension, cardiac hypertrophy and died of renal disease, analogous to progressive kidney disease in humans. KIM-1-transgenic kidneys had elevated expression of the pro-inflammatory chemokine monocyte chemotractant protein-1 (MCP-1) at early time-points. Heterologous expression of KIM-1 in an immortalized proximal tubule cell line triggered MCP-1 secretion and increased MCP-1-dependent macrophage chemotaxis. In KIM-1 mutant mice, experimental kidney fibrosis, secondary to UUO, was ameliorated and levels of MCP-1 were reduced, consistent with a pro-fibrotic role for native KIM-1.

**Conclusions:** Sustained KIM-1 expression, a characteristic of chronic kidney disease in humans, promotes kidney inflammation and fibrosis and provides a molecular link between acute injury and progressive chronic kidney disease.

**Funding:** NIDDK Support

**FR-OR113**

**Myofibroblastic Transformation of Renal Erythropoietin-Producing Cells Governs Fibrosis but Is Reversible in Early Injury Stage**

**Takaharu Ichimura, Shan Mou, Savuth Soeung, Andrew P. McMahon, Joseph V. Bonventre. Renal Div, Brigham and Women's Hospital, Boston, MA.

**Background:** Myofibroblasts are the culprit of renal fibrosis, and anemia develops along with scarring due to insufficient erythropoietin (Epo). We have recently characterized renal Epo-producing cells (REPs) as fibroblast-like cells with neural characters. They transform into myofibroblasts when injured, while exact contributions of REPs to the total myofibroblasts pool, mechanisms underlying this process and phenotypic reversibility are still unclear.

**Methods:** To analyze the myofibroblastic transformation process, we generated efficient monitoring and cell-fate tracing systems for REPs utilizing transgenic (Tg) complementary rescue method and Cre-loxP system. Genetically induced severe anemia in Tg-rescued mice enabled maximal recruitment and isolation of REPs. Transgenic Cre expressions, which are driven by full regulatory region of Epo, enabled tracking of cells with history of Epo expression.

**Results:** By adopting unilateral ureteral obstruction, we discovered that almost all myofibroblasts in cortex and outer medulla are derived from REPs. Transformed REPs were isolated by flow cytometry, and were found to lose their Epo-producing potential by 100%. On the contrary, they produced not only extracellular matrix, but also inflammatory mediators (such as CCL2, IL6, and so on). By removing the obstruction in early injury stage, myofibroblasts reverted to physiological status, regaining normal Epo-producing ability, and stopped producing excess collagen. Microarray analysis showed inflammatory signaling cascades were the top canonical pathways induced in injured kidneys during the transformation process. Thereby, anti-inflammatory therapy accelerated the reversion of myofibroblasts to normal REPs.

**Conclusions:** Our findings demonstrate that REPs are the major source of myofibroblasts, and possess profound plasticity. Modulation of cellular status of REPs is an important strategy to control the balance between beneficial repair/regeneration and deleterious scarring of kidneys.

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

**FR-OR114**

**Multiple Genes of the Renin-Angiotensin System Are Novel Targets of Wnt/β-Catenin Signaling in Kidney Injury**

**Li Li Zhou,1 Yingjian Li,1 Dong Zhou,2 Roderick J. Tan,3 Jing Nie,2 Fan Fan Hou,2 Youhua Liu.1 Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; 3Div of Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China; 1Dept of Medicine, Univ Pittsburgh, Pittsburgh, PA.

**Background:** Activation of the renin-angiotensin system (RAS) plays an essential role in the pathogenesis of chronic kidney and cardiovascular diseases. However, current anti-RAS therapy only displays limited efficacy, partly because of compensatory upregulation of renin expression. Therefore, developing a strategy to simultaneously target multiple RAS genes is necessary for the effective treatment of chronic kidney and cardiovascular diseases.

**Methods:** The promoter region of all RAS genes were analyzed by bioinformatics tool. The expression of RAS genes in cultured cells and kidney tissues were examined by qRT-PCR, Western blot, and immunostaining.

**Results:** By bioinformatics analyses, we uncovered that all RAS genes contained putative TCF/LEF-binding sites in their promoter regions, and β-catenin induced the binding of LEF-1 to these sites in kidney tubular cells. Over-expression of either β-catenin or different Wnt ligands induced the expression of all RAS genes. Conversely, a small molecule β-catenin inhibitor ICG-001 abolished RAS induction. In a mouse model of nephropathy induced by adenovirus, either transient therapy or late administration of ICG-001 was able to abolish an established proteinuria and kidney lesions. ICG-001 inhibited renal expression of multiple RAS genes in vivo, and abolished the expression of other Wnt/β-catenin target genes. As a result, ICG-001 therapy attenuated myofibroblast activation, repressed matrix expression, and inhibited renal inflammation and fibrosis.

**Conclusions:** Collectively, these studies identify all RAS genes as novel downstream targets of Wnt/β-catenin. Our results also indicate that blockade of Wnt/β-catenin signaling can simultaneously repress multiple RAS genes, thereby leading to the reversal of an established proteinuria and kidney injury.

**Funding:** NIDDK Support, Government Support - Non-U.S.
FR-OR115 Blocking the TGF-Beta Type II Receptor in Interstitial Cells Does Not Ameliorate Renal Fibrosis  Leslie S. Gewin,1,2 Roy Zent.1,2,3,4 1Dept of Research, Veterans Affairs Hospital, Nashville, TN; 2Div of Nephrology, Dept of Medicine, Vanderbilt Univ, Nashville, TN.

Background: TGF-beta exerts strong pro-fibrotic effects following injury, but the target cell responsible for mediating these effects is unclear. TGF-beta activates fibroblasts and induces their production of collagen I in vitro, but how TGF-beta signaling in fibroblasts modulates injury in vivo has not been examined.

Methods: To address this, we deleted the TGF-beta type II receptor in interstitial cells using two different tamoxifen-inducible Cre: COL1A2-Cre and Tenascin-C-Cre. The mTmG reporter mouse localized Cre activity, and recombination after tamoxifen administration in vivo was confirmed using PCR. Characterization of these interstitial cells was performed by FACS analysis.

Results: Surprisingly, both Tgbr2flx/flx;COL1A2-Cre and Tgbr2flx/flx;Tenascin-C-Cre mice had equivalent amounts of tubulointerstitial fibrosis compared to their Tgbr2flx/flx littermates killed at 7 and 4 days after unilateral ureteral obstruction (UUO). Fibrosis was measured by picric acid staining, immunohistochemistry for collagen I, IV, and fibronectin, and by immunoblotting renal tissue lysates for collagen I. Cells were isolated from both Tgbr2flx/flx;COL1A2-Cre and Tgbr2flx/flx;Tenascin-C-Cre mice after UUO using FACS to sort out EGFP+ cells. Primary cells from both mice expressed markers typical for fibroblasts. Cells isolated from Tgbr2flx/flx;COL1A2-Cre mice had markedly increased collagen I expression after stimulation with TGF-b1 but those from Tgbr2flx/flx;Tenascin-C-Cre mice had less collagen I at baseline and no significant response to TGF-b1.

Conclusions: These results suggest that interstitial cells with the type II receptor isolated from injured mice do upregulate collagen I expression in response to TGF-b1 in vitro, and this response is not observed in cells lacking the TGF-beta type II receptor. However, the absence of the TGF-beta type II receptor in interstitial cells does not protect against renal injury, indicating that in vitro data may not reliably predict in vivo responses and that TGF-beta signaling in medullary interstitial cells may not be important in modulating UUO-induced tubulointerstitial fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR116 Exploring the Function of Renal Fibroblasts of Extra-Renal Origin Jin Nakamura, Akiko Oguchi, Motoko Yanagita. Nephrology, Kyoto Univ, Graduate School of Medicine, Kyoto, Japan.

Background: We previously reported that most fibroblasts in the renal cortex and outer medulla are myelin protein zero-Cre (P0-Cre) lineage-labeled cells (P0 cells) of extra-renal origin, and that some of them are erythropoietin (EPO) producing cells in the outer medulla are myelin protein zero-Cre (P0-Cre) transgenic mice (Jin Nakamura, Akiko Oguchi, Motoko Yanagita. Exploring the Function of Renal Fibroblasts of Extra-Renal Origin FR-OR116 J Am Soc Nephrol 24: 2013). The cell responsible for mediating these effects is unclear. TGF-beta activates fibroblasts and tubular epithelial cells.

Methods: We utilized P0-Cre inducible simian diphtheria toxin receptor (DTR) transgenic mice (P0-Cre/iDTR mice). The binding of DT to DTR halts protein synthesis within P0 cells, inhibiting the crosstalk between fibroblasts and tubular epithelial cells.

Results: We confirmed that renal fibroblasts and tubular epithelial cells were successfully labeled with DTR in P0-Cre/iDTR mice. DT administration ablated the expression of DTR and fibroblast markers, indicating the effective cessation of protein synthesis in P0 cells. Simultaneously, the expression of EPO was significantly reduced, and did not increase even after the induction of severe anemia. In addition, the expression of tubular injury markers, as well as the proliferation of proximal tubule cells was inhibited. The administration of DT to P0-Cre/iDTR mice with unilateral ureteral obstruction reduced the expression of fibroblast markers, and enhanced the expression of tubular injury markers in diseased kidney. Unlike the results of healthy kidney, tubular proliferation in diseased kidney was attenuated. These results indicate the possible interactions between the fibroblasts and tubular epithelial cells. We are currently searching for the molecules responsible for the interactions.

Funding: NIDDK Support

FR-OR117 Tracing Tubular Cells’ Fate in Folic Acid Induced Kidney Injury Model by Lineage Tagging Jianling Tao,1,2 Peng Guo,3 Katalin Susztak.1 1Renal Electrophysiology and Hypertension Div, Dept of Medicine, Perelman School of Medicine, Univ of Pennsylvania, Philadelphia, PA; 2Div of Nephrology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China; 3Analytical Imaging Facility, Albert Einstein College of Medicine, Yeshiva Univ, Bronx, NY.

Background: Tubulointerstitial fibrosis (TIF) is the final common pathway leading to ESRD. Folic acid (FA) induced acute/chronic TIF model was used to follow the fate of different cell types in the kidney to address which tubule segment is injured and the origin of activated myofibroblasts (epithelial, pericyte).

Methods: We used the mouse model (mTmG) and different cre recombinases were used. Tomato fluorescence turned to GFP (mG) after cre-mediated recombination. Tubule cells were traced by the Pax8XRTA/TREcRed, proximal tubule epithelial cells by PEPCKCre, key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only Underline represents presenting author.

FR-OR136 Synergistic with Secreted Klotho Matthias Wolf,1 Chou-Lung Huang,2 1Pediatric Nephrology, Univ of Texas Southwestern Medical Center, Dallas, TX; 2Internal Medicine, Univ of Texas Southwestern Medical Center, Dallas, TX.

Background: Uromodulin (UMOD) is the most abundant urinary protein and protects against nephrolithiasis. We recently reported that UMOD acts extracellularly to upregulate TRPV5 by impairing its endocytosis. Secreted Klotho (sKL) cleaves the terminal siacid of TRPV5 N-glycan to allow the channel binding to galectin-1, which decreases endocytosis and increases surface abundance of the channel. We examined the mechanism of UMOD regulation of TRPV5, particularly the potential interaction with sKL.

Methods: TRPV5 surface abundance and activity were studied by biotinylation and whole-cell patch-clamp recording in HEK cells expressing TRPV5, UMOD and/or sKL. TRPV5 surface abundance was quantified using a previously described assay. Coexpression of UMOD increased current density (pA/PF) of wild-type TRPV5 (446±37, -UMOD vs 802±45, +UMOD, p<0.0001), but not N-glycan deficient (N355Q) TRPV5 (453±45, -UMOD vs 422±43, +UMOD). Similarly, UMOD increased surface abundance of WT-TRPV3, but not N355Q mutant, supporting that UMOD upregulates TRPV5 requires N-glycosylation. Upregulation of TRPV5 by UMOD was prevented by dominant-negative dynamin or by deletion of caveolin-1 in cells, as was the regulation by sKL. To examine the relationship between UMOD and sKL regulation of TRPV5, we showed that coexpression with sub-threshold dose of sKL or UMOD had no effect. To examine the effects of UMOD at sub-threshold dose of sKL and UMOD in combination markedly increased its surface abundance and current density. The above finding was confirmed using application of purified UMOD and/or purified sKL to the culture medium, supporting the action of UMOD or sKL from both isolated glomeruli and cultured podocytes.

Funding: NIDDK Support
Conclusions: UMOD and sKL increase TRPV5 channel activity synergistically. UMOD forms polymers in urine. One potential mechanism for synergy between UMOD and sKL is stabilization and enhanced galecinit-1 binding to TRPV5 on the apical membrane by UMOD, leading to decreased endocytosis of TRPV5. The effect of UMOD and sKL on TRPV5 may contribute to protection against nephrolithiasis. 
Funding: NIDDK Support

FR-OR120
Mice with Kidney-Specific Deletion of the Sodium/Calcium Exchanger 1 Have Increased Intestinal Calcium Absorption
Olivier Bonny,1,2 Candice Stoudmann,1 Vlasta Zavadova,1 Donald W. Hilgeman,2 Orson W. Moe.1
1Dept of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; 2Service of Nephrology, Lausanne Univ Hospital (CHUV), Lausanne, Switzerland; 1Dept of Internal Medicine and Physiology, John and Charles Pak Center of Mineral Metabolism, Univ of Texas Southwestern Medical Center, Dallas, TX.

Background: Hypercalciuria constitutes a key risk factor in kidney stone formation and the role of the renal sodium/calcium exchanger 1 (NCX1-SLC8A1) in this process is not known. We established a mouse model in which we deleted NCX1 in the distal part of the nephron and showed that these mice are hypercalciuric, have higher urine volume and lower urine pH compared to their WT littermates. Their levels of 1,25(OH)2-vitamin D are elevated, but PTH levels are normal. These mice displayed normal bone architecture at one year of age. We asked how these mice maintain calcium balance while being continuously hypercalciuric and we studied intestinal calcium absorption.

Methods: We used 8 (WT) littermates and 8 NCX1-kidney-specific KO (NCX1-KSKO) mice and performed Ca2+-absorption assay. The contribution of intestinal calcium load in hypercalciuria was studied by challenging the mice with a low calcium diet (0.12%) for one week and by measuring calcium balance in metabolic cages. Results: We compared mRNA levels of the calcium transporters TRPV6, PMCA and NCX1 in the duodenum of NCX1-KSKO and WT mice and found increased TRPV6 expression in NCX1-KSKO mice. Then, we performed Ca2+ absorption assay and found that NCX1-KSKO mice have significant increased intestinal calcium absorption (41% increase, 12 minutes after gavage). We finally exposed the mice to a low calcium diet and looked at complete calcium balance. Both WT and NCX1-KSKO mice stayed in balance even when challenged with low calcium diet.

Conclusions: In summary, we showed that NCX1-KSKO mice have increased intestinal calcium absorption due to higher 1,25(OH)2-vitamin D levels and are able to compensate for chronic hypercalciuria and maintain calcium balance.
Funding: NIDDK Support, Government Support - Non-U.S.

FR-OR121
Expression of the Calcium-Sensing Receptor in Mouse, Rat and Human Kidney
Joao Z. Graça,1,2 Martin Schepelmann,1 Rebecca M. Wadey,1 Sarah C. Brennan,1 Simon Brocklehurst,1 Daniela Riccardi,1 Sally A. Price.1
1AstraZeneca, Macclesfield, United Kingdom; 2Cardiff Univ, Cardiff, United Kingdom.

Background: The calcium sensing receptor (CaSR), a key GPCR for calcium homeostasis, is cloned and characterized in kidney nearly two decades ago. Nevertheless, there is still no consensus in the literature regarding the renal expression pattern and discrepancies have been reported between species. This work aims to elucidate the localisation of the CaSR in mouse, rat and human kidney and thus allow a better understanding of its physiological role.

Methods: CaSR expression was analysed by in situ hybridization (ISH) using a branched-DNA methodology and by immunohistochemistry (IHC) using four antibodies raised against different CaSR epitopes [ADD (Thermo/Abcam); N-term (Anaspec); C-term (custom made, mouse/rat); whole protein (Novus, human)]. These antibodies were selected from a panel of seven antibodies by assessing CaSR immunofluorescence pattern in CaSR-HEK cells. The specificity of the selected antibodies was further confirmed by western blotting in mouse, rat and human kidney. The expression of CaSR along the nephron was assessed by dual labeling with specific markers for the descending thin limb (DTL, aquaporin 1), thick ascending limb (TAL, Tamm-Horsfall), distal tubule (DT, Na+-Cl- cotransporter) and collecting duct (CD, aquaporin 2).

Results: By IHC, CaSR mRNA was detected in the TAL, and to a lesser extent in the DT and CD. By ISH, CaSR was found in proximal and distal convoluted tubule, TAL, and in collecting duct. In mouse, rat and human kidney with the four selected antibodies; generally CaSR immunoreactivity was stronger in the medulla/medullary rays and weaker in the cortex. Moreover, CaSR immunoreactivity was detected in proximal tubule (identified by the brush border), TAL, DT and CD, but not in the DTL.

Conclusions: Our data show that the CaSR is expressed along the nephron, including the TAL, CD and DT, with the strongest expression being seen in the TAL. These findings clarify the renal CaSR expression pattern in mouse, rat and human, and therefore enable the determination of its full pathophysiologcal role.
Funding: Government Support - Non-U.S.

FR-OR122
Elucidation of the Distal Convoluted Tubule Transcriptome Identifies New Candidate Genes Involved in Renal Magnesium Handling
Jeroen H.F. De Buij,1 René J. Bindels,1 Joost Hoenderop.1
1Dept of Physiology, Radboud Univ Nijmegen Medical Centre, Nijmegen, Netherlands; 2Molecular Cancer Research, UMC Utrecht, Utrecht, Netherlands.

Background: The kidney plays a key role in the maintenance of the magnesium (Mg2+) homeostasis. Specifically, the distal convoluted tubule (DCT) is instrumental in fine-tuning of the renal Mg2+ handling. In recent years hereditary Mg2+ transport disorders have helped to identify important players in DCT Mg2+ homeostasis. Nevertheless, several proteins involved in DCT-mediated Mg2+ reabsorption remains to be discovered and a full expression profile of this complex nephron segment may facilitate the discovery of new Mg2+-related genes.

Methods: Transgenic mice expressing eGFP under a DCT-specific parvalbumin promoter were generated, subjected to Mg2+-deficient or Mg2+-enriched diets. Subsequently, the Complex Object Parametric Analyzer and Sorter (COPAS) allowed for the first time isolation of eGFP-positive DCT cells. RNA extracts thereof were analyzed by DNA microarrays comparing high vs. low Mg2+ expressing cells.

Results: Here, we report the Mg2+-sensitive expression of the DCT transcriptome. Several known magnesiumotropic genes, such as Trpm6 and Parvalbumin, were upregulated under low dietary Mg2+. First, examination of the Mg2+-sensitive expression of allputative Mg2+ transporters identified Slc4a5 as potential Mg2+ extrusion mechanism in the DCT. Additionally, based on statistical significance and a fold-change of at least two, 46 genes showed differential expression. Among these, Pchd1, Tcl1a and Umod were identified to be potentially involved in renal Mg2+ handling. To confirm that the selected candidate genes were regulated by dietary Mg2+ availability, the expression levels of Slc4a5, Pchd1, Tcl1a and Umod were determined by qPCR analysis. Indeed, all four genes showed significant upregulation in the DCT of mice fed the Mg2+-deficient diet. Furthermore, GO-term enrichment analysis identified ‘EGF pathway’ and ‘Bone mineralization’ among the enriched pathways in low Mg2+-fed mice.

Conclusions: By elucidating the Mg2+-sensitive expression of the DCT transcriptome, several known magnesiumotropic genes, such as Trpm6 and Parvalbumin, were upregulated under low dietary Mg2+. First, examination of the Mg2+-sensitive expression of all putative Mg2+ transporters identified Slc4a5 as potential Mg2+ extrusion mechanism in the DCT. Additionally, based on statistical significance and a fold-change of at least two, 46 genes showed differential expression. Among these, Pchd1, Tcl1a and Umod were identified to be potentially involved in renal Mg2+ handling. To confirm that the selected candidate genes were regulated by dietary Mg2+ availability, the expression levels of Slc4a5, Pchd1, Tcl1a and Umod were determined by qPCR analysis. Indeed, all four genes showed significant upregulation in the DCT of mice fed the Mg2+-deficient diet. Furthermore, GO-term enrichment analysis identified ‘EGF pathway’ and ‘Bone mineralization’ among the enriched pathways in low Mg2+-fed mice.
Funding: Government Support - Non-U.S.

FR-OR123
New Missense Mutations Linked to Hypomagnesemia with Secondary Hypocalcemia
Joost Hoenderop,1 René J. Bindels,1 Sergio Laizne Vicente,1 Karl P. Schlingmann,2 Martin Konrad.1,3 Physiology, Radboud Univ Nijmegen Medical Centre, Nijmegen, Netherlands; 2General Pediatrics, Univ Münster, Münster, Germany.

Background: Despite recent progress in our understanding of renal magnesium (Mg2+) handling, the molecular mechanisms accounting for transsphenephalic Mg2+ transport are still poorly understood. Mutations in the TRPM6 gene, encoding the epithelial Mg2+ channel TRPM6 (transient receptor potential melastatin 6), have been proven to be the molecular cause of hypomagnesemia with secondary hypocalcemia (HSH). HSH manifests in the newborn period being characterized by very low serum Mg2+ levels (<0.4 mmol/L) accompanied by low serum calcium (Ca2+) concentrations. A proportion of previously described TRPM6 mutations lead to a truncated TRPM6 protein resulting in a complete loss-of-function of the channel.

Methods: The study cohort comprises five families from different ethnic origin with severe hypocalcemia and hypomagnesemia. A non-conservative amino acid exchange in TRPM6. Human embryonic kidney (HEK) 293 overexpressing wild-type and mutant TRPM6 were analyzed by patch-clamp analysis. Cell surface expression of TRPM6 was addressed by biotinylation assays.

Results: The aim of this study was to complement the current clinical picture by adding molecular data from six new missense mutations found in five patients with HSH. To this end, wild-type and mutated TRPM6 channels were expressed in HEK293 cells. Subsequent patch-clamp analysis and cell surface measurements were performed to assess the effect of the various mutations on TRPM6 channel function. To determine the functional implications of the mutations on TRPM6 channel activity, HEK293 cells were transiently transfected with either mock, WT TRPM6 or the different TRPM6 mutants (L389P, E405G, Y411C, L195P, Q458R, S129N). All mutant channels, except Q458R, expressed in HEK293 cells, showed loss-of-function, while an significant trafficking impairment to the plasma membrane surface was observed.

Conclusions: We conclude that the new TRPM6 missense mutations affect gating and ion permeation properties of the ion channel, leading to dysregulated intestinal/renal Mg2+ (re)absorption.
Funding: Government Support - Non-U.S.

FR-OR124
Hepatocytopyrophosphatase: A Novel Phosphaturic Factor in the Liver-Kidney Axis
Kengo Nomura, Sawako Tatsumi, Atsumi Miyagawa, Yuji Shiozaki, Shohei Sasaki, Hiroko Segawa, Ken-Ichi Miyamoto.1,2,3 Physiology, Molecular and Developmental Biology, Tokyo University of Science, Tokyo, Japan.

Background: Inorganic phosphate (Pi) absorption in the renal proximal tubules and small intestine is important for Pi homeostasis. The incidence of partial hepatectomy (PH) has also increased. Marked hypophosphatemia is common after major hepatic resection, but the pathophysiological mechanism remains unknown.

The incidence of liver transplantation has steadily increased, and, as a consequence, the incidence of partial hepatocytopyrophosphatase (PiF) has also increased. The PiF is more than a tumor suppressor; it also has a new role as a phosphaturic factor in the liver-kidney axis.
Methods: We used PH model rats to investigate the molecular basis of hypophosphatemia. PH rats exhibited hypophosphatemia and hyperphosphaturia. Renal and intestinal brush border membrane vesicles isolated from PH rats, The Na—dependent Pi (Na/Pi) uptake was decreased by 50% to 60%. PH rats also exhibited significantly decreased levels of renal and intestinal Na/Pi transporter proteins (NaPi-IIa, NaPi-IIb, and NaPi-IIc). Parathyroid hormone was elevated at 6 h after PH. Hyperphosphaturia persisted, however, even after thyroparathyroidectomy in PH rats. Moreover, DNA microarray data revealed elevated levels of nicotinamide phosphoribosyltransferase (Nampt) mRNA in the kidney after PH. Nampt catalyzes the first rate-limiting step in converting nicotinamide (NAM) to nicotinamide adenine dinucleotide (NAD). Nampt mRNA levels and the total NAD were significantly increased in the proximal tubules. PH rats also exhibited markedly increased levels of urinary NAM and NAM catabolites. In vitro analyses using opossum kidney cells revealed that NAM alone did not affect endogenous NaPi-IIa (Na/Pi-8) levels, but Nampt expression with the addition of its substrate (NAM) led to a marked decrease in the Na/Pi-4 protein levels. FK866, a specific Namp inhibitor, completely blocked this reduction in Namp-induced Na/Pi-4. Further, FK866-treated mice showed elevated renal Pi reabsorption and hypophosphatemia.

Conclusions: The findings of the present study indicate that hepatocaryotically-induced hypophosphatemia is due to abnormal NAM metabolism, including Nampt activation in the renal proximal tubular cells. The present study also suggests that Nam metabolism though the liver-kidney axis is important in Pi homeostasis.

Funding: Other U.S. Government Support

FR-OR125

Regulation of Renal Type IIa Sodium Phosphate Cotransporter (Npt2a) Trafficking by Na—H Exchanger Regulatory Factor 1 (NHERF1)

Eleanor D. Lederer, Rebecca Murray, Nina W. Lesousky, Syed J. Khansmitter, Edward J. Weinman. 

Medical Services, Robley Rex VA Medical Center, Louisville, KY; 2Medicine/Physiology, Univ of Louisville, Louisville, KY, 3Medicine, Univ of Maryland, Baltimore, MD.

Background: The PDZ domain protein NHERF1 plays a critical role as an anchor in the apical membrane (AM) for Npt2a, a proximal tubule transporter critical role for regulation of phosphate homeostasis. We and others have previously demonstrated that NHERF1 deficiency results in defective glycosylation and intracellular accumulation of Npt2a.

Methods: We hypothesized that NHERF1 associates with Npt2a prior to AM insertion and facilitates glycosylation. To test this hypothesis, we examined Npt2a—NHERF1 association in Golgi (G) by density gradient centrifugation of opossum kidney (OK) cells, a model of renal proximal tubule. Cells transfected with GFP—Npt2a wild type or C terminal—TDL deletion mutant constructs were treated with PTH to eliminate expression of surface Npt2a or Npt2e and to low phosphate medium to stimulate Npt2a/2c mRNA production for 8h. Cells were fractionated by sucrose gradient density centrifugation and the fractions containing G or plasma membrane identified by specific markers.

Results: Npt2a or GFP immunoprecipitation of G and PM fractions from cells expressing wild type GFP—Npt2a showed positive immunoblot for NHERF1. GFP—Npt2a lacking the terminal—TDL motif demonstrated failure to undergo complete glycosylation, associate with NHERF1 in the G, integrate into a membrane compartment, or traffic to the AM. Confocal imaging confirmed the diffuse intracellular distribution of the TRL of deletion mutant.

Conclusions: We conclude that Npt2a associates with NHERF1 in the G through the C-terminal PDZ binding domain and that this association is essential for Npt2a glycosylation, membrane incorporation, and AM trafficking. These findings suggest a novel chaperone function for NHERF1 in Npt2a regulation.

Funding: Veterans Affairs Support

FR-OR126

Egr-1 Mediates FGF23-Induced Hypophosphatemia but Does Not Inhibit Renal 1,25 (OH)2D Synthesis

Farranzo Perwad, Martin Y.H. Zhang, Anthony A. Portale. 

Pediatrics, Univ of California San Francisco, San Francisco, CA.

Background: The transcription factor, early growth response 1 (egr-1), is a biomarker of activation of the MAP kinase/extracellular signal regulated kinase 1/2 (ERK1/2) signaling pathway by fibroblast growth factor 23 (FGF23). In Hype mice, excess circulating FGF23 constitutively activates ERK1/2 signaling in the kidney, resulting in increased egr-1 expression and hypophosphatemia and 1,25-dihydroxy vitamin D (1,25(OH)2D) release. These abnormalities are reversed by blockade of FGF23-dependent ERK1/2 signaling.

Methods: To test whether egr-1 itself mediates the renal actions of FGF23, we administered FGF23 to wild-type (WT) and egr-1 null (egr-1/) mice. To explore the molecular mechanisms by which egr-1 mediates renal actions of FGF23, we performed chromatin-immunoprecipitation sequencing (ChIP-seq) with anti-egr-1 antibody.

Results: In WT mice, FGF23 induced hypophosphatemia and suppressed renal NaPi-IIa and Npt2c mRNA expression. In FGF23-treated egr-1/ mice, hypophosphatemic effect was blocked by PTH. FGF23-induced NaPi-IIa mRNA were not suppressed. In contrast, FGF23 induced equivalent suppression of renal Cyp27b1 mRNA and stimulation of Cyp24a1 mRNA expression in both WT and egr-1/ mice. Thus, downstream of FGF receptor binding and ERK1/2 signaling, we can distinguish the effector pathway that mediates inhibition of renal Pi reabsorption from the pathway that mediates inhibition of 1,25(OH)2D synthesis. In kidneys from FGF23-treated WT mice, we demonstrate rapid binding of egr-1 to regulatory DNA elements in proximity to genes that encode key participants in renal Pi cotransport, specifically: renal Na/Pi cotransporters, Npt2a and Npt2c, scaffolding proteins (Nherf-1, Nmerf-2, Ezrin, Gabap-1, and Zonap), and vesicle trafficking proteins (Rab37 and Sly3). In silico gene network analyses identified the following significant functional pathways in the egr-1 ChIP-seq dataset: cytoskeleton remodeling, TGF/NW signaling and FGF signaling pathways.

Conclusions: These data suggest that the phosphatase effect of FGF23 is mediated, at least in part, by activation of the transcription factor, egr-1. We have thus identified the FGF23-dependent egr-1 cistrome in the kidney.

Funding: Other NIH Support - HL062329, HL081785, T32 EB001650, T32 HL78285

FR-OR127

PTH Increases FGF23 Transcription by Activating the Orphan Nuclear Receptor Nurr1 Both In Vitro and in Experimental CKD and This Is Mediated by the Calcimimetic R568

Nicholas W. Chavkin, Matthew H. Crouthamel, Cecilia M. Giacchelli. 

Bioengineering, Univ of Washington, Seattle, WA.

Background: Erk1/2 phosphorylation and loss of SM22 α expression. Phosphate-induced ERK 1/2 phosphorylation was elevated to a similar extent in PiT-1 WT and E74K, and extent of matrix mineralization correlated with transport activity.

Methods: Wildtype (WT) and PiT-1 mutants PiT-1 mRNAs were similarly expressed, and protein localized to cell membranes in transduced VSMCs. VSMCs containing the PiT-1 mutations had decreased to a similar extent in PiT-1 WT and E74K expressing VSMCs compared to vector control. SM22α mRNA levels were decreased to a similar extent in PiT-1 WT and E74K expressing VSMCs compared to vector control. SM22α mRNA levels were decreased to a similar extent in PiT-1 WT and E74K expressing VSMCs compared to vector control. SM22α mRNA levels were decreased to a similar extent in PiT-1 WT and E74K expressing VSMCs compared to vector control.

Conclusions: Phosphate-induced matrix mineralization was much higher in VSMC expressing WT PiT-1 compared to E74K, and extent of matrix mineralization correlated with transport activity.

Funding: Veterans Affairs Support - HL081785, T32 EB001650, T32 HL78285

FR-OR128

Phosphate Transport-Dependent and -Independent Functions of the Sodium Dependent Phosphate Transporter, PiT-1, in Vascular Smooth Muscle Cell Mineralization

Nicholas W. Chavkin, Matthew H. Crouthamel, Cecilia M. Giacchelli. 

Bioengineering, Univ of Washington, Seattle, WA.

Background: Elevated serum phosphate is associated with increased vascular calcification in patients with chronic kidney disease. In vitro, elevated phosphate induces vascular smooth muscle cell (VSMC) mineralization, and this can be blocked by knocking down PiT-1. In this study, we aim to determine the contribution of phosphate transport—dependent and— independent functions of PiT-1 on VSMC mineralization.

Methods: Wildtype (WT) and PiT-1 mutants containing different point mutations of amino acids proposed to be required for phosphate uptake (E74K, S132A, and S623A) were generated and stably expressed in PI T-1 deficient mouse VSMCs derived from PiT-1 fl/fl Sm22α Cre transgenic mice. Cells were characterized for gene and protein expression by Q—PCR and immunocytochemistry. Sodium—dependent phosphate uptake, ERK1/2 phosphorylation, and VSMC calcification were analyzed using published analytical methods.

Results: WT and mutant PiT-1 mRNAs were similarly expressed and localized to cell membranes in transduced VSMCs. VSMCs containing the PiT-1 mutations had reduced sodium—dependent phosphate uptake compared with those containing WT PiT-1, with S132A and S623A having intermediate levels and E74K exhibiting the lowest levels. Phosphate—induced ERK 1/2 phosphorylation was elevated to a similar extent in WT—1 WT and E74K expressing VSMCs compared to vector control. SM22α mRNA levels were decreased to a similar extent in PiT-1 WT and E74K VSMCs compared to vector control.

Conclusions: ERK1/2 phosphorylation and loss of SM22α expression are phosphate uptake—independent activities of PiT-1, whereas stimulation of VSMC matrix mineralization by PiT-1 is predominantly phosphate uptake—dependent. Together, the data suggest that both phosphate uptake—dependent and— independent functions of PiT-1 contribute to processes important for matrix mineralization.

Funding: Other NIH Support - HL062329, HL081785, T32 EB001650, T32 HL78285

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

Underline represents presenting author.
Genetic Loss of Function Mutations in Zebrafish and Human CRB2, a Regulator of Epithelial Polarity, Are Associated with Podocyte Foot Process Effacement and Focal Segmental Glomerulosclerosis

Arindam Majumder,1 Shazia Ashraf,2 Svjetlana Lovric,2 Heon Yang Gee,2 Friedhelm Hildebrandt.1
1Immunology, Genetics, and Pathology, Uppsala Univ, Uppsala, Sweden; 2Div of Nephrology, Harvard Medical School, Boston Children’s Hospital, Boston, MA.

Background: Podocytes are polarized epithelial cells, a central component of the glomerular filtration barrier, and a major pathological target in kidney glomerular disease. In published work, we have identified a requirement for zebrafish crb2b, a conserved regulator of epithelial polarity, in podocyte morphogenesis. The Crb proteins are EGF-like domain transmembrane proteins which interact at the intersection of epithelial polarity, cell signaling, and membrane biosynthesis.

Methods: We study podocyte polarity in zebrafish crb2b mutants and we ask whether the CRB2 gene may be affected in human nephrotic syndromes.

Results: We present a null allele in zebrafish, crb2b
, which phenocopies our published morpholino results and independently confirms a role for crb2b in podocyte differentiation. In human CRB2 expression is conserved from zebrafish to humans. A combination of SNP homozygosity mapping and exome re-sequencing were used to screen for mutations in human CRB2 FSGS families. Analysis of the CRB2 sequence in 30 consanguinous sibling pairs identified a homozygous 1859 G > C missense mutation resulting in Cys 620 > Ser. The conserved Cys residue lies in an extracellular EGF like-repeat. The functional consequence of this mutation was tested in zebrafish crb2b mutants. Conclusions: Our genetic analyses in both zebrafish and humans indicate a requirement for CRB2 function in podocyte cell structure and function. These results suggest that some nephrotic syndromes may be due to fundamental misregulation of podocyte apical basal polarity.

Funding: Government Support - Non-U.S.

Gene-Gene Interactions in APOL1-Associated Nephropathy

Jasmin Divers, Nichollete D. Palmer, Lingyi Lu, Carl D. Langefeld, Michael V. Rocco, Pamela J. Hicks, Mariana Murca, Lijun Ma, Donald W. Bowden, Barry I. Freedman.

Wake Forest School of Medicine, Winston-Salem, NC.

Background: Two APOL1 nephropathy variants confer risk for non-diabetic end-stage kidney disease (ESKD) in African Americans (AAs). Modifying factors likely contribute as not all genetically high-risk individuals develop ESKD.

Methods: We tested variants from a prior discovery GWAS aimed at detecting single nucleotide polymorphisms (SNPs) that potentially interact with APOL1 to alter ESKD risk in 864 AA cases with non-diabetic ESKD and 612 non-nephropathy controls. The top 42 discovery interactive SNPs were re-examined in DNA from two new AA cohorts: 503 additional unrelated non-diabetic ESKD cases and 892 non-nephropathy controls (combined discovery + replication sample had 1,367 ESKD cases and 1,504 controls) and an independent family-based cohort including 608 1st degree relatives of non-diabetic ESKD probands. Logistic regression and mixed models were fitted to test for interaction effects. Two large cohort meta-analyses were performed in ESKD and albuminuria/eGFR in families.

Results: Seventeen SNPs replicated APOL1-interaction with ESKD in the same direction as the discovery GWAS analysis with interaction p-values < 0.05 in combined replication + discovery ESKD with CRH1 or CRH2.

Conclusions: We present a null allele in zebrafish, crb2b, which phenocopies our published morpholino results and independently confirms a role for crb2b in podocyte differentiation. In human CRB2 expression is conserved from zebrafish to humans. A combination of SNP homozygosity mapping and exome re-sequencing were used to screen for mutations in human CRB2 FSGS families. Analysis of the CRB2 sequence in 30 consanguinous sibling pairs identified a homozygous 1859 G > C missense mutation resulting in Cys 620 > Ser. The conserved Cys residue lies in an extracellular EGF like-repeat. The functional consequence of this mutation was tested in zebrafish crb2b mutants. Conclusions: Our genetic analyses in both zebrafish and humans indicate a requirement for CRB2 function in podocyte cell structure and function. These results suggest that some nephrotic syndromes may be due to fundamental misregulation of podocyte apical basal polarity.

Funding: NIDDK Support

Whole Exome Sequencing (WES) for Disease Gene Discovery in Familial IgA Nephropathy

Xiewen Song,1 Nicole M. Roslin,2 Bushra Joarder,3 Meng Yi Xu,4 Amireza Haghighi,5 Melody Ren,6 Mitchell Li Cheong Man,7 Andrew D. Paterson,7 York P. Pei,8 1Div of Nephrology, Univ Health Network, Toronto, Ontario, Canada; 2Program in Genetics and Genomic Biology, Hospital for Sick Children, Toronto, Canada.

Background: Multiple rare disease genes with high effect size have been implicated by genome-wide linkage analysis of familial IgA (fIgA) and none has been identified.

Methods: To identify disease genes for fIgA, we performed WES using AB Solid 5500xL platform in 21 patients from 15 well-characterized families (each with at least one known disease gene). We screened one or more affected individuals with persistent hematuria (fIgA, proteinuria).

Results: We present a null allele in zebrafish, crb2b
, which phenocopies our published morpholino results and independently confirms a role for crb2b in podocyte differentiation. In human CRB2 expression is conserved from zebrafish to humans. A combination of SNP homozygosity mapping and exome re-sequencing were used to screen for mutations in human CRB2 FSGS families. Analysis of the CRB2 sequence in 30 consanguinous sibling pairs identified a homozygous 1859 G > C missense mutation resulting in Cys 620 > Ser. The conserved Cys residue lies in an extracellular EGF like-repeat. The functional consequence of this mutation was tested in zebrafish crb2b mutants. Conclusions: Our genetic analyses in both zebrafish and humans indicate a requirement for CRB2 function in podocyte cell structure and function. These results suggest that some nephrotic syndromes may be due to fundamental misregulation of podocyte apical basal polarity.

Funding: NIDDK Support

Genomic Disorders in the Chronic Kidney Disease in Children (CKiD) Cohort

Miguel Verbistky,1 Simone Sanna-Cherchi,2 Krzysztof Kiryluk,1 Brittany J. Perry,1 Frederick J. Kaskel,2 Susan L. Furth,3 Bradley A. Warady,4 Craig S. Wong,4 Ali G. Ghavri,5 1Nephrology, Columbia Univ, New York, NY; 2Pediatric Nephrology, Children’s Hospital at Montefiore, Bronx, NY; 3Pediatric Nephrology, Children’s Hospital of Philadelphia, Philadelphia, PA; 4Pediatric Nephrology, Children’s Mercy Hospital, Kansas City, MO; 5Pediatric Nephrology, Univ of New Mexico, Albuquerque, NM.

Background: Previous studies reported a high prevalence of pathogenic copy number variants (CNVs) in children with Renal Hypoplasia (RHD). We followed up these data in the Chronic Kidney Disease in Children (CKiD) cohort, an observational study of pediatric nephropathy.

Methods:PennCNV was used to determine CNV calls in 420 CKiD samples genotyped on the Illumina Omni2.5 beadarrays (N=420). To identify rare pathogenic CNVs, we compared our data to 23,362 controls.

Results: Participants were phenotypically classified into Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT; N=216), which includes Renal Hypoplasia (RHD-69) and non-CAKUT (N=204, e.g. glomerular disorders). CNVs were diagnostic of 12 known syndromes in 15 individuals (5.6%): 10 (4.6%) in CAKUT and 5 (2.5%) in non-CAKUT participants, compared to 318 (1.4%) controls. Recurrent CNVs included 17p12 (INNFB) and 16p11.2 deletions. Additionally, 20 large, likely pathogenic CNVs were identified in another 19 children (4.5% of cohort): 9 (4.2%) in CAKUT, and 10 in 4.9% non-CAKUT. Genomic imbalances were most common in RHD patients (10% with known and 4.3% with likely pathogenic CNVs). In several cases, the microarray data indicated an alternative renal diagnosis.

Funding: Government Support - Non-U.S.
Conclusions: As significant number of children with CKD have an unsuspected genomic imbalance, particularly those with RHD. Moreover, most of the identified genomic disorders are rare, showing a known association with neurodevelopmental phenotypes. The diagnosis of CNV disorders has clinical implication for risk stratification, prediction of complications and personalized management of pediatric patients with CKD.

Funding: NIDDK Support

FR-OR134

Mutations in a Large VNTR of MUC1 Are Frequent in Autosomal Dominant Medullary Cystic Kidney Disease (MCKD) Vincent Mornier,1 Simon Hollebecque,2 Said Lebbah,3 Andre Megarbane,2 Andrea Gnikre,2 Brendan Blumenstiel,1 Anthony J. Bleyer,4 Andrew Kirby,5 Bertrand Knebelmann,4 Corinne Antignac,6 1Genetic Dept, Necker Hospital, Paris, France; 2Nephrology Dept, Necker Hospital, Paris, France; 3Broad Institute, Cambridge, MA; 4INSERM U983, Univ Paris Descartes, Paris, France; 5Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC; 6Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA; 7Genetic Medical Unit, Saint Joseph Univ, Beirut, Lebanon.

Background: MCKD is a rare autosomal dominant tubulo-interstitial kidney disease, sometimes associated with renal cysts and gout/hyperuricemia. UMOD mutations have been described in patients with hyperuricemia (MCKD2). Mutations in the MUC1 gene encoding mucin 1 were very recently identified in MCKD1 patients (Kirby et al, Nature Genet, 2013) using a sophisticated approach associating cloning of the genomic region, capillary sequencing and de novo assembly since next generation sequencing failed to identify them. All patients harbor a single cystine insertion in one copy of the 60-base repeat unit of the long CG-rich coding VNTR of MUC1. The frameshift is predicted to result in a mutant protein which is expressed in the distal tubule and collecting duct.

Methods: Using an approach coupling PCR amplification of patient DNA cleaved by Msel (that selectively cleaves the unmutated repeat sequence) and probe-extension assay (SNAPshot), we tested 26 new families.

Results: We detected the presence of the cystine insertion in 14/26 families. In addition, we detected a new 5bp deletion, which is predicted to result in the same mutant protein as the cystine deletion. Among 14/15 families with mutations, 101 individuals were affected, with detailed clinical information available for 75 patients. 58 reached ESRD at a mean age of 46 yrs (20-82 yrs) with high intrafamilial variability. Early gout occurred in only 1 case and hyperuricemia in 3 (2 from the same family). Renal cysts were present in 10/40 pts.

Conclusions: These results show that MUC1 mutations represent a frequent cause of MCKD.

FR-OR135


Background: The eukaryotic transcription unit includes the promoter enhancer interaction, which is essential for transcription. Enhancers can be upstream or downstream of the transcription start site. What separate the transcript units are the insulators. These are the important regulatory elements in the genome. Each regulatory element is associated with certain specific histone tail modifications. Epigenetic modifications are characterized by their cell type specificity. We used different combination of histone modifications ChIP-seq data to annotate the single nucleotide polymorphisms (SNPs) that are associated with kidney function and chronic kidney disease (CKD).

Methods: The human kidney epithelial cell epigenome was generated from ChIP-seq using H3K4me1/2/3, H3K27ac, H3K27me3, and H3K36me3 to target the human kidney epithelial cells (HCK8). The sequencing results were analyzed with the algorithm ChromHMM. The annotated human kidney epigenome map with annotated regulatory elements were used for mapping CKD associated SNPs (n=37) published in three different studies.

Results: Kidney specific epigenome was generated from HCk8 cell ChIP-seq. The outputs of the ChromHMM were states and patterns of regulatory elements, which are enhancers, promoters, transcribed regions, insulators, and repressed regions. Next, we compared the SNPs annotated with the kidney regulatory elements to nine cell types published in ENCODE project. The results revealed that CKD associated SNPs have strong cell type specificity enrich in human enhancers. Furthermore, to exclude the possibility that all the SNPs are enriched in kidney specific enhancers, we used 36 control SNPs from unassociated studies. These SNPs did not show cell type specific gene regulatory region pattern.

Conclusions: CKD SNPs are enriched in the kidney specific gene regulatory regions, especially in the enhancers. This approach can potentially be used for prioritizing SNPs found in genome-wide association studies.

Funding: NIDDK Support

FR-OR136

The 4D Study: 11 Years of Follow-Up, Effects on Mortality and Morbidity of 4 Years Atorvastatin Treatment in 1255 Patients with Diabetes Mellitus on Hemodialysis, a Randomized, Controlled Trial Vera Krane,1 Kay-Reinke Schmidt,1 Lena Johanna Gutjahr-Lengsfeld,1 Brittia Stahl,1 Monika Mehligh,1 Susanne Kempp,1 Winfried Marx,2 Christoph Wanner.1 1Dept of Medicine I, Div of Nephrology, Univ Hospital, Univ of Würzburg, Würzburg, Germany; 2Synlab Medical Services GmbH, Mannheim, Germany.

Background: Findings of large randomized trials of lowering LDL-cholesterol in dialysis patients have shown controversial results, limited evidence exists about the long-term effects. The aim of this follow-up of the German Diabetes Dialysis Study (4D Study) is to assess long-term effects of atorvastatin treatment in hemodialysis (HD) patients.

Methods: 1255 patients with type 2 diabetes mellitus on HD were randomly allocated to either 20mg atorvastatin daily or placebo, median follow-up was 4 years. Post-trial statin treatment was at the discretion of the patients' nephrologists. The primary outcome of the 4D study was a composite of death from cardiac causes, nonfatal myocardial infarction (MI) and stroke. Analysis was by intention to treat.

Results: In and post-trial follow-up yielded a mean duration of 11.5 years in both groups. Overall, 90% of patients died. Post-trial statin use (51% and 48%) and LDL levels were similar in both groups. Allocation to atorvastatin during the in-trial period yielded an average reduction in LDL cholesterol of 42%. Over the entire time period, a proportional non-significant 9% decrease in the combined endpoint of cardiac death, MI and stroke (95% CI, 0.78 to 1.07) was detected. However, the risk of all cardiovascular events combined was significantly reduced (RR 0.83, 95% CI 0.70-0.97) whereas the incidence of all cerebrovascular events combined did not differ between groups (RR 0.94, 95% CI 0.72-1.23). No significant effect of atorvastatin on fatal infection (RR 0.97, 95% CI, 0.76-1.23), or all-cause death (RR 0.93, 95% CI 0.82-1.04) was detected. No case of rhabdomyolysis was reported.

Conclusions: After 4 years of atorvastatin treatment, no significant effect on the 11 year endpoint of cardiac death, MI and stroke was detected. However, there was a significant 17% relative risk reduction in all cardiovascular events combined and no evidence of emerging hazards.

Funding: Government Support - Non-U.S.

FR-OR137

Unchanged Heart Function and Blood Pressure after Cholecalciferol Treatment–A Randomized Controlled Trial Frank H. Mose,1 Henrik Vase,2 Thomas Larsen,1 Anne Sophie Pinholt Kancir,1 Renata Kosierkiewicz,2 Bartlomiej B.J. Jonczy,2 Anna Ewa Ozaczowska-Kulik,3 Ingrid Moeller Thomsen,1 Jesper N. Bech,1 Erling B. Pedersen,1 1Dept of Medical Research, Holstebro Hospital and Aarhus Univ, Denmark; 2Dept of Medicine, Holstebro Hospital, Denmark; 3Dept of Cardiology, Aarhus Univ Hospital, Denmark.

Background: In dialysis patients vit-D3 improved biochemical endpoints, but the effect of vit-D3 supplementation on cardiovascular function and BP is unknown. The aim of this study was to test the hypothesis that vit-D3 supplementation improves cardiac function and reduces BP and pulse wave velocity (PWV) in patients on chronic dialysis.

Methods: In a randomized, placebo-controlled, double-blind study, we investigated the effect of the 75 µg vit-D3 per day for 6 months, in patients on chronic dialysis. We performed two-dimensional echocardiography, with doppler and tissue-doppler imaging, 24-h ambulatory BP (24-h BP), PWV, augmentation index (Aix), central BP (cBP) and brain natriuretic peptide (BNP) at baseline and after 6 months.

Results: Sixty-four patients were allocated to the study, and 50 patients (42 on hemodialysis and 8 on peritoneal dialysis) completed the trial (25 in vit-D3 and 25 in placebo group). Mean age 68 years (range 46 to 88), 32 were men, BMI 23.9±4.4 kg/m², HD duration 25±10 years, plasma parathyroid hormone (PTH) 30±10 mIU/L, 25(OH)D 28 (29.5) nmol/L. Age, sex, BMI and P-25(OH)D were not significantly different between groups at baseline. After 6 months, Vit-D3 had no impact on left atrial or ventricular structure. LV systolic and diastolic function was not changed by vit-D3. 24-hour BP decreased significantly in placebo group and in-significantly in vit-D3 group, but with no difference between treatments (p=0.314 for systolic BP and p=0.344 for diastolic BP). PWV, cBP, Aix and BNP were not changed in placebo or vit-D3 group at follow-up. P-25(OH)D increased significantly compared to placebo (88 (67,125) vs. 34 (21,56); p<0.001).

Conclusions: In conclusion, 6 months vit-D3 treatment in patient on chronic dialysis did not improve 24-h BP, arterial stiffness or cardiac function.

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

FR-OR138


Background: Atrial fibrillation (AF) is increasingly common in patients on hemodialysis (HD). Although warfarin is indicated to prevent ischemic strokes in most patients with AF, evidence for its use in HD patients is limited and conflicting. In this observational cohort study, we examined the net safety of initiating warfarin for AF in a large, nationally-representative cohort of patients on chronic HD.

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

Underline represents presenting author.

68A
Methods: We identified from the USRDS all adult HD patients who were newly diagnosed with AF during a hospitalization from 2007-10, who participated in the low income study program of Medicare Part D, and who had no history of warfarin use in 26 months prior to admission. Patients who filled a first prescription for warfarin within 30 days of discharge were considered users; all others were non-users. We excluded patients who died within 30 days of discharge. We applied Cox regression to a propensity-score matched cohort of warfarin users and non-users to estimate the hazard ratios (HR) for all-cause mortality and the combined outcome of gastrointestinal bleeding (GBB), any stroke, or death.

Results: Among 9316 patients, 1330 (14%) initiated warfarin. We matched 1329 warfarin users to 1329 non-users whose observed baseline characteristics were exquisitely balanced. Over 3163 person-years of follow-up, we observed 1083 deaths, 189 GBB, and 149 strokes. Warfarin initiation was associated with a decreased risk of both all-cause mortality [HR 0.85; 95% confidence interval (CI): 0.75-0.95] and the composite outcome (HR: 0.87, 95% CI: 0.78-0.98).

Conclusions: In HD patients with hospitalized incident AF, warfarin use was associated with a decreased risk of both all-cause mortality and a composite outcome of GB, any stroke, and death, indicating net benefit of warfarin use in this indication. This is at odds with several previous studies that have suggested an increased risk of adverse outcomes in users. Given the uncertainty surrounding warfarin for AF in HD patients, further clinical trials are warranted.

Funding: NIDDK Support

FR-OR139

Irbesartan Shows No Beneficial Blood Pressure Independent Effects on Intermediate Cardiovascular Risk Markers in Hemodialysis Patients

Christian D. Peters,1 Krista D. Kjaergaard,1 J Dam Jensen,1 Kent L. Christensen,2

Intermediate Cardiovascular Risk Markers in Hemodialysis Patients

Methods: We identified all adult HD patients who were newly diagnosed with AF during a hospitalization from 2007-10, who participated in the low income study program of Medicare Part D, and who had no history of warfarin use in 26 months prior to admission. Patients who filled a first prescription for warfarin within 30 days of discharge were considered users; all others were non-users. We excluded patients who died within 30 days of discharge. We applied Cox regression to a propensity-score matched cohort of warfarin users and non-users to estimate the hazard ratios (HR) for all-cause mortality and the combined outcome of gastrointestinal bleeding (GBB), any stroke, or death.

Results: Among 9316 patients, 1330 (14%) initiated warfarin. We matched 1329 warfarin users to 1329 non-users whose observed baseline characteristics were exquisitely balanced. Over 3163 person-years of follow-up, we observed 1083 deaths, 189 GBB, and 149 strokes. Warfarin initiation was associated with a decreased risk of both all-cause mortality [HR 0.85; 95% confidence interval (CI): 0.75-0.95] and the composite outcome (HR: 0.87, 95% CI: 0.78-0.98).

Conclusions: In HD patients with hospitalized incident AF, warfarin use was associated with a decreased risk of both all-cause mortality and a composite outcome of GB, any stroke, and death, indicating net benefit of warfarin use in this indication. This is at odds with several previous studies that have suggested an increased risk of adverse outcomes in users. Given the uncertainty surrounding warfarin for AF in HD patients, further clinical trials are warranted.

Funding: NIDDK Support

FR-OR141

Fluid Overload in Hemodialysis (HD) Patients: Development and Validation of a ‘Big Data’ Predictive Analytic

Steven M. Brunelli,1 Karthik Ramakrishnan,1 Scott Sibb,2 Irina Goykhman,3 Chhaya B. Patel,1 Robert Provenzano,1 Stephen D. Murray,2 David B. Van Wyck,2 Allen R. Nissensohn,3 Mahesh Krishnan,1 1DaVita Clinical Research, MN; 2DaVita Labs, FL; 3DaVita HealthCare Partners Inc, CO.

Background: Fluid management is poor for many HD patients, with consequences that include increased morbidity, mortality, and utilization of healthcare resources. The ability to prospectively identify patients at high risk of imminent fluid-related hospitalization (FRH) would enable targeted implementation of avoidance strategies, and the more efficient allocation of resources. The aim of this study was to derive an empirical clinical risk algorithm using available clinical data to predict risk of FRH in the subsequent 3 months.

Methods: Demographic and clinical data were abstracted from the DaVita Clinical Data Warehouse. FRH events were identified from Centers for Medicare and Medicaid Services claims data. In the derivation set, predictor variables were considered as of Sept 2009 and used to predict risk of FRH in Q4 2009. In the validation set, predictors were considered as of June 2009; predicted and observed Q3 2009 FRH were compared.

Results: The derivation set contained 60,114 patients; the validation set contained 57,245 patients. Sixty-seven variables were identified and included in the model (C-statistic, 0.71). In the validation set, the model demonstrated excellent calibration over the 20-fold range of risk observed; patients in the highest decile of predicted risk demonstrated more than 3-fold greater risk of observed FRH (risk ratio, 3.2 [CI: 2.9, 3.7]; rate ratio, 3.4 [CI: 3.1, 3.8]).

Conclusions: The algorithm accurately and reproducibly predicts risk of FRH and can be tailored to accommodate more or less restrictive definitions of risk. Use of the algorithm will permit identification of high risk patients in whom to target interventions, and allow for the judicious allocation of resources.

Funding: Pharmaceutical Company Support - DaVita HealthCare Partners Inc
FR-OR142

Plasma Long-Chain Acylcarnitines Predict Cardiovascular Mortality in Incident Dialysis Patients

Sahir Kalim,1 Claire B. Clish,2 Julia Beth Wenger,1 Sammy Elmiriah,1 Robert W. Yeh,1 Joseph James Deferio,1 Kerry A. Pierce,2 Amy Deik,3 Robert E. Gerszten,2,3 Ravi I. Thadhani,1 Eugene P. Rhee,1,4

1Nephrology, RWTH, Aachen, Germany; 2Cardiology, RWTH, Aachen, Germany; 3Clinical Epidemiology, Leiden Univ, Leiden, Netherlands.

Background: Cardiovascular (CV) mortality in end stage renal disease is mainly driven by sudden cardiac death and recurrent heart failure due to uremic cardiomyopathy (UC). An early detection of UC might identify patients at risk and can have clinical impact in therapeutic decision-making. 2-dimensional strain echocardiography (2DSE) is a recently developed method to determine myocardial function in a multidimensional fashion.

Methods: In an animal study using two rat models of UC we tested whether 2DSE is superior to routine echocardiography to detect early changes in myocardial contractility. In a clinical study 2DSE parameters, ejection fraction (EF) and clinical characteristics were assessed in 171 ESRD patients, patients were followed up for 2.5 years. Primary endpoint was CV-mortality and secondary endpoint was all-cause mortality.

Results: Animal study-Using 2DSE in two rat models of UC early (4-6 weeks) after induction of kidney disease we observed that global radial and circumferential strain parameters were significantly decreased whereas fractional shortening (FS) and cardiac output (CO) remained unchanged. Furthermore, compared to FS and CO, 2DSE parameters showed better correlations with histologic hallmarks of UC (grade of interstitial fibrosis and cardiomyocyte cross-sectional area). Clinical study-During the follow-up period, EF and various 2DSE parameters were significant risk factors for CV mortality in a multivariate Cox model (EF hazard ratio-HR 0.97 95% confidence interval CI 0.95-0.99, P=0.012, peak global longitudinal strain HR 1.17 95% CI 1.07-1.28, P=0.001, peak systolic and late diastolic longitudinal strain rates HR 4.7, 95%CI 1.23-17.64, P=0.023, HR 0.25, 95%CI 0.08-0.79 P=0.019, respectively). Multivariate cox-regression analysis revealed circumferential early diastolic strain rate among others as an independent risk factor for all-cause mortality (HR 0.43; 95%-CI 0.25-0.74; p=0.002).

Conclusions: 2DSE can detect UC early in rats and predicts cardiovascular and all-cause mortality in ESRD patients.

Funding: Private Foundation Support

FR-OR143

Speckle Tracking Echocardiography Detects Uremic Cardiomyopathy Early and Predicts Cardiovascular Mortality in End-Stage Renal Disease

Rafael Kramann,1 Vincent Brandenburg,2 Thilo Knueger,1 Jürgen Flecke,2 Georg Schlieper.1

1Nephrology, RWTH, Aachen, Germany; 2Cardiology, RWTH, Aachen, Germany; 3Clinical Epidemiology, Leiden Univ, Leiden, Netherlands.

Background: Circumferential early diastolic strain rate among others as an independent risk factor for 95%-CI 0.08-0.79 p=0.019, respectively). Multivariate cox-regression analysis revealed

Methods: In two independent nested case-control studies, we applied liquid chromatography-mass spectrometry based metabolite profiling to plasma obtained from participants of a large cohort of incident hemodialysis patients.

Results: First, 100 individuals who died of a cardiovascular cause within one year of initiating hemodialysis (cases) were randomly selected alongwith 100 individuals who survived for at least one year (controls), matched for age, sex, and race. Four long-chain acylcarnitines achieved the significance threshold adjusted for multiple testing (P=0.0003), and remained associated with 1-year cardiovascular death after multivariable adjustment: oleoylcarnitine (odds ratio (OR) per SD 2.3 [95% confidence interval, 1.4-3.8]; P=0.001), linoleoylcarnitine (OR per SD 2.4 [1.4-4.1]; P=0.002), palmitoylcarnitine (OR per SD 1.8 [1.2-2.8]; P=0.006), and stearoylcarnitine (OR per SD 1.6 [1.1-2.5]; P=0.025). The association between oleoylcarnitine and 1-year cardiovascular death was then replicated in an independent sample (n= 300, OR per SD 1.8 [1.1-1.9]; P=0.008). Addition of oleoylcarnitine to clinical variables improved net reclassification (NRI, 0.38 [95% CI 0.20-0.56]; P=0.0001). In physiologic profiling studies, we demonstrate that the fold change in plasma acylcarnitine levels from the aorta to renal vein and from pre- to post hemodialysis samples exclude renal or dialytic clearance of long-chain acylcarnitines as confounders in our analysis.

Conclusions: Our data highlight clinically meaningful alterations in acylcarnitine homeostasis at the time of dialysis initiation which may represent an early marker, effector, or both of uremic cardiovascular risk.

Funding: NIDDK Support, Private Foundation Support

FR-OR144

Low Serum Bicarbonate Is Associated with Lower Cardiac Mortality (CM) in Hemodialysis (HD) Patients


Dept of Medicine, Univ of Utah, Salt Lake City, UT.

Background: Recent data suggest ↑ serum bicarbonate (bicarb) is associated with ↑ mortality. However, the associations of lower serum bicarb with mortality is controversial. Therefore, we examined the associations of lower than normal serum bicarb with mortality using the HEMO Study data.

Methods: The HEMO study was a 2x2 factorial design randomized controlled trial of dialysis dose and dialysis flux of 4146 prevalent HD pts. Patients were enrolled in the study from March 1995 until October 2000 and followed through December 2001. Causes of deaths were adjudicated by an outcomes committee. The associations of baseline pre-dialysis serum bicarb with all-cause mortality (ACM) and cardiac mortality (CM) were examined in Cox proportional hazard regression models adjusted for age, gender, race, diabetes, duration of dialysis, ICED score, Kt/v group, flux group, enPCR, arthralgia, pre HD dialysis serum albumin, K, Ca and P.

Results: Mean age was 58±14 yrs, 56% were female , 63 % were black and 69% had diabetes. Serum bicarb , Ca and K levels were 21.5±3.6, 9.29±.97 and 4.86±.77 mEq/L respectively. There were 16.8 ACM and 9.0 CM events per 100 patient years, respectively. The associations of serum bicarb with ACM and CM are summarized in Figure 1.

Conclusions: A U-shaped association between serum HDL cholesterol level and all-cause and CV mortality exists in HD patients with HDL around 50 mg/dL, associated with a rise in all-cause and cardiovascular mortality. All-cause and CV mortality HR was 1.28 (1.20-1.38) and 1.08 (1.01-1.16) for HDL<30 mg/dL and 1.05 (1.00-1.10) and 1.08(1.00-1.16) for HDL≥60 mg/dL, respectively (reference: HDL 30–60 mg/dL).

Funding: NIDDK Support

FR-OR145

Elevated Serum High Density Lipoprotein Cholesterol Level Is Paradoxically Associated with Increased Overall and Cardiovascular Mortality in Patients on Hemodialysis

Hamid Moradi,1,2 Elani Streja,1,2 Nosratola D. Vaziri,1 Moti L. Kashyap,2 Gregg C. Fonarow,1 Kamary Kalantar-Zadeh.3,2 Harvard Simmons Center, Orange, CA; 1Univ of California, Irvine, CA; 2Univ of California, Los Angeles, CA.

Background: High density lipoprotein (HDL) confers protection against atherosclerosis by different several mechanisms. Although in the general population, increasing levels of HDL are associated with reduced cardiovascular (CV) mortality, this association is not well known in patients with chronic disease states such as end stage renal disease. We hypothesize that the association of serum HDL concentration with all-cause and CV mortality in hemodialysis patients is different from the general population.

Methods: We examined the survival impact of serum HDL level in a 3-year (6/2004-6/2007) cohort of 33,109 maintenance hemodialysis patients being treated in clinics of a large dialysis organization using Cox models adjusted for demographics and case-mix variables and cubic splines were plotted.

Results: In this cohort the mean age (mean + SD) was 60±15 years old and included 45% women, 33% African-Americans, and 61% diabetics. In the fully adjusted models, higher HDL concentrations up to 50 mg/dL were associated with better overall survival, while HDL above 60 mg/dL was associated with a rise in all-cause and cardiovascular mortality. All-cause and CV mortality HR was 1.28 (1.20-1.38) and 1.08 (1.01-1.16) for HDL<30 mg/dL and 1.05 (1.00-1.10) and 1.08(1.00-1.16) for HDL≥60 mg/dL, respectively (reference: HDL 30–60 mg/dL).

Funding: Private Foundation Support

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

70A
SA-OR001

Mortality, Cardiovascular and End-Stage Renal Disease Outcomes among Older Live Kidney Donors

Peter P. Reese,1 Roy D. Bloom,1 Harold I. Feldman,1 Paul Rosenbaum,1 Wei Wang,2 Philip Saynisch,2 Nicole Tarsi,2 Nabania Mukherjee,2 Amit X. Garg, Adam S. Mussell,1 Orit Even-Shoshan,1 Raymond R. Townsend,1 Jeffrey H. Silber.1

1Univ of Pennsylvania; 2Children’s Hospital of Philadelphia; 3Univ of Western Ontario.

Background: Older individuals (≥55 y/o) have been accepted for live kidney donation more commonly over the past two decades. Given strong associations of both older age with worse renal function and cardiovascular (CV) disease, nephrectomy could make older donors vulnerable to death, CV events and end-stage renal disease (ESRD).

Methods: We performed a matched cohort study of older individuals who underwent nephrectomy between the years 1996–2006 and participants in the Health and Retirement Study (HRS). Each donor was matched to an HRS participant who was free of important comorbidities close to the date of the donor’s nephrectomy. Among 5125 donors, 3368 (65%) were matched to healthy comparators using demographics, economic environment and body mass index. The primary outcome was death, ascertained from death registries. Secondary outcomes ascertained for pairs with Medicare claims were a) death/CV diagnoses, and b) ESRD.

Results: In each group, the mean age was 59 y/o and 6% were African-American. In median follow up of 7.8 years, mortality was not significantly different between donors and matched non-donors (p=0.70). Among pairs in Medicare, the risk of ESRD was higher for donors (HR 7.4; 95% CI 2.91, 18.8; p<0.001), although the number of donors with ESRD was small (n=20).

Conclusions: These findings suggest that kidney donation does not expose carefully selected older individuals to a higher risk of death or cardiovascular disease. While ESRD was rare, older donors have an elevated risk of this outcome.

Funding: NIDDK Support, Private Foundation Support

SA-OR002

Donor Tubular Phosphate Handling Independently Predicts Recipient Outcomes after Living Donor Kidney Transplantation

Marco van Londen, Jelmer Kor Humalda, Johannes S. Sanders, Stephan J.L. Bakker, Gerjan Navis, Martin H. De Bore. Dept of Nephrology, Univ Medical Center Groningen, Netherlands.

Background: Identification of pre-transplantation (pre-Tx) donor factors associated with recipient outcomes may help to improve prognosis after kidney transplantation. Tubular injury leads to reduced expression of NaPi cotransporters and reduced phosphate (Pi) transport. We investigated whether pre-Tx parameters of Pi metabolism in living donors and in recipients were associated with recipient outcomes after transplantation (post-Tx).

Methods: In 130 donors, pre-Tx TmP-GFR, serum and urinary Pi, plasma fibroblast growth factor 23 and parathyroid hormone, fractional Pi excretion and TmP-GFR (tubular maximum Pi reabsorption per GFR) were determined. In corresponding recipients GFR was measured 1 year post-Tx, and follow-up data documented. Associations between pre-Tx donor factors and recipient post-Tx GFR were tested by linear regression. Next, a multivariate Cox regression model for a composite endpoint of rejection, graft failure or recipient mortality was built using pre-Tx donor factors, recipient factors, and transplant characteristics.

Results: Pre-Tx GFR in donors (age 52±10 yrs, 48% men) was 118±24 ml/min. GFR one year post-Tx in recipients (age 48±19 yrs, 61% men) was 60±19 ml/min. In multivariate regression, pre-Tx donor TmP-GFR (standardized β 0.30, P=0.003) and donor age (β -0.28, P=0.01) were independent determinants of recipient 1-yr post-Tx GFR (final model R²=0.29). During follow up of 2.4 [1.2-3.2] yrs, 29 recipients had rejection, 3 graft failure and 9 died. Donor pre-Tx TmP-GFR was independently associated with the composite endpoint (HR 0.25 [95% CI 0.08-0.72] per 1 mg/dl TmP-GFR, P=0.01), along with age, cold ischemia time and recipient gender. Other Pi-related factors were not associated with recipient outcome.

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

SA-OR003

New K/DIGO Guidelines and Kidney Transplantation: Is the Cystatin-C Based Recommendation Relevant?

Ingrid Masson,1 Nicolas Maillard,2 Pierre Delanaye.2

1Nephrology Dialysis Renal Transplantation, Univ Hospital, Saint-Etienne, France; 2Dialysis, Univ Hospital, Liege, Belgium.

Background: In 2013, K/DIGO guidelines published recommendations for evaluation and management of chronic kidney disease (CKD). These guidelines propose a new framework for the evaluation of CKD, especially in patients with altered glomerular filtration rate (GFR). They suggest measuring cystatin C in adults with GFR estimated by the CKD-EPI creatinine-based equation (eGFRcys) 45–59 mL/min/1.73 m² to confirm the diagnosis of CKD. Although derived from studies unrelated to kidney transplantation, the K/DIGO guidelines aim to target the transplant population as well. Herein, we sought to determine whether the new K/DIGO strategy to detect decreased GFR might be applicable in renal transplantation.

Methods: In 670 kidney transplant recipients (KTR), we analyzed the performance of the combined CKD-EPI equation (eGFRcys) to reclassify KTR in comparison with inulin clearances (mgFRcys) by using the analytical methodology developed in these guidelines. Serum creatinine was measured by an IDMS traceable enzymatic method; cystatin C by IFCC-traceable nephelometric method.

Results: In the whole cohort, 192 patients had eGFRcys 45–59 mL/min/1.73 m² but mGFRcys was above 60 mL/min/1.73 m² in 39 of them (20%). When using eGFRcys in these 192 patients, only 181 (94%) had also eGFR below 60 mL/min/1.73 m². In the 39 patients with eGFRcys >60 but mGFRcys ≥60 mL/min/1.73 m², only 8 were correctly reclassified by the eGFRcys equation. Estimating GFR by eGFRcys led to 20% (39/192) of errors in CKD classification. Following the strategy suggested by the guidelines, errors in classification were actually marginally corrected (18%, 34/192).

Conclusions: The K/DIGO guidelines recommend the use of the eGFRcys to improve the detection of CKD in patients whom eGFRcys 45–59 mL/min/1.73 m². In the present study, we show that this recommendation cannot be extended to transplant recipients.

SA-OR004

Differential Diagnosis of Acute Kidney Allograft Dysfunction Using Urinary Cell mRNA Profiles

Thangamani Muthukumar, Marie Matignon, Catherine Snopkowski, Carol Y. Li, John R. Lee, Darshana Dadhania, Manikkam Suthanthiran. Cornell Univ.

Background: A noninvasive diagnostic test that distinguishes acute rejection (AR) from acute tubular injury (ATN) is an unmet need in clinical renal transplantation. Methods: We tested the hypothesis that urinary cell mRNA profiles distinguish AR vs. ATN by profiling urine specimens collected at the time of allograft biopsy from 84 kidney transplant recipients with allograft dysfunction: 52 AR (ACR-26 and AMR-26) and 32 ATN. We measured absolute levels (copies/ug total RNA) of a mechanistically informative panel of 26-nRNAs using qPCR assays. We used discriminant analyses to develop a model to distinguish AR from ATN and validated it by a 10-fold cross-validation. We used decision curve analysis (Vickers AJ, Med Decis Making 2006) and determined whether the diagnostic test (urinary cell mRNA profile) is clinically useful.

Results: Neither creatinine nor tacrolimus levels differed between patients with AR or ATN. Urinary cell levels of 23 of the 26-nRNAs were statistically different (P<0.05) between AR and ATN. A composite score derived from a model of a combination of 6 of the 26-nRNAs assayed had a prediction accuracy of 94% (ROC-AUC: 0.98; 95%CI: 0.95-1.00).

Conclusions: A lower donor pre-Tx TmP-GFR, indicating a reduced maximum tubular Pi reabsorption capacity, independently predicts a lower recipient GFR one year post-Tx and an increased risk of rejection, graft failure or recipient mortality. These data are the first to link donor tubular function to recipient outcomes, and warrant further dissection of underlying mechanisms.

Funding: Government Support - Non-U.S.
SA-OR006
The Contribution of Post Transplant Disease Recurrence to Graft Failure in Glomerulonephritis

**Maria Pippa**,1 **Vianada S. Stel,**1 **Fergus J. Caskey,**2 **Kitty J. Jager.1**

1. On Behalf of the ERA-EDTA Registry Study Group, ERA-EDTA Registry, Amsterdam, Netherlands; 2. Richard Bright Renal Unit, Bristol, United Kingdom.

**Background:** Glomerulonephritis (GN) continues to predominate as one of the leading causes of established renal failure and subsequent need for transplantation. Post-transplant disease recurrence (PTDR) is a significant cause of long term graft loss, however there is little consensus in the rate of graft loss due to PTDR. We studied the contribution of PTDR to graft failure in those with a primary renal diagnosis (PRD) of GN.

**Methods:** Data on all adult first kidney transplants (Tx) performed between 1991 and 2011 in 11 countries reporting to the ERA-EDTA Registry were used. In those with a PRD of GN (IgA, MPGN I, MPGN II, FSGS and membranous nephropathy (MNP)) 5 year and 15 year death censored graft survival was studied using Kaplan Meier and Cox regression analysis whilst adjusting for gender, age at the start of RRT and age at Tx. Adult polycystic kidney disease (APKD) was the control group. Any additional risk of graft loss when compared to APKD was assumed to be due to PTDR.

**Results:** 12,646 individuals were included in the study, 6279 with GN and 6367 with APKD. Overall, 15 year adjusted graft survival was lowest in MN (56.3%) and highest in IgA (66.8%). No difference in 5, 10 or 15 year adjusted graft survival was found between APKD and IgA (15 year HR 1.04; 95% CI 0.92-1.16). Significantly worse graft survival was seen in all other GNs: MPGN II (HR 2.27; 95% CI 1.67-3.09), MPGN I (HR 1.88; 95% CI 1.58-2.23), MN (HR 1.4; 95% CI 1.18-1.67) and FSGS (HR 1.39; 95% CI 1.18-1.63).

**Conclusions:** This is the first study examining graft survival outcomes in a large European Tx population with various GNs over a 15 year period. We found no difference in graft survival in IgA compared to APKD but worse outcomes in other GNs. As short term graft function continues to improve further studies are required to understand the determinants of long term graft survival. Further analyses will focus on long term graft outcomes with different donor types as such information would aid the patient in counselling particularly when considering donor type.

SA-OR007
Albuminuria and Cardiovascular Disease, Kidney Failure and Death in Stable Kidney Transplant Recipients

**Alina A. John,**1 **Andrew S. Levey,**1 **Myra A. Carpenter,**2 **Lawrence G. Hunsicker,**2 **Robert K. Kail,**3 **John W. Kusek,**4 **Marc A. Pfeffer,**5 **Scott D. Solomon,**6 **Matthew R. Wein,**6 **Daniel E. Weiner.1**

1. Tufts; 2. Iowa; 3. NIDDK; 4. BWH; 5. MD.

**Background:** Despite improvement in early graft loss, overall graft survival remains suboptimal. While albuminuria is a known risk factor for adverse outcomes in the general and CKD populations, the relationship between albuminuria and outcomes in kidney transplant recipients (KTRs) remains uncertain.

**Methods:** In a post-hoc analysis of the Folic Acid for Vascular Outcomes Reduction in Transplantation (PAVORIT) Trial, a large randomized trial of homocysteine lowering in stable KTRs, we evaluated the relationship between albuminuria and risk of cardiovascular disease, end-stage renal disease (ESRD) and all-cause death. Multivariable Cox proportional hazards models, adjusting for age, sex, race, treatment allocation, country, systolic and diastolic blood pressure, history of CVD, diabetes and smoking, cholesterol, BMI, eGFR, diabetes type, transplant vintage, and calcineurin inhibitor use, were used.

**Results:** In 3,460 participants with complete data, 1,912 (55%) had an albumin to creatinine ratio (ACR) <30 mg/g, 1,113 (32%) ACR of 30-299 mg/g, and 435 (12%) ACR of ≥300 mg/g at baseline. Median (IQR) ACR was 24 mcg/g (9-97) and mean eGFR 49 ± 12 ml/min/1.73m². Mean age was 52 ± 9 years, 17% were black, and 37% women; median time from baseline was 4.0 ± 1.5 years, a total of 494 cardiac events, 281 kidney failure events and 395 deaths occurred. Following adjustment, each doubling of ACR was associated with significantly increased risk of cardiovascular outcomes [HR=1.05 (1.02, 1.09), kidney failure [HR=1.43 (1.36-1.50)], and all-cause mortality [HR=1.14 (1.09-1.18)].

**Conclusions:** In stable KTRs, albuminuria was independently associated with risk of CVD, kidney failure and death. Future studies are needed to evaluate whether reducing albuminuria improves these clinical outcomes.

Funding: NIDDK Support

SA-OR008
5 Years Follow-up on ZEUS: Improved Renal Function of an Everolimus/Entero-Coated Mycophenolate Sodium Regimen after Calcineurin Inhibitor Withdrawal in De Novo Renal Transplant Patients

**Wolfgang Arm,**1 **Ute Eisenberger,**1 **Oliver Wirzke,**2 **Claudia Sommerer,**1 **Petra Reinke,**2 **Martina Porstner,**2 **Christoph May,**2 **Eva-Maria Paulus,**2 **F. Lehner,**2 **Klemens Budde.1**

1. ZEUS Study Group, Germany; 2. Novartis Pharma, Germany.

**Background:** Follow-up (FU) on renal function (RF), efficacy and safety after conversion to an Everolimus(EVR)/Entero-Coated Mycophenolate Sodium(EmpC/MPS) regimen after cyclosporine A(CSA) withdrawal in de novo kidney allograft recipients at month (Mo)60 after transplantation (Tx).

**Methods:** In this prospective, open-label, controlled, multi-center study renal Tx patients were randomized to zanosar™ (a mycophenolate sodium enteric coated) (IS) regimen consisting of either EVR/EC-MPS or CsA/EC-MPS. After completion of 12Mo core-study pts were included in an observational FU.

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

Underline represents presenting author.
Results: 300 pts were rdz to either EVR+EC-MPS (n=155) or CsA+EC-MPS (n=145). Mo60 visit was completed by 227 (76%) pts. RF expressed as eGFR (Nankivell, ITT) was 73A ± 23A mL/min/1.73m2 at the time of transplantation. HLA antibody identification was performed using Luminex Single Antigen Bead assay. The capacity of serum HLA antibodies to fix complement was tested using the CH50 assay.

Methods: All recipients had negative complement-dependent-cytotoxicity cross-match post-transplantation.

Results: Of the 176 patients studied, 23% (n=41) had donor-specific anti-HLA antibodies (DSA), and 20% of the DSA+ patients (n=8) had Clq binding capacity. Mean fluorescence intensity values of DSA were higher in DSA+/Clq- group (7282 ± 3472). Comparing to DSA negative and DSA+/Clq- patients, DSA+/Clq+ patients had more history of previous kidney transplantation, higher class II panel reactive antibody levels, acute antibody-mediated rejection and transplant glomerulopathy. There was no difference in terms of allograft function between the groups.

Conclusions: Positive Clq assay was seen in 20% of the DSA+ patients 10 years after transplantation and it is significantly associated with AMR and transplant glomerulopathy.

Prevalence and Clinical Significance of Clq Binding anti-HLA Antibodies in Patients with Functioning Allografts More Than 10 Years after Kidney Transplantation
Sumeyye Cali Inal, Adriana Colovai, Michal L. Melamed, Enver Akalan. Renal Div, Albert Einstein College of Medicine, Bronx, NY.

Background: We aimed to investigate the prevalence and clinical significance of Clq binding anti-HLA antibodies in patients with functioning grafts more than 10 years post-transplantation.

Methods: All recipients had negative complement-dependent-cytotoxicity cross-match at the time of transplantation. HLA antibody identification was performed using Luminex Single Antigen Bead assay. The capacity of serum HLA antibodies to fix complement was tested using the CH50 assay.

Results: Of the 176 patients studied, 23% (n=41) had donor-specific anti-HLA antibodies (DSA), and 20% of the DSA+ patients (n=8) had Clq binding capacity. Mean fluorescence intensity values of DSA were higher in DSA+/Clq- group (7282 ± 3472). Comparing to DSA negative and DSA+/Clq- patients, DSA+/Clq+ patients had more history of previous kidney transplantation, higher class II panel reactive antibody levels, acute antibody-mediated rejection and transplant glomerulopathy. There was no difference in terms of allograft function between the groups.

Conclusions: Positive Clq assay was seen in 20% of the DSA+ patients 10 years after transplantation and it is significantly associated with AMR and transplant glomerulopathy.

Circulating MicroRNAs Correlate with Diabetic Nephropathy and Systemic Microvascular Damage and Normalize after Simultaneous Pancreas-Kidney Transplantation
Roel Bijkerk,1,2 Meriem Khairouin,1 Jacques Duijs,1 Kristel C.J.H. ter Horst,1 Aiko P.J. De Vries,1 Elco de Koning,1 Johan W. De Fijter,1 Ton J. Rabelink,1,2 Anton Jan Van Zonneveld,1,2 Marlies Reinders.1,2 Nephrology, LUMC, Netherlands; ‘Einhoven Laboratory for Experimental Vasculard Research, LUMC, Netherlands.

Background: Simultaneous pancreas-kidney transplantation (SPK) is an advanced treatment option for type 1 diabetes (T1D) patients with extensive microvascular disease and neuropathy (DN). Circulating microRNAs (miRNAs) can be sensitive biomarkers and their functional properties could provide insight into disease state. By assessing miRNA profiles in healthy control subjects and T1D patients before and following SPK we aimed to identify differentially expressed subsets of miRNAs that associate with microvascular destabilization and disease state.

Methods: Circulating miRNA expression was determined using TaqMan® Human miRNA Array Card in plasma of DN (n=8) and SPK patients (n=8) and compared with healthy controls (n=3). In addition, the SPK patients were studied longitudinally before, 1, 6 and 12 months after SPK. Microvascular morphology and mean capillary density were visualized using sidestream darkfield imaging of the oral mucosa. Furthermore, circulating levels of angiogenic factors, including angiopoietin-1 (Ang1), angiopoietin-2 (Ang2), VEGF and soluble thrombomodulin (sTM) were measured using ELISA.

Results: In our study we identified miR-25, 27a, 123b, 130b, 132, 181a, 320 and 660 to have elevated expression levels in plasma of DN patients as compared to healthy controls, whereas miR-223 and 574-3p expression was decreased. After SPK, expression levels of these miRNAs normalized and positively correlated with GFR and HbA1c levels. Interestingly, the expression of miR-126, 130b and 132, which are known to be pro-angiogenic, correlated with Ang2 levels. In addition, miR-130b showed a strong correlation with microvascular tortuosity and stenosis.

Conclusions: Circulating miRNAs profiles correlate with DN and systemic microvascular destabilization. Following SPK, these profiles normalized concomitantly with microvascular stabilization supporting the potential use of miRNA profiles to assess disease progression.

SA-OR010
Impaired KLHL3-Mediated Ubiquitination of WNK4 Activates OSR1 and SPAK Kinases-NaCl Cotransporter (NCC) Signaling and Causes Hypertension
Mai Wakabayashi, Takayasu Mori, Kiyoshi Iseoe, Eisei Sohara, Koichiro Susa, Yuya Araki, Motoko Chiga, Eriko Kikuchi, Naohiro Nomura, Yutaro Mori, Tatemitsu Rai, Sei Sasaki, Shinichi Uchida. Dept of Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Mutations in two WNK kinase genes, WNK1 and WNK4, cause pseudohypoaldosteronism type II (PHAII) characterized by hypertension, hyperkalemia and acidosis. Recently, mutations in Kelch-like 3 (KLHL3) and Cullin3 were also identified to cause PHAII. However, the pathogenic role of the mutations of KLHL3 and Cullin3 genes was not well understood. In this study, we investigated how these three genes interacted with each other and how they were involved in the pathogenesis of PHAII.

Methods: Results: Methods: KLHL3 was co-immunoprecipitated with WNK4, but not with OSR1, SPAK, or NCC. PHAII-causing mutations in either KLHL3 or WNK4 dramatically decreased the binding of two proteins. Overexpression of KLHL3 and Cullin3 with WNK4 dramatically decreased WNK4 protein expression, and this decrease was blunted by the PHAII mutations in WNK4, KLHL3, or Cullin3. KLHL3 coexpression with WNK4 significantly induced the ubiquitination of WNK4, which was also impaired by the PHAII mutations in WNK4, KLHL3 and Cullin3. In vitro ubiquitination assay confirmed that WNK4 is a direct substrate of KLHL3-Cullin3 E3 ubiquitin ligase complexes, and that the impaired ubiquitination of WNK4 would be a common mechanism of pseudohypoaldosteronism type II (PHAII) caused by mutations in KLHL3 and Cullin3.

Conclusions: All recipients had negative complement-dependent-cytotoxicity cross-match post-transplantation.

Results: Of the 176 patients studied, 23% (n=41) had donor-specific anti-HLA antibodies (DSA), and 20% of the DSA+ patients (n=8) had Clq binding capacity. Mean fluorescence intensity values of DSA were higher in DSA+/Clq- group (7282 ± 3472). Comparing to DSA negative and DSA+/Clq- patients, DSA+/Clq+ patients had more history of previous kidney transplantation, higher class II panel reactive antibody levels, acute antibody-mediated rejection and transplant glomerulopathy. There was no difference in terms of allograft function between the groups.

Conclusions: Positive Clq assay was seen in 20% of the DSA+ patients 10 years after transplantation and it is significantly associated with AMR and transplant glomerulopathy.

Analyses of KLHL3 Mutants That Cause Pseudohypoaldosteronism Type II
Yutaro Mori, Mai Wakabayashi, Takeyasu Mori, Yuya Araki, Eisei Sohara, Tatemitsu Rai, Sei Sasaki, Shinichi Uchida. Dept of Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Recently, we reported that WNK4 is a substrate of KLHL3-Cullin3 (CUL3) E3 ubiquitin ligase complexes, and that the impaired ubiquitination of WNK4 would be a common mechanism of pseudohypoaldosteronism type II (PHAII) caused by mutations in KLHL3 and Cullin3. Among various PHAII-causing KLHL3 mutants, we revealed that R528H mutant (a kelch domain mutant) showed less binding to WNK4, thereby causing less ubiquitination and increased abundance of WNK4 within cells. However, pathogenic mechanisms of other PHAII-causing KLHL3 mutants remained to be determined.

Methods: We transiently expressed four PHAII-causing KLHL3 mutants (E85A in BTB domain, C164F in BAC domain, S410L and E85A in Cullin3 domains) in PHAII model mice. WNK4 protein was also increased in KLHL3-mutated PHAII patients.

Conclusions: All recipients had negative complement-dependent-cytotoxicity cross-match post-transplantation.

Results: Of the 176 patients studied, 23% (n=41) had donor-specific anti-HLA antibodies (DSA), and 20% of the DSA+ patients (n=8) had Clq binding capacity. Mean fluorescence intensity values of DSA were higher in DSA+/Clq- group (7282 ± 3472). Comparing to DSA negative and DSA+/Clq- patients, DSA+/Clq+ patients had more history of previous kidney transplantation, higher class II panel reactive antibody levels, acute antibody-mediated rejection and transplant glomerulopathy. There was no difference in terms of allograft function between the groups.

Conclusions: Positive Clq assay was seen in 20% of the DSA+ patients 10 years after transplantation and it is significantly associated with AMR and transplant glomerulopathy.
SA-OR013
KLHL2 Interacts with and Ubiquitinites WNK Kinases  Daisuke Takahashi, Takayasu Morii, Makai Hayashi, Yutaro Morii, Koichiro Susa, Moko Zenya, Tatsunari Iri, Eisei Sohara, Sei Sasaki, Shinichi Uchida. Dept of Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Mutations in the WNK1 and WNK4 genes result in an inherited hypertensive disease, pseudohypopaldosteronism type II (PHAI). Recently, the KLHL3 and Cullin3 genes were also identified as responsible genes for PHAI. We report that WNK1 is a substrat for the KLHL3 and Cullin3 ligase complexes, and subsequent increase of WNK4 in the kidney would be a common mechanism of PHAI caused by mutations of WNK4, KLHL3 and Cullin3. Since WNK isoforms are widely expressed in the body, it is not clear whether all of the WNK isoforms are regulated only by KLHL3. To explore the regulation of WNKs and other regulatory proteins, we focused on KLHL2 (Mayven), a human homolog of drosophila kelch that shares the highest similarity with KLHL3 (86% amino acid identity with KLHL3 in Kelch domain).

Methods: To determine the interaction between KLHL2 and WNK kinases, we performed mass spectrometry, immunoprecipitation and fluorescence correlation spectroscopy. The effect of KLHL2 coexpression on the abundance of WNK kinases was determined by immunoblotting. Ubiquitination of WNK isoforms by KLHL2 was studied in vivo (HEK293T cells) and in vitro.

Results: We found that KLHL2, as well as KLHL3, was co-immunoprecipitated with all four WNK isoforms. The direct interaction of KLHL2 with WNKs was confirmed on fluorescence correlation spectroscopy. Co-expression of KLHL2 and Cullin3 decreased the abundance of WNK1, WNK3 and WNK4 in HEK293T cells, and a significant increase of WNK4 ubiquitination by KLHL2 and Cullin3 was observed both in HEK293T cells and in an in vitro ubiquitination assay.

Conclusions: We have identified the function of KLHL2 as an E3 ubiquitin ligase for WNK kinases. Different combinations of KLHL2 and KLHL3 with WNKs could regulate WNK kinase signaling in different kinds of cells.

Funding: Government Support - Non-U.S.

SA-OR014
WNK3 Regulates Blood Pressure through the Regulation of Vascular OSRI/SPAK-NKCC1 Phosphorylation Cascade  Moko Zenya, Eisei Sohara, Katsuyuki Ori, Motoko Chiga, Koichiro Susa, Takayasu Morii, Daisuke Takahashi, Tatsunari Iri, Sei Sasaki, Shinichi Uchida. Dept of Nephrology, Graduate School of Medical and Dental Sciences, Bunkyo-ku, Tokyo, Japan.

Background: NKCC1 is involved in the regulation of vascular smooth muscle cell contraction. The WNK-SPAK-NKCC1 phosphorylation cascade in vascular smooth muscle cells was found to be important in the regulation of vascular tone. Moreover, we have recently reported that WNK3 knockout mice showed lower blood pressure only when mice were fed low-salt diet, through extra-renal mechanisms. In this study, we investigated whether the WNK-SPAK-NKCC1 cascade in mouse aortic tissue is regulated by dietary salt intake, and the mechanisms responsible, focusing on WNK3.

Methods: The phosphorylations of SPAK and NKCC1 were examined in the aorta of wild-type and WNK3 knockout mice fed high-salt, normal or low-salt diet. In addition, the effects of angiotensinII (AngII) on their phosphorylations and blood pressure were also examined.

Results: Phosphorylation of SPAK and NKCC1 was significantly reduced in the aorta in high-salt fed mice, and was increased in the aorta in low-salt fed mice, indicating that the WNK-SPAK-NKCC1 phosphorylation cascade in the aorta was indeed regulated by dietary salt intake. Acute and chronic AngII infusion increased phosphorylation of SPAK and NKCC1 in the aorta of WNK3 knockout mice, indicating that activation of the WNK-SPAK-NKCC1 phosphorylation cascade induced by low-salt diet and AngII is dependent on WNK3. Indeed, increases in blood pressure by AngII infusion was diminished in WNK3 knockout mouse.

Conclusions: We demonstrated that dietary salt intake regulates the WNK3-SPAK-NKCC1 phosphorylation cascade in mouse aortic tissue through AngII. We clarified for the first time the physiological role of WNK3 in vivo.

Funding: Government Support - Non-U.S.

SA-OR015
mPGES-1 Deletion Increases Blood Lithium Concentration and Induces Colon Injury via Elevated Oxidative Stress  Zhanjun Jia, Ying Sun, Tatemitsu Rai, Sei Sasaki, Shinichi Uchida. Dept of Nephrology, Graduate School of Medical and Dental Sciences, Bunkyo-ku, Tokyo, Japan.

SA-OR016
Acetazolamide: An Improved Treatment for Lithium-Induced Nephrogenic Diabetes Insipidus?  Theun de Groot, Anne P. Sinke, Marleen L.A. Kortensev, Ruben Baumgarten, Olivier Devuyrst, Johannes Loufing, Jack F. Wetzels, Peter M.T. Deen. 1 Radboud Univ Nijmegen Medical Centre, Nijmegen, 2 St. Exp. Lab. Medical Sciences; 3 Zernike Centre for Integrat Human Physiology, Switzerland; 4 Univ Zurich, Switzerland.

Background: Lithium causes nephrogenic diabetes insipidus (Li-NDI) and hyponatremia (HCTZ) in its most common form. Acetazolamide (ACZ) is a diuretic for Li-NDI patients. The antidiuretic action of HCTZ in Li-NDI is generally ascribed to increased proximal sodium and water uptake, compensating for sodium loss due to NaCl-co-transporter (NCC) inhibition. Earlier, we found that HCTZ also reduces Li-NDI in mice with a marked reduction in urine sodium, suggesting that inhibition of carbonic anhydrase by HCTZ plays a role. To test whether inhibition of only carbonic anhydrases could be a useful alternative therapy, the effect of acetazolamide (ACZ) in Li-NDI was tested.

Methods: Mice were fed a lithium-enriched diet (Li-Diet) for 7 days. Mice were fed with or without Li-Diet. All mice were divided in 4 groups, with and without acetazolamide treatment for Li-NDI patients. The antidiuretic action of HCTZ in Li-NDI is generally ascribed to increased proximal sodium and water uptake, compensating for sodium loss due to NaCl-co-transporter (NCC) inhibition. Earlier, we found that HCTZ also reduces Li-NDI in mice with a marked reduction in urine sodium, suggesting that inhibition of carbonic anhydrase by HCTZ plays a role. To test whether inhibition of only carbonic anhydrases could be a useful alternative therapy, the effect of acetazolamide (ACZ) in Li-NDI was tested.

Results: Treatment of mpkCCD cells with ACZ attenuated the lithium-induced downregulation of endogenous AQP2. ACZ did not affect transcellular voltage, and, upon co-incubation with amiloride, resulted in significantly higher levels of AQP2, indicating that the action mechanism of ACZ differs from that of amiloride. Treatment of Li-NDI mice with ACZ revealed a significant antidiuresis and increased urine osmolality, which was indistinguishable from Li-NDI mice treated with HCTZ/amiloride. However, unlike HCTZ/amiloride, ACZ treatment did not result in hyponatremia, hyperkalemia, hypercalcaemia, metabolic acidosis and increased serum lithium concentrations. Moreover, ACZ rescued AQP2 expression over the entire length of the collecting duct, whereas HCTZ/amiloride only increased AQP2 levels in the renal papilla.

Conclusions: In conclusion, our data reveal that inhibition of carbonic anhydrases attenuates lithium-induced downregulation of AQP2 and NDI development. Moreover, ACZ appeared as effective as the conventional treatment to rescue Li-NDI, but caused fewer side effects. ACZ may represent a better therapeutic agent than HCTZ/amiloride to treat Li-NDI.

Funding: Private Foundation Support

SA-OR017
Mechanism of Acidosis-Induced Adaptive Proliferation of Collecting Duct Intercalated Cells  Lydie Cheval, Suresh K. Ramakrishnan, Christophe Klein, Alain Doucet. Centre de Recherche des Cordeliers, Paris, France.

Background: Kidneys adapt to acid load by increasing proton secretion by collecting duct a intercalated cells (AIC). This adaptation stems in part from increased number of AICs. We reported previously that acid loading induces proliferation of AICs of mouse outer medullary collecting duct (OMCD) and that this process depends on the production of growth and differentiation factor 15 (Gdf15), a member of TGFb super family (JASN, 19:1965-1974, 2008). Here we investigated the mechanisms of Gdf15 production and action in OMCDs.

Methods: Acidosis was induced by feeding mice a NH4Cl-enriched diet (0.7M). OMCDs were microdissected from collagenase-treated kidneys. mRNAs were quantified by RT-quantitative PCR, number of AICs was counted after immunolabeling with an AE1 antibody. The angle of AICs doublets with the axis of the tubule was determined after confocal imaging of isolated OMCDs and 3D reconstruction.

Results: Within 2 days, acidosis induced a 3-fold over expression of p53. NH4Cl-induced over expression of Gdf15 and cyclin D1 were abolished in p53−/− mice which, accordingly, developed stronger acidosis. Treatment with the pan-erbB tyrosine kinase inhibitor cetinibin (60mg/Kg/day, IP) did not alter the over expression of Gdf15 but attenuated development of AICs. Moreover, PCNA and cyclin D1, and accordingly mice developed stronger acidosis. In control mice, the angle of the doublets of AICs was evenly distributed from 0 to 90°. Conversely, in acidic mice, the number of doublets increased and they were preferentially oriented in parallel with the tubule axis.

Conclusions: AICs induced by NH4Cl produce Gdf15 and cyclin D1, which are involved in the proliferation of AICs through activation of ErbB receptor. This adaptive proliferation is dependent on p53 over expression.

Funding: Government Support - Non-U.S.
SA-OR018
Multifunctional Role of the N-Terminal Variable (V1) Domain of the Sodium-Bicarbonate Cotransporter NBCe1-A: Patch Formation, Trafficking and Gating
Harry S. Gill,1 Casey N. Watkins,1 Anastas Popratiloff.2 1Dept of Medicine, The George Washington Univ & Div of Renal Diseases & Hypertension, Washington, DC; 2Center for Microscopy & Image Analysis, The George Washington Univ, Washington, DC.

Background: the electronegotic NBCe1-A is an integral membrane cotransporter that reabsors Na+ and HCO3- across the basolateral membrane of the proximal tubule. Naturally occurring mutations (Q99S, R294S) in the cytoplasmic N-terminal domain of NBCe1-A (Nt) lead to Type II acidosis. NBC1 family members contain a large Nt with two variable regions, one at the extreme N terminal (V1).

Methods: The Nt structure was solved by X-ray crystallography. To investigate the role of the Nt in NBCe1-A transport, truncated Surface-plasmon resonance (SPR) and light-scattering (MALSEC-TEC) experiments were used to evaluate pH-sensitive self-associations of the Nt. The mutants were also fused with the green fluorescent protein and expressed in cultured human proximal tubular (HK2) cells to evaluate self-associations at the plasma membrane by confocal microscopy.

Results: We present the Nt crystal structure at 2.4 Å resolution. The structure reveals that the Nt dimerizes by two-interlocking arms and that has two variable regions, one at the extreme N terminal (V1) that gates substrate entry into the Nt and another large solvent accessible loop (V2) that extends about 20 Å from the core Nt structure. The SPR and MALSEC-TEC experiments indicate that the V1 domain is responsible for Nt self-associations. In agreement, punctate clusters and large patches of full-length NBCe1-A are observed at the plasma membrane. Trafficking to the membrane is significantly affected in several Nt mutants.

Conclusions: We conclude that NBCe1-A molecules form patches in the plasma membrane of PT cells in the presence of intracellular HCO3-. Secondly, we have discovered a novel role for V1 domain of NBCe1-A in membrane trafficking. These findings illuminate the role of the Nt of NBCe1-A in HCO3- sensing and transport and provide insight to the pathogenic processes observed in a subset of patients with truncating and point mutations in the gene encoding NBCe1-A.

Funding: NIDDK Support

SA-OR019
Missense Mutation T485S Alters NBCe1-A Electrogenicity Causing Proximal Renal Tubular Acidosis Quansheng Zhu,1 Xuezi Max Shao,1 Liyo Kao,1 Rustam Azimov,2 Alan Mark Weinstein,3 Debra Newman,3 Weixin Liu,4 Ira Kurz1 1Dept of Medicine, Univ of California, Los Angeles, Los Angeles, CA; 2Dept of Physiology and Biophysics, Weill Medical College of Cornell Univ, New York, NY.

Background: the electronegotic sodium-base cotransporter, NBCe1-A plays a critical role in reabsorbing filtered bicarbonate in the proximal renal tubule. Eight missense mutations in NBCe1-A have been reported to cause proximal tubular acidosis (pRTA), of which the Thr485 to Ser mutation minimally perturbs the transporter structure and retains the electrogenic sodium-carbonate cotransport. The disease mechanism of T485S is intriguing because Thr and Ser are structurally and chemically similar.

Methods: We expressed human NBCe1-A in HEK 293 cells and explored the molecular mechanism of the T485S pRTA mutation using a combined approach of intracellular pH assays, whole cell patchclamping, computational molecule simulation and small molecule probing.

Results: Wild-type NBCe1-A mediates electronegotic sodium-base cotransport with a 1.2 charge transport stoichiometry. Using nitrilotriacetic acid as a surrogate for carbonate, our data suggested that wild-type NBCe1-A mediates electronegotic sodium carbonate cotransport. T485S causes the transporter to become electroneutral with a loss of sodium-coupled nitrate transport. The underlying mechanism appears to involve a change of carbonate for nitrate transport. The location of Thr485 in the V1 domain, truncation mutants were rationally generated. Surface-plasmon-resonance (SPR) and whole cell patch-clamping experiments, computational modeling and small molecule probing. These findings predicted that NBCe1-A mediates electronegotic sodium base carbonate cotransport, which is required for a functional renal bicarbonate transport system.

Conclusions: These studies confirm that wild-type NBCe1-A mediates electronegotic sodium-coupled bicarbonate transport as a consequence of a Thr485 to Ser mutation.

Funding: NIDDK Support, Private Foundation Support

SA-OR020

Background: Seventeen hundred mg of NaCl is filtered by the glomerulus daily, more than two thirds is reabsorbed from the proximal tubule. The molecular determinants of proximal tubular Na+ reabsorption are coupled to bicarbonate reabsorption and the cytosolic C-terminus of NHE3 contains a putative CAII binding site. We therefore hypothesize that NHE3 and CAII: molecules involved in the combined flux of Na+ and HCO3-, physically and functionally interact to increase Na+ reabsorption from the proximal tubule.

Methods: Physical interaction studies included: immunostaining of mouse kidney, a proximity ligation assay and a microtitre plate assay with NHE3 GST-fusion constructs and stably over-expressed in opossum kidney cells (OK) NHE3-GST and activity measured as the rate of intracellular pH recovery, induced by an acid load and detected with the fluorescent ratiometric probe BCECF-AM. Acidification was induced by switching cells from a bicarbonate free medium, to one containing bicarbonate and 5% CO2.

Results: Murine renal sections immunostained for CAII and NHE3 demonstrate colocalization in the brush border. That the two proteins were closer than 40 nm apart was revealed by a proximity ligation assay. A direct physical interaction was confirmed with GST pull-down assays. OK-NHE3-GST cells demonstrate significant recovery of intracellular pH than controls that is both Na+ dependent and inhibited by 100 nM EIPA. Inhibition of endogenous CAII activity with acetazolamide significantly decreased NHE3 activity, an effect that was not observed when acidification was induced in the absence of CO2 and HCO3-. To ascertain whether CAII binding per se activates NHE3, we observed that the over-expressed NHE3trans is coiled with: CAII, a catalytically dead CAII mutant (CAII-V414Y) or an expressed mutant NHE3 (NHE3mut) with: CAII, a catalytically dead CAII mutant (CAII-V414Y) using a co-immunoprecipitation assay (CAII-HEX). These studies revealed an increase of NHE3 activity induced by CAII coexpression that was absent in the presence of the V413Y or HEX mutant.

Conclusions: These studies confirm that CAII binds to and increases NHE3 activity likely augmenting Na+ and HCO3-reabsorption from the proximal tubule.

Funding: Government Support - Non-U.S.
Conclusions: In summary, PECs do not differentiate into podocytes in models of glomerular hypertension or in aging mice. Instead, our findings further strengthen the notion that PECs play a major role in glomerular diseases, specifically in FSGS and crescentic glomerulonephritis.

Funding: Government Support - Non-U.S.

SA-OR023

Epigenetic Role of Wolf-Hirschhorn Syndrome Candidate 1-Like 1 in Glomerulonephritis

Yugo Ito,1 Zentaro Kiuchi,1 Yukino Nishihori,1 Kunimasa Yan.1 1Pediatrics, Kyorin Univ School of Medicine, Tokyo, Japan; 2Medical Biochemistry and Biophysics, Karolinska institute, Stockholm, Sweden.

Background: We previously reported that Wolf-Hirschhorn syndrome candidate 1-like 1 (WHSC1L1) is a novel epigenetic molecule in the podocytes, which activates nephrin promoter through tri-methylating HistoneH3K4 (2012 ASN Kidney Week). The present study aimed to explore the functional role of WHSC1L1 in glomerulonephritis.

Methods: Zebrafish embryos depleted of WHSC1L1 by using the antisense morpholino oligonucleotides (MO) against the translation initiation site, the donor sites on exon1 and the acceptor sites on exon3 were established. The phenotypic changes of the WHSC1L1 morphants were observed and compared with control zebrafish. PAS staining and electron microscopy were performed to verify the histological change of nephrin and morphology of the podocytes and their foot processes. RT-PCR was performed to compare the expression level of nephrin mRNA in WHSC1L1 morphants and control zebrafish. WHSC1L1 morphants was used to evaluate the function of glomerular filtration barrier.

Results: Disruption of WHSC1L1 expression in MOs was confirmed by RT-PCR and Western blot study. Morphant embryos injected with WHSC1L1 MOs developed cardiac edema, dorsal body axis curvature and short stature in 89.9% of the translation initiation site, the donor sites on exon1 and the acceptor sites on exon3 were established. The phenotypic changes of the WHSC1L1 morphants were observed and compared with control zebrafish. PAS staining and electron microscopy were performed to verify the histological change of nephrin and morphology of the podocytes and their foot processes. RT-PCR was performed to compare the expression level of nephrin mRNA in WHSC1L1 morphants and control zebrafish. WHSC1L1 morphants was used to evaluate the function of glomerular filtration barrier.

Conclusions: The present study suggests that WHSC1L1 plays a pivotal role in glomerulonephritis.

SA-OR024

Regulation of Glomerular DAF by HO-1

Maria Detsika,1 Pu Duann,2 Elias A. Lianos.2 1Medicine, Univ of Athens, Greece; 2Div of Nephrology, Univ of Medicine and Dentistry of New Jersey.

Background: Rat glomeruli express Decay accelerating factor (DAF) exclusively in glomerular epithelial cells (GEC) attenuating complement (C) activation-mediated injury. C activation also induces Heme oxygenase (HO-1). Although HO-1 induction affects cytoprotection via heme degradation products, an alternative mechanism may involve DAF regulation. This was explored in normal rat glomeruli.

Methods: hmox1- and hmox1-/- rats were obtained by Zinc Finger Nuclease (ZFN)-mediated HO-1 gene disruption. Rats with GEC targeted HO-1 overexpression (GECHO-1) were treated for 18h with Metalloporphyrins (MPs): Heme or Cobalt Protoporphyrin (CoPP). Underline represents presenting author.

Results: A 60-70% reduction in constitutive HO-1 levels and complete HO-1 absence was observed in hmox1-/- and hmox1-/- GECs respectively. HO-1 induction affected cytoprotection via heme degradation products, an alternative mechanism may involve DAF regulation. This was explored in normal rat glomeruli.

Conclusions: HO-1 dysfunction results in urinary albumin loss, a hallmark of cardiovascular disease and kidney failure. However, the earliest molecular events leading to filter damage are not well understood. Our previous studies have implicated the ion channel TRPC5 in podocyte injury.

Funding: NIDDK Support, Private Foundation Support

SA-OR025

TRPC5 Inhibition Protects the Kidney Filter by Preventing Podocyte Cytoskeletal Collapse

Thomas Schaldecker,1 Sookyung Kim,1 Constantine Tarabaris,1 Samy Hakroush,2 Philip M. Castonguay,1 Lisa M. Buvall,1 Astrid Weins,1,2 Anna Greka.1 1Dept of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA; 2Dept of Pathology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA.

Background: Kidney filter damage results in urinary albumin loss, a hallmark of cardiovascular disease and kidney failure. However, the earliest molecular events leading to filter damage are not well understood. Our previous studies have implicated the ion channel TRPC5 in podocyte injury.

Methods: We utilized TRPC5 knockout mice and two models of acute podocyte injury to study the role of TRPC5 in vivo. Using a novel small molecule inhibitor of TRPC5, we also explored whether pharmacologic inhibition of the channel confers protection from albuminuria, filter barrier collapse, and podocyte injury. We developed a method for calcium imaging in isolated kidney glomeruli in addition to live imaging of podocyte actin dynamics to investigate the role of TRPC5 in the initiation of kidney filter damage.

Results: Loss of TRPC5 or its inhibition abrogates podocyte cytoskeletal collapse, by blocking Rac1 and stabilizing synaptopodin. Importantly, genetic deletion or pharmacologic inhibition of TRPC5 protects mice from filter damage.

Conclusions: This study reveals TRPC5 as the Ca2+ permeable channel responsible for filter barrier collapse, and identifies TRPC5 inhibition as a therapeutic strategy for the prevention or treatment of albuminuric disease.

Funding: NIDDK Support, Private Foundation Support

SA-OR026

Rac1 Activation in Podocytes Induces Rapid Foot Process Effacement and Proteinuria

Haiyang Yu,1 Hani Suleiman,1 Alfred Hyougung Kim,1 Jeffrey H. Miner,1 Shreeram Akilesh,2 Andrey S. Shaw.1,2 1Dept of Pathology and Immunology, Washington Univ in St. Louis, Saint Louis, MO; 2Howard Hughes Medical Institute, Washington Univ in St. Louis, Saint Louis, MO; 2Dept of Medicine, Washington Univ in St. Louis, Saint Louis, MO; 1Dept of Pathology, Univ of Washington, Seattle.

Background: The exact nature of foot process effacement is not known, but recent studies proposed that it might reflect the Rac1-induced actin reorganization. Here we inductively expressed constitutively active Rac1 specifically in podocytes in a transgenic mouse model, and observed rapid onset of foot process effacement and proteinuria after doxycycline induction, which was validated as a direct effect of active Rac1 by a super-resolution imaging method.

Methods: Dox-inducible knock-in mouse model stochastic reconstitution optical microscopy (STORM).

Results: To test the effects of Rac1 activation in vivo, we generated a transgenic mouse with inducible expression of active-Rac1. The transgene was knocked into the Hprt1 locus in ES cells by homologous recombination. Transgenic mice were generated and bred to the Podocin-rtTA strain and a new strain we generated, Nphrin-rtTA. Proteinuria was detectable after 2 days of doxycycline induction, peaked at day 4, and gradually decreased. The transgene were patchy-expressed, but the magnitude of proteinuria correlated with efficiency of transgene expression with the Nphrin-rtTA more broadly expressed. We validated focal foot process effacement by TEM and showed that the amelioration of proteinuria correlated with the loss of transgene-positive podocytes. The patchy expression of transgene allowed us to test whether areas of focal foot process effacement correlated with transgene expression. Correlating STORM with freeze-eject electron microscopy, we showed that only transgene positive podocytes were effaced.

Conclusions: Here we show that activation of Rac acutely induces foot process effacement. Our data support the hypothesis that foot process effacement is the in vivo correlate of Rac activation and that Rac activation may lead to podocyte loss.

SA-OR027

Brain Derived Nuerotrophic Factor (BDNF) Repairs Podocyte Damage by Inducing Actin Polymeryzation through Brain-Specific microRNAs

Maria Pia Rastaldi,1 Min Li,1 Silvia Armelloni,1 Cristina Zennaro,1 Alessandro Corbelli,1 Masami Ikehata,1 Anna Mondini,1 Deborah Mattinzoli,1 Changli Wei,3 Jochen Reiser,3 Piergiorgio Messa.1 1Dept of Pathology and Immunology, Washington Univ in St. Louis, Saint Louis, MO; 2Howard Hughes Medical Institute, Washington Univ in St. Louis, Saint Louis, MO; 1Dept of Medicine, Washington Univ in St. Louis, Saint Louis, MO; 1Dept of Pathology, Univ of Washington, Seattle.

Background: Podocyte damage is the hallmark of focal segmental glomerulosclerosis (FSGS), a devastating glomerulopathy that needs better treatment. Podocytes are ramified cells sharing numerous properties with neurons and BDNF improves neuronal cell function.

Methods: BDNF was added to control and damaged (proteamine sulfate, PS. Puromycin aminonucleoside, PA) podocytes. BDNF and its receptors were used for permeability tests. In D. Rerio larvae and Balb/c mice BDNF was administered after pericardial oedema and nephritic proteinuria were induced by adriamycin (Adr). TrkB was silenced in vitro and in vivo.

Results: Increased number and length of processes, via LIMK-1 overexpression, were observed in control podocytes after BDNF incubation. Lin phosphorylation, were observed in control podocytes after BDNF incubation. LIMK-1 protein increase was not parallelly by mRNA changes, leading to investigate

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

76A
miRNA involvement, which demonstrated BDNF opposite actions on brain-specific miRNAs; reduced miRNA134 and increased miRNA132 directly and indirectly (by reducing 250GAP) silenced the blockade on LIMK1 translation. Double transfection experiments confirmed opposite effects on process formation, actin polymerization and coflin phosphorylation.

In vitro, BDNF repaired podocyte damage due to PS or PA and reduced albumin permeability in 3D cultures. In vivo, BDNF reduced pericardial oedema, restored podocyte morphology and nephrin and TrkB levels in D. Rerio larvae exposed to adriamycin. In Balb/c mice, adriamycin-induced glomerulosclerosis was repaired by BDNF and proteinuria diminished. All effects were reversed by BDNF-TRKB interaction, being abolished by TrkB silencing.

Conclusions: On the whole, our results support the possibility that BDNF could be a promising option for treating proteinuric diseases characterized by podocyte injury. Funding: Private Foundation Support, Government Support - Non-U.S.

SA-OR028
Loss of Prohibitin-2 in Podocytes Leads to Proteinuria and Renal Failure in Mice
Christina Ising1, Bernhard Schermmer, Andreas Linkermann, Sebastian Braehler, Donscharte Kerschjaschki, Christine E. Kurschat, Thomas Benzing, Paul T. Brinkkoetter.

1Dept II of Internal Medicine and Center for Molecular Medicine Cologne, Univ of Cologne, Cologne, Germany; 2Div of Nephrology and Hypertension, Christian-Albrechts Univ, Kiel, Germany; 3Clinical Institute of Pathology, Medical Univ of Vienna, Vienna, Austria.

Background: SPFH domain-containing proteins support the formation of functional lipid microdomains within cellular membranes. Prohibitin-2 (PHB2), a member of this family, has recently been reported to control mitochondrial cristae morphogenesis and biogenesis of oxidative phosphorylation system complexes. Genetic deletion of Phb2 in mice results in embryonic lethality.

Results: Here, we studied the role of PHB2 at the kidney filtration barrier by conditional deletion of Phb2 gene expression in podocytes and demonstrate development of progressive proteinuria, glomerulosclerosis and endstage renal failure. In contrast to previous observations in proliferating fibroblasts this phenotype was not associated with mitochondrial apoptosis because we did not detect increased caspase-3 cleavage in post-proliferative podocytes, suggesting an additional, previously unidentified mechanism of mitochondrial apoptosis because we did not detect increased caspase-3 cleavage in post-proliferative podocytes, suggesting an additional, previously unidentified mechanism of mitochondrial apoptosis.

Conclusions: These data indicated that besides its well established role at the filtration barrier, PHB2 can also modulate cell motility and calcium signaling and cell motility in the development of glomerulosclerosis.

SA-OR029
Increased Podocyte [Ca²⁺], Correlates with Cell Motility in an In Vivo Imaging Model of Kidney Fibrosis
James L. Burford, Karie G. Villanueva, Anne Riquier-Brison, Janets Peti-Peterdi. Physiology and Biophysics, Univ of Southern California, Los Angeles, CA.

Background: Recent genetic and cellular studies highlighted the role of podocyte calcium ([Ca²⁺]i) signaling and cell motility in the development of glomerulosclerosis. However, our mechanistic understanding of podocyte [Ca²⁺]i dynamics is limited to a few calcium channels and knowledge learned from in vitro approaches. Recently, we developed a serial multiphoton microscopy (MMP) approach to directly visualize changes in podocyte [Ca²⁺]i in vivo. We explored the role of podocyte [Ca²⁺]i in a disease state using the unilateral ureteral obstruction (UO) model of progressive renal fibrosis.

Methods: Podocin Cre Gcamp3 mice were subjected to UO and serial MMP at days 7-14 after UO. Vasculature were labeled red with the plasma marker Alexa594-fluorescent intensity (Fi) of Gcamp3 mice showed low baseline [Ca²⁺]i (average fluorescent intensity (Fi) of Gcamp3 Fi= 5.16), while regions where visceral-to-parietal adhesions and parietal podocyte layers developed due to podocyte detachment showed increased [Ca²⁺]i and increased cell motility, and their causative role in progressive glomerulosclerosis. P2 receptor-mediated purinergic [Ca²⁺]i signaling in podocytes may be an important new mechanism in podocyte injury and a promising new therapeutic target in glomerular disease.

SA-OR030
Podocyte Detachment Induced by PAI-1 and uPAR-Mediated β1 Integrin Internalization
Namiko Kobayashi, Toshiharu Uno, Kumi Ohashi, Kazuo Sakamoto, Satoshi Hara, Yasutoshi Takashima, Taiji Matsusaka, Toshio Miyata, Michio Nagata.

1Renal Pathology, Univ of Tsukuba, Tsukuba, Japan; 2Internal Medicine, Tokai Univ School of Medicine; 3United Centers, Tohoku Univ.

Background: We previously reported that transgenic mice with podocyte-specific injury (NEP mice) showed microangiopathy at the site of podocyte injury, and plasminogen activator inhibitor-1 (PAI-1) was increased in serum and urine of NEP mice. Both PAI-1 and uPAR bind to uPAR, and make complex with integrin on cell membrane. Internalization of the complex induces the cell detachment as a result of reduction of cell-matrix adhesion molecules. The present study was aimed to show that PAI-1 was involved in podocyte detachment through the complex with uPAR-internalization by using NEP mice and podocyte cell line.

Methods: Two groups of NEP mice, with or without PAI-1 inhibitor (PI) were induced podocyte injury by LMB2 injection on day 0. PI was administered from day 0 to 12. Histological and clinical parameters were analyzed on day 12. Then, we treated cultured podocytes either with PAI-1/uPA complex (P/UpA), uPAR, or antibody for blocking uPAR with P/UpA (P/UpA). After incubation, attached cells were counted, and localization of β1 integrin and uPAR was detected by immunofluorescence. Cytoplasmic β1 integrin was analyzed by Western blot.

Results: In vivo, BPAR complex may act on the podocytes detachment via internalization of β1 integrin through the uPAR mechanism.

SA-OR031
Blood Pressure and Mortality at Advanced CKD and Incident ESRD: The CRIC Study
John W. Kusek, Claudia M. Lora, Eva Lustigova, Chi-Yuan Hsu, 1UCSF; 2U Penn; 3Case Western; 4KPNC; 5Tulane; 6NIDDK; 7UIC.

Background: In observational studies of hemodialysis (HD) patients, lower blood pressure (BP), even within the "normal" range, is associated with higher mortality. Whether this paradoxical association is present in advanced CKD is unknown.

Methods: Participants of the Chronic Renal Insufficiency Cohort had standardized BP measures at yearly visits. We studied the association between mortality and systolic BP (SBP) measured at the: 1) first study visit after reaching eGFR of <30 ml/min/1.73m² ("advanced CKD SBP") (N=1,705); 2) first study visit after starting HD ("HD study visit SBP") (N=404); and 3) HD unit ("pre-HD SBP") (N=404). We performed a survival analysis, fitting a quadratic term for BP.

Results: Among 1,705 participants with advanced CKD, median eGFR was 25±4 ml/min/1.73 m² and SBP was 131 (±24) mm Hg. There were 390 deaths over 4.7 (±2.3) years. Adjusting for demographics, tobacco use, BMI, diabetes, and cardiovascular disease, there was a linear association between advanced CKD SBP and mortality. Among the 404 participants who subsequently started HD, mean pre-HD SBP was 152 (±22) mm Hg and HD study visit SBP was 132 (±25) mm Hg. There were 98 deaths after the start of HD over 2.8 (±1.7) years. A U-shaped association between pre-HD SBP and mortality was observed. There was a linear association between HD study visit SBP and mortality (Figure). Conclusion: At advanced CKD, higher SBP was associated with higher mortality. Among those who started HD, a U-shaped association between pre-dialysis SBP and mortality was observed. In contrast, there was a linear association between mortality and SBP measured outside the HD unit, which may be a more appropriate target for therapy.
SA-OR032
Masked and Sustained Hypertension Are Associated with Increases in Left Ventricular Mass and Pulse Wave Velocity in CKD – The CRIC Study
Paul E. Drewz,1,3 Arnold B. Alper,2 Amanda Hyre Andersen,2 Denise C. Babineau,2 Carolyn S. Brecklin,2 Jeanne Charleston,2 Jing Chen,2 Yonghong Huan,2 Susan P. Steigerwald,2 Jonathan T. Taliercio,2 Raymond R. Townsend,2 Matthew R. Weit,2 Malboob Rahman.3 1University of Minnesota; 2CRIC Investigators.

Background: The goal of this study was to evaluate whether white-coat (WCH), masked (MH), and sustained hypertension (SH) are associated with increases in left ventricular mass index (LVMI) and pulse wave velocity (PWV).

Methods: In the Chronic Renal Insufficiency Cohort study, 24 hour ambulatory blood pressure (ABP) was measured between 2008 and 2012. Clinic blood pressure (BP) was measured in triplicate. WCH was defined as clinic BP ≥135/85mmHg and daytime ABP <135/85mmHg and nighttime ABP ≥140/90mmHg. MH by a clinic BP <140/90mmHg and daytime ABP measured in triplicate. SH was de-masked (ABP) was measured between 2008 and 2012. Clinic blood pressure (BP) was masked (MH), and sustained hypertension (SH) are associated with increases in left ventricular hypertrophy (LVH) and pulse wave velocity (PWV).

Results: ABP was obtained in 1439 participants; echocardiography was obtained in 1230 and PWV in 1345 of these participants. In adjusted linear models, both MH and SH were associated with increased LVMI and PWV (table). In adjusted logistic regression models, MH was associated with increased odds for a PWV ≥10/sem/sec and SH was associated with increased odds for both left ventricular hypertrophy (LVH) and a PWV ≥10/sem/sec.

<table>
<thead>
<tr>
<th>LVMI</th>
<th>PWV ≥10/sem/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>MH</td>
<td>1.61 (1.0-2.5)</td>
</tr>
<tr>
<td>SH</td>
<td>2.04 (1.4-3.0)</td>
</tr>
</tbody>
</table>

Conclusions: In a large cohort of participants with CKD, both MH and SH were associated with vascular injury and target organ damage. Ambulatory BP may better characterize the relationship between BP and adverse outcomes in patients with CKD.

SA-OR033
The Clinical Impact of Renal Artery Denervation on Blood Pressure and Renal Function in Patients with Uncontrolled Hypertension: From the Renal Artery Denervation (RDN) study

E. Schmieder,3 Giuseppe Mancia,4 Krzystof Narkiewicz,5 Bryan Williams,6 Felix Zadeh.3

Background: Renal artery denervation (RDN) has been demonstrated to safely lower blood pressure (BP) in controlled clinical trials. To further evaluate the safety and efficacy of this minimally invasive treatment in "real world" patients with hypertension the Global SYMPlicity Registry (GSR) was initiated.

Methods: The GSR is a prospective, multicenter (~200 sites), open-label study designed to evaluate the effect of RDN with the Symplicity™ renal denervation system in adults with uncontrolled hypertension. Data collected includes of BP measurements at each follow-up, renal function, procedural events and safety events possibly related to RDN.

Results: A total of 509 patients with baseline BP ≥160/100 mmHg for ≥6 months were randomized to Symplicity RDN or standard of care (SOC). Baseline characteristics for 409 patients with baseline BP ≥160/100 mmHg for ≥6 months included mean age 60±12 yrs, 65% males, and 6% diabetics. Mean baseline BP was 175±4/106±2 mmHg and baseline eGFR was 65±16 mL/min/1.73m2; 97% of patients had an eGFR >45 mL/min/1.73m2. BP dropped -16±5/21±2 (-7.1±3.3 mmHg) to those with baseline eGFR 60-69 (-13.3±2.1/5.8±13.3 mmHg and -15.7±20.9/-7.7±12.0 mmHg). No serious procedural-related complications or adverse events related to RDN were reported.

Conclusions: RDN using the Symplicity catheter significantly and safely lowers BP in patients with uncontrolled hypertension. Renal function does not impact the drop in blood pressure.

Funding: Pharmaceutical Company Support - Medtronic, Inc.

SA-OR034
Apolipoprotein L1 Gene Variants Associate with Increased Systolic and Diastolic Blood Pressure in Younger African Americans Independent of Renal Function

Girish N. Nadkarni, Erwin P. Bottinger. Dept of Nephrology, Mount Sinai Icahn School of Medicine.

Background: Polymorphisms at the APOL1 locus confer a substantial increase in risk of non-diabetic renal diseases in African Americans, including renal disease associated with hypertension. Little evidence has emerged to date, to suggest that APOL1 variants can increase hypertension risk independent of kidney disease. We aimed to assess the association of these variants and blood pressure in African Americans.

Methods: We utilized PCR and ASPE APOL1 G1/G2 genotype testing. The clinical and demographic parameters were abstracted using the electronic health record (EHR) from consented Mount Sinai Biobank participants. The primary outcome variables of interest were systolic and diastolic blood pressures (SBP and DBP) averaged over a nine-year period. We utilized multivariable logistic regression to assess this association.

Results: We had data on 4765 participants. Of these, 36% were male, 36% had a history of diabetes mellitus and 42% had a history of antihypertensive medication use. Mean protein was measured in a 24 hour sample at baseline.

Funding: Private Foundation Support

SA-OR035
Evaluation of Blood Pressure and Risk of ESRD/Mortality in Resistant Hypertension

John J. Sim,1 Jiaxiao Shi,1 Csaba P. Kovessy,2 Kamyr Kalantar-Zadeh.3 1Nephrology & Hypertension, Kaiser Permanente Los Angeles Med Ctr, Los Angeles, CA; 2Memphis VA Med Ctr; 3UC Irvine Med Ctr.

Background: Blood pressure (BP) goals in hypertension (HTN) have been challenged. Even less is known about resistant hypertension (RH) in terms of the comparative risk of BP on clinical outcomes. RH likely has chronic physiologic compensations including vascular remodeling and higher threshold perfusion BP. We hypothesize that a similar J shaped curve exists within RH and furthermore the nadir BP associated with best ISRD and mortality outcomes are higher than what is observed in the general HTN population.

Methods: Retrospective longitudinal study of Kaiser Permanente Southern California health system (1/1/2006-12/31/2009) performed. RH defined as HTN individuals with uncontrolled BP on 3 meds or requiring ≥4 shared decision making. Demographic, comorbidity, laboratory, medication, and outcomes data extracted from the electronic medical records. ISRD defined as eGFR<15, dialysis, or renal transplant. Serial BP during and up to 4 years follow up averaged and multivariable hazard ratios (HR) calculated for every 10 mm Hg increment systolic BP (SBP) using 130-139mm as reference.

Results: The RH cohort of 50,020 was comprised of 43% females, 46% whites, 19% blacks, 18% Hispanics, and 6% Asians. Mean age was 70 yrs. Adjusted HR (95% CI) for combined ESRD/mortality compared to SBP 130-139mm group were 3.0 (3.7-3.3), 1.6 (1.5-1.7), 1.1 (1.0-1.1), 1.4 (1.3-1.5), 2.5 (2.3-2.7), 3.2 (3.1-3.9), & 4.2 (3.6-5.0) for SBP ≥110, 110-119, 120-129, 140-159, 160-169, & ≥170 respectively. Males, blacks, CKD, & DM also had increased HR for ESRD/mortality (not shown).

Systolic Level

Conclusions: Among a large ethnically diverse RH cohort, we found a J curve in BP and risk for ESRD/Mortality with the nadir systolic BP at 130-139. This was not different to what was observed in our general HTN population (not shown).

Funding: Private Foundation Support

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

Underline represents presenting author.

 oral Abstract/Saturday
SA-OR036
Renal Artery Denervation Can Safely Lower Blood Pressure in Patients with Severe Treatment-Resistant Hypertension: Results from the Symplicity HTN Trials

Markus Schlaich,1 Henry Krum,2 Murray Ezrer,2 Michael Böhm,3 Roland E. Schmieder,4 Baker IDI Heart and Diabetes Institute, Melbourne, Australia; 1Monash Univ, Melbourne, Australia; 2Univ Erlangen-Nürnberg, Erlangen, Germany; 3Univ of Saarland, Homburg.

Background: The sympathetic nervous system is an important contributor to the pathogenesis of hypertension. Renal artery denervation (RDN) catheter reduces sympathetic nerve activity and blood pressure (BP). The Symplicity HTN-1 and Symplicity HTN-2 trials evaluated the safety and effectiveness of RDN in subjects with severe treatment-resistant hypertension (systolic BP >160 mmHg or >150 mmHg for subjects with diabetes while on ≥3 antihypertensive drugs, including a diuretic).

Methods: Inclusion criteria included an eGFR ≥45 mL/min/1.73 m². Renal imaging was performed pre-procedure and renal arteries <4mm in diameter or <20 mm in length or with significant abnormalities were excluded. Changes in office BP, serum chemistries, and all RDN-related safety events were followed every 6 months.

Results: A total of 213 (mean age 57 yrs) were treated. Mean baseline BP was 178±19/98±15 mmHg and mean baseline eGFR was 82.7±19.9 mL/min/1.73 m². BP was significantly lower than baseline after RDN by -24±23/-10.13 mmHg at 6 months, -26±24/-12.13 mmHg at 1 year and -30±24/-13.14 mmHg at 2 yrs (p<0.01 for all). Mean eGFR was 81.7±20.2 at 6 months and 80.8±18.6 mL/min/1.73 m² at 1 yr. Mean eGFR was 76.8±22.8 mL/min/1.73 m² in 43 subjects followed through 2 yrs. Procedural complications included 2 renal artery dissections and 4 pseudoaneurysms all treated without further sequelae. Transient acute renal failure deemed unrelated to RDN occurred in 3 patients. There was one progression of a pre-existing stenosis unrelated to RDN and one new moderate stenosis that did not require treatment.

Conclusions: RDN significantly lowers BP without adverse consequences on renal function. Further studies are warranted to assess a potential renoprotective role of RDN in patients with both normal and impaired renal function.

Funding: Pharmaceutical Company Support - Medtronic, Inc

SA-OR037
Preeclampsia and End-Stage Renal Disease: A United States Renal Data System Linkage Study

Andrea G. Kattah,1 Sanket Agarwal,1 Dawn C. Scantlebury,2 Michelle M. Mielke,3 Amy L. Weaver,3 Wendy White,3 Reem A. Asad,4 Vesna D. Garovic,1 Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 1Div of Health Sciences Research, Mayo Clinic, Rochester, MN; 2Dept of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN; 3Div of Cardiovascular Diseases, Mayo Clinic, Rochester, MN.

Background: Preeclampsia has been implicated in the future development of hypertension (HTN) and renal disease. Recent data from registry-based studies suggest that preeclampsia is a risk factor for end-stage renal disease (ESRD). However, the magnitude of the association and the contributions of comorbidities remain unknown.

Methods: We performed a case-control study using a cohort of Olmsted County, MN residents who gave birth between 1976-1982 (n=8362). The ESRD cases were identified by linkage with the United States Renal Data System (USRDS); cases were matched to 2 controls based on maternal date of birth, age at first pregnancy, parity and length of follow-up. Medical records from all pregnancies were reviewed for evidence of preeclampsia, preeclampsia superimposed on HTN, or eclampsia and for comorbidities, including diabetes mellitus (DM) and HTN. Exclusion criteria were ESRD prior to pregnancy and refusal of research authorization.

Results: A total of 23 cases of ESRD were identified; 2 had ESRD prior to pregnancy and 1 denied authorization for medical record review, leaving 20 available ESRD cases for analyses. The mean (SD) age at diagnosis of ESRD was 52.6 ± 8.1 years. Per chart review, 8/20 (40%) cases vs. 5/40 controls (12.5%) had preeclampsia, preeclampsia superimposed on HTN or eclampsia (OR 4.5, 95% CI 1.1-21.4, p<0.04). DM and HTN were more common in cases than controls (50% vs. 15%, 80% vs. 45%, respectively). After adjusting for DM (OR 3.5, 95% CI 0.7-18.1, p=0.13) and HTN (OR 3.1, 95% CI 0.7-15.5, p=0.17), the OR for ESRD was attenuated.

Conclusions: Preeclampsia is associated with a higher odds of ESRD. However, after adjusting for DM and HTN, the association was attenuated and no longer significant. Larger population-based studies that rely on chart review or prospective studies are needed to confirm the association of preeclampsia and ESRD.

Funding: Other NIH Support - P50 AG 44170 from the National Institute on Aging, and the Society for Womens Health Research (SWHR) ISIS Network award

SA-OR038
Variability in Timing of Dialysis Initiation in Children

Allison Dart,1 Susan M. Samuel,2 Manish M. Sood,3 B. Todd Alexander,3 Steven Arora,6 Robin L. Erickson,4 Braden J. Manns,2 Michael Zappitelli,2 Univ of Manitoba; 2Univ of Calgary; 3Univ of Alberta; 4Univ of Saskatchewan; 5McGill Univ; 6McMaster Univ; 1Canadian Kidney Knowledge Translation and Generation Network (CANN-NET).

Background: The benefits of initiating chronic dialysis in children must be balanced against increased complexity of care and potential complications. We assessed variability in eGFR at dialysis initiation and evaluated the association of patient, facility and regional factors with early vs. late dialysis initiation.

Methods: Incident Canadian dialysis patients <22 yrs, between 2001-2010 from 9 Canadian provinces were identified from the Canadian Organ Replacement Registry. The outcome was early vs. late dialysis initiation (eGFR ≥ vs. < 10.5 ml/min/1.73m²). We examined the associations of age at dialysis initiation, sex, ethnicity, ESRD etiology, distance from nearest pediatric facility, initial modality (peritoneal vs. hemodialysis), income quintile, era (2001-05 vs. 2006-10), pediatric vs. adult facility, and geographic region (West, Ontario, East), on the outcome using multiple variable logistic regression models.

Results: Thirty % of 540 children started dialysis with eGFR ≥10.5ml/min/1.73m² (21-31% across regions; 12-79% across facilities). This proportion increased from 29% in 2001 to 37% in 2010 (Figure 1). Mean eGFR at dialysis initiation by facility was also variable (7.15 ml/min/1.73m²). Factors independently associated with early start were genetic cause of ESRD (OR=3.2; 95% CI 1.5-6.7) and later era (OR=1.5; 95% CI 1.0-2.3). Sensitivity analysis using eGFR threshold of 12 ml/min/1.73m² revealed similar results.

Conclusions: Approximately one third of children initiated dialysis with eGFR ≥ 10.5 ml/min/1.73m². The proportion initiating early increased during the study period and considerable practice variation exists across facilities and regions.

Funding: Private Foundation Support

SA-OR039
The Impact of Estimated Glomerular Filtration Rate Reporting on the Timing of Dialysis Initiation

Manish M. Sood,1 Paul Komenda,2 Claudio Rigatto,1 Brett M. Hiebert,3 Navdeep Tangri,2 Medicine, St. Boniface Hospital, Winnipeg, Canada; 3Medicine, Seven Oaks Hospital, Winnipeg, Canada; 4Cardiac Sciences, St. Boniface Hospital, Winnipeg, Canada.

Background: Automatic reporting of the estimated glomerular filtration rate (eGFR) by laboratories has been widely implemented during the last decade. Concurrently, a steady increase in the eGFR at dialysis initiation has been reported. We hypothesize that automatic eGFR reporting may be leading to earlier dialysis initiation, based on level of eGFR, rather than clinical symptoms. The purpose of this study was to examine trends in the eGFR at dialysis initiation before and after eGFR reporting.

Methods: All incident dialysis patients from four Canadian provinces that implemented, province-wide, automatic laboratory reporting of eGFR were included in the study (N=27, 088). Data were obtained from the Canadian Organ Replacement Registry (CORR) from Jan 1, 2001 to Dec 31, 2010. The primary outcome was the mean eGFR level at dialysis initiation. An interrupted time series and adjusted multilevel models were used to determine the change in eGFR at dialysis initiation, pre- and post-reporting.

Results: We observed a linear increase in the mean eGFR at dialysis initiation from 9.1 to 10.8 ml/s/min during the study period. In an unadjusted interrupted time series analysis, there was no change in the trajectory of the eGFR at dialysis initiation, before or after eGFR reporting. In multi-level models, there was no change in the slope of the eGFR at dialysis initiation after adjustment for case-mix and facility characteristics (post-eGFR reporting X time interaction p=0.6).

Figure 1: Crude percent of children initiating dialysis with an eGFR > 10.5 ml/min/1.73m² according to incident year

Funding: Private Foundation Support
Conclusions: Automatic laboratory-based eGFR reporting did not impact the eGFR at dialysis initiation in a large incident hemodialysis cohort. Concerns that widespread eGFR reporting leads to earlier dialysis initiation are not supported by this study.

SA-OR040

The Impact of Estimated Glomerular Filtration Rate Reporting on the Initiation of Dialysis with an Arteriovenous Fistula  
Manish M. Sood,1 Paul Komenda,2 Claudio Rigatto,2 Brett M. Hiebert,1 Navdeep Tangri,2 Medicine, St. Boniface Hospital, Winnipeg, Canada; 2Medicine, Seven Oaks Hospital, Winnipeg, Canada; 3Cardiac Sciences, St. Boniface Hospital, Winnipeg, Canada.

Background: The effect of automatic laboratory reporting of the estimated glomerular filtration rate (eGFR) on dialysis-related quality of care remains unknown. We set out to examine trends in the presence of an AVF at dialysis initiation before and after eGFR reporting.

Methods: All incident dialysis patients from four Canadian provinces that implemented province-wide, automatic laboratory reporting of eGFR with a known vascular access at dialysis initiation were included in the study (N=25,201). Data were obtained from the Canadian Organ Replacement Registry (CORR) from Jan 1, 2001 to Dec 31, 2010. The primary outcome was the proportion of AVF use at dialysis initiation. An interrupted time series and multilevel models adjusted for patient and facility characteristics were used to determine the change in AVF proportion pre- and post-reporting.

Results: The proportion of patients initiating hemodialysis with an AVF use decreased gradually over the study period from 19.0 to 14.6%. In an interrupted time series analysis, there was improvement in AVF usage at dialysis initiation after eGFR reporting, and this effect was predominantly seen in patients over 60 years. In multi-level models, there was improvement in the slope for AVF usage at dialysis initiation after adjustment for case-mix and facility characteristics, predominantly in patients over 60 (post-eGFR reporting X time (age >60) interaction p=0.3, post-eGFR reporting X time (age 60-74) interaction p=0.01, post-eGFR reporting X time (age >74) interaction p=0.008).

Conclusions: Automatic laboratory-based eGFR reporting is associated with an increased likelihood of starting hemodialysis with an AVF in patients over 60.

SA-OR041

Early Nephrology Referral Reduces Economic Costs during the Period before and after Initiation of Renal Replacement Therapy: Comprehensive Prospective Study of the Clinical Research Center for End Stage Renal Disease in Korea  
Jeonghan LEE,1 Jung Pyo Lee,2 Hye Min Jang,1 Ji-Young Choi,1 Yong-Lim Kim,1 Chul Woo Yang,1 Shin-Wook Kang,2 Yong Su Kim,1 Chun Soo Lim,2 1Dept of Internal Medicine, Hallym Univ Hangang Sacred Heart Hospital, Seoul, Korea; 2Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; 1Dept of Statistics, Kyungpook National Univ, Daegu, Korea; 3Dept of Internal Medicine, The Catholic Univ of Korea College of Medicine, Seoul, Korea; 4Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; 5Dept of Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea.

Background: We evaluated the health care costs according to referral time of patients with CKD to a nephrology clinic.

Methods: A total of 941 patients who start dialysis from 2008 to 2011 were prospectively enrolled. Early referral was defined as patients who were referred to a nephrologist more than a year before dialysis and visited nephrology 2 or more times, and other patients whose referral time was less than a year were considered as late referral. Cost information was acquired from the claim data of Korea Health Insurance Review and Assessment Service.

Results: Total amount of medical costs during the first 12 months after initiation of dialysis was not different between the two groups. However, costs during the first 1 month of early referral patients were lower than those of late referral patients (3029 ± 2210 versus 3438 ± 2821 US dollars, P = 0.025). Total 12 months health care costs before initiation of dialysis were lower in the early referral group (6206 ± 5873 versus 8610 ± 7820 US dollars, P < 0.001). In multivariable analysis, early referral reduced significantly health care costs (2513 ± 443 US dollars, P < 0.001) during the 12 months before dialysis start and the first month (400 ± 182 US dollars, P = 0.028) after initiation of renal replacement therapy.

Conclusions: Early referral of CKD patients to a nephrologist is associated with decreased medical costs during the predialysis and early period of dialysis.

SA-OR042

Hemodialysis Facility and Patient Level Treatment Time and Ultrafiltration Rate Practices in the United States  
Rajiv Saran,1 Brett W. Plattner,1 Chad M. Cogan,2 Casey Parrotte,1 Alissa Kapke,2 Yi Li.1 1Univ of Michigan; 2Arbor Research Collaborative for Health.

Background: Longer dialysis treatment time(TT) and lower ultrafiltration rates(UFR) are associated with lower mortality in hemodialysis(HD) patients(p). However, TT<240 min is still common in the US. We sought to examine US dialysis practice with respect to TT and UFR and characterizing pts receiving longer TT.

Methods: May 2012 CROWNWeb data on 235,629 pts from 4,313 dialysis facilities, pt characteristics significantly associated with TT>240 min included younger age, men, African American race, shorter dialysis vintage, higher intradialytic weight loss, congestive heart failure, diabetes mellitus, higher BMI, and lower UFR.

Results: 66% of pts received TT<240 min. Based on the estimated regression coefficients, pt characteristics significantly associated with TT>240 min included younger age, men, African American race, shorter dialysis vintage, higher intradialytic weight loss, congestive heart failure, diabetes mellitus, higher BMI, and lower UFR.

The figure displays the variation in the distributions of clinically relevant TT/UFR combinations at the facility level. In a median US dialysis facility 15% of pts received TT>240 min and UFR<10. In contrast, 50% US dialysis facility had at least 40% pts receiving TT<240 min and UFR<10, and 30% pts receiving TT<240 min and UFR>10.
Conclusions: In current US dialysis practice, the majority of pts on 3x/week dialysis have a TT=240 mins. Pi-level analysis suggests that longer TT in the US is utilized among pts with adverse prognostic factors. A proportion of facilities are able to provide TT=240 min and lower UFR to a sizable number of pts, demonstrating the potential feasibility of expanding this practice pattern.

Funding: Other U.S. Government Support

SA-OR043

Nephrology Care Influence Patient Mortality among United States Dialysis Facilities Hua Hao,1 Howard Chang,2 Ritam Chowdhury,1 Rachel E. Patzer,1 1 Dept of Epidemiology, RSHP, Emory Univ; 2 Dept of Biosocialistics and Bioinformatics, RSHP, Emory Univ; 1 Div of Transplantation, Emory Univ School of Medicine, Atlanta, GA.

Background: Previous ESRD nephrology care is important for better clinical outcomes for patients with end stage renal disease (ESRD). The aim of this study was to determine the association between pre-ESRD nephrology care and the standardized mortality ratio (SMR) among dialysis facilities in the US.

Methods: A total of 5,387 dialysis facilities were identified from the Dialysis Facility Report data 2007-2010. A marginal generalized estimating equation model assuming exchangeable covariance structure was used to estimate the relationship between pre-ESRD nephrology care, timing of pre-ESRD nephrology care, and facility level SMR.

Results: The percentage of patients who received pre-ESRD nephrology care within a facility was significantly associated with facility-level SMR. A 10% increase in pre-ESRD nephrology care was associated with a 0.50% (95% CI, 0.10%-0.80%, P=0.0067) decline in facility SMR. After considering the timing of pre-ESRD nephrology care, for every 10% increase in the percentage of patients who received pre-ESRD nephrology care within a dialysis facility, there was a 0.70% (95% CI, 0.10%-1.20%, P=0.001) and 1.00% (95% CI, 0.60%-1.50%, P=0.0001) decrease in facility SMR for patients who received pre-ESRD care >6 months and >12 months prior to ESRD, respectively.

Conclusions: As the percentage of patients who received pre-ESRD nephrology care within a facility increased, the facility-level SMR decreased. The timing also played a significant role in mortality reduction where earlier access to nephrology care resulted in a steeper decline in the mortality. This suggests that targeted interventions to improve access to pre-ESRD nephrology care could reduce mortality among ESRD patients in dialysis facilities.

SA-OR044


Background: Infections cause many dialysis patient hospitalizations and deaths. To better understand practices related to infection risk, CDC administers an annual survey to dialysis centers via the National Healthcare Safety Network (NHSN). Methods: The 2012 National Survey of Dialysis Centers Practices Survey, required for NHSN participation, includes self-reported center characteristics, infection prevention strategies, and vascular access practices. Surveys completed in 2012 by U.S. hemodialysis centers were analyzed. Chi-square test was used for comparisons.

Results: Of 5666 centers, 589 (10.4%) were hospital-affiliated centers (HAC). Adherence to CDC recommendations for hepatitis C screening (16.2%), and catheter (CVC) exit site care using chlorhexidine (27.7%) or antimicrobial ointment (15.1%) was low. These practices were more common in HAC than freestanding centers (FSC).

Conclusions: Other infection prevention strategies vary and recommended practices are underused. HAC may be more aware of CDC recommendations than FSC. Understanding implementation barriers among FSC is important to reducing infections.

Funding: Pharmaceutical Company Support - DaVita Rx

SA-OR045

Targeted Medication Therapy Management (MTM) Improves Outcomes for Dialysis Patients and the Healthcare System Joshua K. H Howell, May Hoang, Maricela Lara Nevarez, Kelly C. Chillingworth, Tracy Furgiuele. DaVita Rx, Coppell, TX.

Background: The Affordable Care Act expanded MTM services to become a core component of the Medicare Part D program. Identification of medication-related problems and avoidance of adverse drug events are important clinical outcomes. Accurate and timely medication management is associated with improved outcomes and reduced costs.

Methods: Data from 212 patients (new to dialysis [<90 days] or ≤14 days since hospital discharge) who received a medication review were assessed by review of patient records. Each participant received a comprehensive medication review conducted via telephone by a pharmacist. Interventions which resulted in an avoided hospitalization/ER visit were determined and independently verified by pharmacists based on the clinical impact of the medication-related problem.

Results: 279 unique interventions were identified that resulted in potential avoidance of hospitalization/ER visit. Modeled mean cost savings for the healthcare system were $642,436; median cost savings were $440,911.

Conclusions: These data suggest that a pharmacist medication review program for vulnerable patient populations has the potential to improve patient outcomes and reduce overall healthcare costs through avoided hospitalizations. Association between hospitalization rates for patients receiving program interventions will be needed to validate these findings.

Funding: Pharmaceutical Company Support - DaVita Rx

SA-OR046


Background: Kidney transplant (KT) is the treatment of choice for majority of ESRD patients. Navigation of the evaluation process is a challenge, contributing to variations in timing for KT evaluation. We analyzed the association between the infrastructure for patient navigation and the timing of referral and evaluation for KT.

Methods: Invitations were sent to 3180 nephrologists in the eastern US. From 822 interested, 250 were randomly invited to complete a questionnaire about demographics, practice characteristics, and availability of infrastructure in their practice for patient navigation of the KT process. Excluding 9 with incomplete responses yielded 216 participants for a 2-step analysis: 1) association between practice characteristics and availability of infrastructure (formal protocol for KT referral, designated coordinator for KT work, outreach activities by a transplant center (TC)); 2) association between infrastructure and timing of KT referral and evaluation. Chi-square and stepwise logistic regression were performed.

Results: A protocol (52%) was more likely among nephrologists in large groups (>10 members) (60%, 3.80, p=0.003). Coordinator availability (46%) was more likely among academic nephrologists (OR:2.56, p=0.002) and those in large groups (OR:2.30, p=0.02). TC outreach was more likely for respondents (51%) attending transplant-related CME.
SA-OR047  
Living Kidney Donor Assessment: Challenges, Uncertainties and Controversies among Transplant Nephrologists and Surgeons  
Allison Tone,1,2 Jeremy Chapman,1 Germaine Wong,1,2,3 Jonathan C. Craig,1,2  
1Sydney School of Public Health, The Univ of Sydney, NSW, Australia; 2Centre for Kidney Research, The Children’s Hospital at Westmead, NSW, Australia; 3Centre for Transplant and Renal Research, Westmead Hospital, NSW, Australia.  

Background: The assessment of living kidney donors presents unique ethical challenges and complex psychosocial implications. We aimed to ascertain the perspectives of transplant nephrologists and surgeons on living kidney donor assessment.  

Methods: Semi-structured, face-to-face interviews were conducted with 110 transplant nephrologists and surgeons from 43 transplant units in 12 countries from Europe, Australasia, and North America.  

Results: The challenge of defining acceptable risk to the donor was central to five themes identified: burden of responsibility (personal accountability, policing morality, democratic decision making, meeting legal obligations, optimizing outcomes and innovation, relinquished control); medical protectiveness (prognostic uncertainty, scepticism of donor risk perception, avoidance of undue coercion, concerns for dubious motivations and coercion, safeguard donor well-being, ethical information disclosure); respecting donor autonomy (facilitated informed decision-making, conceding to donor risk acceptance, benefit of the doubt, donor mandate to maintain health, acceptable altruism); driving ideologies (preserving equity, championing living donation, cognisance of anti-paternalism); and contextual pressures (evolving donor demographic, resource limitations).  

Conclusions: Living kidney donor assessment involves complex interactions between safety and the donor’s autonomy and respecting their autonomy. Authoritative and well-described transplant unit, hospital and public policy positions would make explicit the considerations which are often implicit, and reduce the uncertainty within which living kidney donors are assessed today.  

Funding: Government Support - Non-U.S.  

SA-OR048  
Impact of Hypertension Management in Patients with Chronic Kidney Disease on Outcomes after End-Stage Renal Disease  
Elaine Ku,1 David V. Glidden,2 Barbara A. Grimes,1 Kirsten L. Johansen,1 Mark J. Sarnak,2 Hocine Tighiouart,2 Chi-Yuan Hsu,1 1UCSF; 2Tufts Medical Center.  

Background: There is controversy regarding whether strict blood pressure (BP) control (<140/90 mm Hg) is indicated in patients with chronic kidney disease (CKD) since primary results of randomized controlled trials showed this strategy does not reduce rates of kidney function loss. However, it is possible that strict BP control has other beneficial effects beyond reducing risk of end-stage renal disease (ESRD), such as lowering mortality and cardiovascular disease burden at the start of ESRD.  

Methods: The Modification of Diet in Renal Disease (MDRD) study is a well-known CKD trial conducted from 1989-1993 that randomized 840 CKD patients to strict (mean arterial pressure <92 or <98 mm Hg depending on age) vs. usual BP control (<107 mm Hg). We extended follow-up of MDRD study enrollees via cross-linkage with US Renal Data System (USRDS) and National Death Index to ascertain ESRD onset and death (prior to ESRD) through 12/31/2007. Deaths after onset of ESRD were ascertained via USRDS through 12/31/2009.  

Results: Of the 840 MDRD enrollees, 616 developed ESRD by 12/31/2007. There were 306 cases of ESRD in the strict BP arm and 310 cases of ESRD in the usual BP arm (unadjusted Cox models hazard ratio [HR] 0.93, 95% CI 0.79-1.08; p = 0.34). Prior to ESRD, there were 66 deaths in the strict BP arm and 40 deaths in the usual BP arm (HR 1.48; 95% CI 1.02-2.09; p = 0.05). After onset of ESRD, there were 132 deaths in the strict BP arm and 179 deaths in the regular BP arm (HR 0.80; 95% CI 0.54-1.25; p = 0.40). In Cox model of time to event since dialysis initiation. When considering all deaths regardless of timing relative to ESRD, mortality risk was lower in the tight blood pressure control group (HR 0.81; 95% CI 0.67-0.99; p = 0.04).  

Conclusions: Although strict BP control may not delay progression of CKD to ESRD, this strategy appears to be associated (even years after end of active intervention) with reduced risk of death after onset of ESRD. Post-ESRD outcomes should be considered when formulating BP targets for CKD patients.  

Funding: Other NIH Support - National Cancer Institute  

SA-OR049  
Physical Activity and Risk of Kidney Failure in the Singapore Chinese Health Study  
Tzezen H. Jafar,1 Jin Ai Zhen,2 Woon-Puay Koh,1 Khuan Yew Chow,3 1Duke-NUS Graduate Medical School, Singapore; 2National Registry of Diseases Office, Health Promotion Board, Singapore; 3Saw Swee Hock School of Public Health, National Univ of Singapore, Singapore.  

Background: The relationship between physical activity and risk of kidney failure is not clear. We analyzed data from the Singapore Chinese Health Study to investigate whether physical activity reduces the risk of kidney failure.  

Methods: The Singapore Chinese Health Study is a population-based cohort of 63,257 Chinese adults enrolled between 1993 and 1998. Self-reported information on habitual physical activity at baseline. Incidence of kidney failure was identified via record linkage with the nationwide Singapore Renal Registry until 2008, defined by one of the following: 1) serum creatinine level of more than or equal to 500 μmol/L (5.7 mg/dL), 2) estimated GFR <15 mL/min/1.73m2, 3) undergoing hemodialysis or peritoneal dialysis, 4) kidney transplantation. Multivariable models were built and Cox proportional hazard regression analysis was performed to assess the association between physical activity with kidney failure after adjusting for age, education, dialect, herbal medications, body mass index, physician-diagnosed hypertension and diabetes.  

Results: Mean age of subjects was 55.6 years; 44% were men. A total of 671 incident cases of kidney failure occurred during a median follow-up of 13.3 years. Individuals who were physically active had significantly reduced adjusted risk of kidney failure [hazard ratio (HR) 0.79; 95% CI 0.58-0.83] compared to those who were inactive. The risk reduced with increase in intensity from moderate to vigorous/strenuous (p for trend= 0.0001), and with increase in duration of moderate physical activity to 4-6 hours/week (adjusted p for trend = 0.01). Vigorous activity or strenuous of 30 minutes to 2 hour/week independently reduced the risk of kidney failure (HR = 0.63; CI 0.42-0.92).  

Conclusions: Physical activity is associated with decreased risk of kidney failure. The risk reduction appears to be dose-dependent with increase in intensity and duration of moderate physical activity. Even a short duration of vigorous physical activity predicts additional risk reduction.  

Funding: Other NIH Support - National Cancer Institute  

SA-OR050  
Race, Dietary Acid Load and Risk of ESRD among Low Income Americans with CKD  
Deidra C. Crews,1 Tanushree Banerjee,2 Donald E. Wesson,3 Hal Morgenstern,2 Nilka Rios Burrows,4 Rajiv Saran,4 Desmond Williams,4 Neil R. Powe,5 1Johns Hopkins Univ; 2Univ of California, San Francisco; 3Texas A&M College of Medicine; 4Univ of Michigan; 5Centers for Disease Control and Prevention.  

Background: Racial disparities in risk of ESRD are most profound among individuals of low socioeconomic status (SES). High dietary acid load (e.g., diet poor in produce-fruits/vegetables) is positively associated with CKD progression to ESRD. Whether the effect of dietary acid load on risk of ESRD differs by race is unknown.  

Methods: We examined data on 159 Hispanic-black (NHB), and 760 non-Hispanic white (NHW) adults with CKD (eGFR<15-59/mL/min/1.73 m2), aged >20 years, and with an annual household income <300% of the federal poverty guideline, from the 1999-2004 National Health and Nutrition Examination Survey. Dietary acid load was estimated using the net acid excretion (NAE) formula by Remer and Manz and 24h dietary recall data. ESRD events were ascertained via linkage with the Medicare ESRD registry through 2008. ESRD was defined as death with ESRD in the past year, new ESRD in the past year, and current ESRD since 2008.  

Results: Compared with NHWs at baseline, NHBs were younger, more likely to have diabetes and/or albuminuria and had greater NAE (49.1 vs. 45.3 mEq/d). Overall, 94 (12.4%) participants [36 (38.3%) NHBs and 58 (61.7%) NHWs] developed ESRD during an average of 6.4 years of follow up. NHBs had a higher risk of developing ESRD than NHWs with an unadjusted HR of 13.7 (95% CI 13.6-13.8) for ESRD comparing NHBs with NHWs, adjusting for age, sex, diabetes, hypertension, baseline eGFR, urinary albumin/creatinine, daily caloric intake, and NAE. The modification of the NAE effect by race was examined by including an interaction term in the Cox model.  

Conclusions: Among low SES adults with CKD, the detrimental effect of high dietary acid load on progression to ESRD appears to be greater for NHWs than for NHBs, and is worthy of further investigation in other populations.  

Funding: Other U.S. Government Support, Private Foundation Support
SA-OR051
Persistent Alkalosis Is Associated with High Risk of Heart Failure in Patients with CKD: A Report from the Chronic Renal Insufficiency Cohort (CRIC) Study.
Mirela A. Dobrig,1 Wei Yang,2 Lawrence J. Appel,2 Keith A. Bellovich,3 Harold I. Feldman,4 Jing Chen,2 Michael J. Fischer,2 L. Lee Hamm,2 Thomas H. Hostetter,1 Bernard G. Jaar,2 Radhakrishnya Reddy Kallim,4 Sylvia E. Rosas,3 Julie J. Scialla,4 Myles S. Wolf,4 Mahboolb Raham.3 Case Western Reserve Univ;4 CRIC Study.

Background: The aim of the study is to evaluate the effect of serum bicarbonate change over 1 year on clinical outcomes in a large cohort of participants with CKD.

Methods: Serum bicarbonate was measured at baseline and after 1 year in 3394 CRIC participants with CKD. Participants were divided in 4 groups of serum bicarbonate change: Normal [22-26 mEq/L] at baseline and year 1, n=1288; Improved - abnormal at baseline who became normal at year 1, n=674; Worsening/persistent alkalosis <22 mEq/L at baseline and year 1, n=257 plus all who became <22 mEq/L at year 1, n=349; Worsening/persistent acidosis >26 mEq/L at baseline and year 1, n=433 plus all who became >26 mEq/L at year 1, n=593. Renal outcomes were defined as ESRD or 50% eGFR decline. Cardiovascular outcomes were defined as atherosclerotic (myocardial infarction, stroke, peripheral arterial disease) or CHF events. Multivariable Cox proportional hazards models were used to test the associations of interest.

Results: The risk of developing heart failure was 37% higher for participants in the alkalosis group (HR 1.37; 95%CI 1.02-1.84, p=0.04) compared to participants in the normal group, after adjusting for demographic, co-morbidities, medications including diuretics, eGFR and proteinuria.

<table>
<thead>
<tr>
<th>eGFR category</th>
<th>Improved</th>
<th>Worsening/persistent alkalosis</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR at baseline</td>
<td>60(50-61)</td>
<td>60(50-61)</td>
<td>60(50-61)</td>
</tr>
<tr>
<td>eGFR at 1 year</td>
<td>56(47-63)</td>
<td>52(43-59)</td>
<td>60(50-61)</td>
</tr>
<tr>
<td>Death</td>
<td>40</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Renal event</td>
<td>200</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>All-cause</td>
<td>150</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Conclusions: In a cohort of participants with CKD, persistent alkalosis was an independent risk factor for heart failure events.

Funding: Other NIH Support - T32 Training Grant : 5T32DK007470 (PI: John Sedor)

SA-OR054
The Effects of Allopurinol on Metabolic Acidosis and Endothelial Functions in the Hyperuricemic Patients with Stage 2-4 Chronic Kidney Disease.
Mehmet T. Sezer,1 Dilara Bayram,2 Atla Altunalt,3 Sahil Inal,1 Veyssel Kadir.2
1Internal Medicine, Saleymen Demirli Univ School of Medicine, Isparta, Turkey; 2Nephrology, Saleymen Demirli Univ School of Medicine, Isparta, Turkey.

Background: An elevated serum uric acid level is reported to be associated with endothelial dysfunction which is common in chronic kidney disease (CKD). At the same time, endothelial dysfunction and metabolic acidosis have emerged as important risk factors for progression of kidney disease. In this study, we aimed to investigate the effects of allopurinol on metabolic acidosis and endothelial functions in hyperuricemic stage 2-4 CKD patients.

Methods: Thirty patients (14 male/16 female) with stage 2-4 CKD and serum uric acid levels over 5.5 mg/dL were included in the study group. They were prescribed 300 mg/day po allopurinol for 3 months. Age and gender matched CKD patients (n=30) with similar clinical characteristics (13 male/17 female) were taken as the control group and they were not given allopurinol. Endothelial functions were measured via flow mediated dilatation (FMD) over forearm. Additionally, pH and HCO3 levels in venous blood, glomerular filtration rate (GFR) and proteinuria levels were calculated in all patients at the beginning and at the third month of follow up.

Results: Clinical and Laboratory findings were similar in both groups in the first visit. FMD was found to be significantly increased in allopurinol group (5.80 ± 2.56 vs 6.27 ± 2.70; p=0.006) whereas it decreased significantly in the control group (6.27 ± 1.62 vs 5.71 ± 1.90; p=0.005) between the two visits. When FMD variations within two groups were evaluated via the repeated ANOVA - general linear model, it was clearly significant. Additionally, uric acid levels were found to be inversely correlated with GFR and HCO3 levels.

Conclusions: The primary finding in this study was that decreased uric acid levels with allopurinol in hyperuricemic CKD patients have beneficial effects over endothelial dysfunction and serum HCO3 levels. We assume that decreasing uric acid levels seems to be helpful in order to restore endothelial functions, prevent metabolic acidosis and slow down the progression to end stage renal disease.

Funding: Pharmaceutical Company Support - AbbVie
SA-OR055
Validation of the Kidney Failure Risk Equation in an International Consortium

CKD Prognosis Consortium.

Background: Predicting the progression of CKD can enable early and appropriate nephrology care. We previously developed and validated laboratory based kidney failure risk equations (KFREs) for the progression of CKD to kidney failure in patients referred for nephrology care in Canada. Evaluation in other countries and in non-referred CKD populations is needed.

Methods: We meta-analyzed individual level data from 34,569 patients with CKD Stages 3-5 from 12 cohorts spanning 7 countries. We assessed models containing 3 (age, sex, estimated glomerular filtration rate [GFR]), 4 (+albuminuria) and 8 (+serum albumin, calcium, phosphorous, and bicarbonate) variables from the original publication. We compared hazard ratios for constituent predictors, discrimination, calibration, net reclassification index (NRI), and integrated discrimination index (IDI) for all models.

Results: The original 4- and 8-variable KFREs obtained similar hazard ratios for constituent predictors and achieved excellent discrimination (C statistic >0.84 – Table). Calibration of the original KFREs was adequate at 5 years, and improvements in NRI and IDI were observed in comparison with a 3-variable model (NRI 18%, IDI 5% for the 4-variable, and 25% and 6% for the 8-variable model). Performance in subgroups by age, race, and diabetes status was similar.

Conclusions: The previously developed KFREs accurately predict the progression of CKD Stages 3-5 to kidney failure across a wide range of studies. The abbreviated 4-variable equation is simple and highly accurate. Integration in routine clinical practice should be evaluated.

SA-OR056
CKD Management Program Improved Access to Nephrology Care and Stabilized Renal Replacement Therapy Incidence in Birmingham, UK
Hugh C. Rayner, Jyoti B. Baharani, Indranil Dasgupta, Vijayan Suresh, Robert Mark Temple, Mark E. Thomas, Stephen A. Smith.

Background: Heart of England (HEFT) provides ESRD care for c.0.72m population with mixed ethnicity and large areas of deprivation. From 2001-11 the England unadjusted RRT incidence rate increased 11.1% per year. In 2003/4 HEFT introduced a CKD management program with primary care education, multidisciplinary predialysis and conservative care (Nephron Clin Pract 2010;115:c283-8), routine eGFR reporting, and diabetes CKD surveillance (Rayner BMJ Qual Saf 2011). In 2006, national financial incentives for primary CKD care were introduced. We have studied access to nephrology care and trends in RRT and end of life care at HEFT.

Methods: Incident CKD5 patients >=75yrs (eGFR<15 x2 >3 mths apart Jan2010 - Jun2011) in HEFT pathology database linked with a nephrologist by UK Renal Registry. RRT = dialysis + pre-emptive transplant. Variation over time analyzed by statistical process control.

Results: In 2010/11 50/55 incident CKD5 patients >=75yrs were known to a nephrologist. From 1998, mean age at start of RRT (62 yrs) and eGFR at start of dialysis (7.8) were stable. From 2005 the unadjusted RRT incident rate stabilized (fig). RRT incidence at the neighboring centre was stable. Patients known to a nephrologist who died with eGFR <10 without dialysis increased (fig); mean age at death increased linearly from 70 in 1993 to 82yrs in 2012. From 2004, 105/189 patients (56%) who died with eGFR <10 without dialysis received multidisciplinary care; 07/189 (36%) received planned conservative care.

SA-OR057
Change in GFR and Subsequent Mortality: Meta-Analysis of 37 Cohorts in the CKD Prognosis Consortium

Background: Change in estimated GFR (eGFR) is frequently used to track CKD progression in clinical practice, trials and cohort studies but its association with mortality has not been studied extensively.

Methods: Change in eGFR was estimated as % change from the first to last eGFR (CKD-EPI creatinine) in a 2-year baseline period. We modeled the hazard ratios (HRs) of subsequent mortality as a spline function of %change in eGFR after adjusting for age, sex, race, first eGFR, and co-morbid conditions. We used random effects meta-analyses to combine results stratified by first baseline eGFR (<60 & ≥60) across studies.

Results: Mortality follow-up of 910,660 participants from 32 cohorts for a mean of 4.2 years after the 2-year baseline period showed 91,398 deaths for baseline eGFR <60 (n=333,722) and 45,063 deaths for baseline eGFR ≥60 (n=576,938). Change in eGFR had a non-linear association with mortality (Figure for eGFR<60). A decline in eGFR was consistently associated with higher subsequent mortality risk (adjusted HR for -5% vs. 0% change in eGFR were: 1.8 at eGFR <60 and 1.5 at eGFR ≥60; p<0.001). Similar results were obtained for a 1- or 3-year change in eGFR. Hazards ratios were largely similar for those with eGFR ≥60 or when stratified by ACR levels.

Conclusions: Declines in eGFR are strongly and consistently associated with subsequent risk of mortality adjusted for the first eGFR and covariates. These findings support using smaller changes than ~57% (equivalent to doubling of serum creatinine) in clinical research.

Figure: Adjusted mortality hazard ratio vs. % 2-year change in eGFR.

SA-OR005
Validation of the Kidney Failure Risk Equation in an International Consortium

CKD Prognosis Consortium.

Background: Predicting the progression of CKD can enable early and appropriate nephrology care. We previously developed and validated laboratory based kidney failure risk equations (KFREs) for the progression of CKD to kidney failure in patients referred for nephrology care in Canada. Evaluation in other countries and in non-referred CKD populations is needed.

Methods: We meta-analyzed individual level data from 34,569 patients with CKD Stages 3-5 from 12 cohorts spanning 7 countries. We assessed models containing 3 (age, sex, estimated glomerular filtration rate [GFR]), 4 (+albuminuria) and 8 (+serum albumin, calcium, phosphorous, and bicarbonate) variables from the original publication. We compared hazard ratios for constituent predictors, discrimination, calibration, net reclassification index (NRI), and integrated discrimination index (IDI) for all models.

Results: The original 4- and 8-variable KFREs obtained similar hazard ratios for constituent predictors and achieved excellent discrimination (C statistic >0.84 – Table). Calibration of the original KFREs was adequate at 5 years, and improvements in NRI and IDI were observed in comparison with a 3-variable model (NRI 18%, IDI 5% for the 4-variable, and 25% and 6% for the 8-variable model). Performance in subgroups by age, race, and diabetes status was similar.

Conclusions: The previously developed KFREs accurately predict the progression of CKD Stages 3-5 to kidney failure across a wide range of studies. The abbreviated 4-variable equation is simple and highly accurate. Integration in routine clinical practice should be evaluated.
Background: The generation of ROS, specifically superoxide (·O2−), by damaged or dysfunctional mitochondria, has been postulated to be a primary initiating event in the development of diabetes complications. The glomerulus is a primary site of diabetic injury, and podocyte loss is one mechanism that leads to glomerulosclerosis and in diabetics. The current studies were designed to determine the potential role of oxidative stress in the progression of diabetic nephropathy.

Methods: We generated podocyte-specific EGFR knockout mice (EGFR−/−) by crossing EGFRflx/flx mice with podocin-Cre mice and induced diabetes in EGFR−/−mice and their wild type littermates (WT) by streptozotocin injections. Results: EGFR−/− and their WT control mice on a 129SVJ background developed similar levels of hyperglycemia and polyuria, but EGFR−/− developed significantly less albuminuria/urinary albumin/creatinine ratio at 32 weeks of hyperglycemia WT vs EGFR−/−: 170.80 ± 12.93 vs 80.88 ± 6.14 μg/mg, P<0.01, n=4-6). Furthermore, increased fibronectin deposition in glomeruli was attenuated in EGFR−/− diabetic mice. Immunoblotting of isolated glomerular lysates revealed that up-regulation of cleaved caspase 3 and down-regulation of β-actin, a marker of cellular stress, was reduced in diabetic mice compared with the controls. These results also revealed up-regulation of phospho-EGFR, phospho-smad2/3, and TGFβ1 expression were markedly inhibited in EGFR−/− diabetic mice. Furthermore, in WT diabetic mice, administration of either a mitochondria-targeted antioxidant, mito-TEMPO, or a cell-permeable NADPH-oxidase inhibitor, apocynin, also attenuated up-regulation of phospho-EGFR, phospho-smad2/3 and TGFβ1 expression, and blunted the altered expression of cleaved caspase 3 and Bcl-2 expression in glomeruli.

Conclusions: This study demonstrates that EGFR plays an important role in oxidative stress-induced podocyte loss and glomerular ECM expansion in the pathogenesis of diabetic nephropathy.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR059
Podocyte VEGF-A and eNOS Loss of Function Lead to Diffuse Glomerulosclerosis in Mice Alida Tuft,1 Pardeep Kumar Aggarwal,1 Gilbert W. Moeckel,1 Pediatrics/Nephrology, Yale Univ, New Haven, CT; 2Pathology, Yale Univ, New Haven, CT.

Background: Vascular endothelial growth factor-A (VEGF-A) and nitric oxide (NO) are essential for glomerular filtration barrier homeostasis, and are disrupted in diabetic nephropathy. While NO availability is consistently low, both high and low VEGF-A have been reported in patients with diabetic nephropathy.

Methods: Here we examine the effect of inducible podocyte VEGF-A knockdown (podocin-ERT2/ERT-O-VEGF−/− – VEGF−/−) in diabetic mice and in endothelial nitric oxide synthase knockout mice (eNOS KO). Diabetes was induced with streptozotocin (STZ) using the ADMCC protocol. Proteinuria was measured in plasma and urine by ELISA and colorimetric methods, respectively.

Results: Podocyte VEGF-A−/− caused diffuse glomerulosclerosis and in eNOS−/− mice developed microaneurisms, arteriolar hyalinosis, massive proteinuria (>30 fold above non-diabetic controls and eNOS KO mice). Diabetes was induced with streptozotocin injections. ApoE−/− mice were treated with the specific Nox1/4 inhibitor GKT37831. Animals were killed after 24 weeks and kidneys were assayed for assessment of renal structure and function as well as ROS production. In vitro, Nox4 was silenced in human podocytes and exposed to high glucose and TGFβ for gene expression and ROS measurement.

Conclusions: Collectively, these results identify Nox4 is a key source of ROS responsible for kidney injury in diabetes and provide proof of principle for an innovative small molecule approach to treat and/or prevent DN.

Funding: Government Support - Non-U.S.

SA-OR061
Altered Metabolic Substrate Utilization and Mitochondrial Dysfunction Characterizes Diabetic Nephropathy Pradeep Kavavmilly, Kelli Sas, Jaeman Byun, Hongyu Zhang, Charles Burant, Frank C. Brosius, Subramaniam Pennathur. Univ of Michigan, Ann Arbor, MI.

Background: Diabetic nephropathy (DN) is the most common cause of end-stage renal disease in the United States. While it is well-recognized that diabetes leads to altered carbohydrate, amino acid and fatty acid metabolism, the utilization and flux of these substrates in vivo has not been systematically studied.

Methods: We developed a comprehensive targeted metabolomic platform for simultaneous quantitative analysis of glycolytic, tricarboxylic acid (TCA) and fatty acid oxidation intermediates by liquid chromatography electrospray ionization tandem mass spectrometry (LC/ESI/MS/MS) and gas chromatography-mass spectrometry (GC/MS). Animals which exhibit characteristic features of DN (BKS db/db) were used as a model system to examine the dynamic changes in substrate utilization.

Results: Static metabolite levels of several metabolites including acylcarboxylates, glycolytic, and TCA cycle were markedly and statistically significantly increased in diabetic renal cortex and mitochondria (1.5 to 6-fold). Proximal tubule and renal cortical mitochondria from diabetic renal cortex exhibited reduced ATP production and increased proton leak indicating diminished function and compromised membrane integrity.

Conclusions: Taken together, these results show a metabolic reprogramming in the diabetic kidney leading to mitochondrial dysfunction and oxidative stress. The altered metabolic profile in mouse diabetic kidney is mirrored in urine samples of DN patients, suggesting that a subset of these metabolites may serve as potential biomarkers of DN.

Funding: NIDDK Support

SA-OR062
Autophagy Is Beneficial for Podocytes during Diabetes-Induced Nephropathy Olivia Lenor,1 Magali Jasiek,1 Pierre-Louis F. Tharaux,1,2 1Paris Cardiovascular Research Centre - PARCC, INSERM, Paris, France; 2Univ Paris Descartes, Sorbonne Paris Cité, Paris, France.

Background: Diabetic nephropathy (DN) is the major microvascular complication of diabetes and the leading cause of ESRD in industrialized countries. The development of CKD in patients with diabetes can take several decades and may manifest despite tight glycemic and blood pressure control. With the current standard therapies only partial renal protection is obtained, thus, it is of particular importance to understand more about the pathogenesis of DN and to identify novel therapeutic targets. Recently, autophagy pathways have been shown to be critical to survival signal in several cell types during stress-induced lesions.

Recently, Huber and coll. demonstrated the importance of autophagy in podocytes in the preservation of glomerular cells functions during aging. Moreover, we found that high glucose induces autophagy in podocytes. Thus, we hypothesized that autophagy could be involved in podocyte cell survival during diabetes-induced nephropathy.

Methods: We characterized the effects of high glucose on mouse primary podocytes cell function and survival and on the induction of autophagy. We also studied the development of diabetic nephropathy in streptozotocin-treated diabetic mice with a podocyte-specific disruption of the autophagy pathway.

Results: In freshly isolated podocytes, we demonstrated that high glucose induced podocyte autophagy. Furthermore, high glucose-induced autophagy is associated with a decrease in podocin and WT1 expression. Next, autophagy pathway was disrupted in vivo using a genetic deletion of Atg5 specifically in podocyte using the Cre-lox system (NPHP5Cre). We found that genetic deletion of autophagy in podocytes dramatically sensitized mice towards the development of diabetic nephropathy in mice. Indeed,
SA-OR065

miRNA Profiling in Human Diabetic Nephropathy Francesca Conserva,1 Paola Pontrelli,1 Matteo Accetturo,1 Anna Maria Di Palma,1 Salvatore Di Paolo,2 G. Grandaliano,2 Loreto Gesuludo.1 1Dept of Emergency and Organ Transplant - Nephrology Unit, Univ of Foggia, Italy; 2Dept of Biomedical Sciences - Nephrology Unit, Univ of Foggia, Italy

Background: Diabetic Nephropathy (DN) is a clinical complication of Diabetes. Up to date there is still no cure for DN and this condition has rapidly become the primary cause of End Stage Renal Disease (ESRD). As widely acknowledged, microRNA expression is tightly connected to protein synthesis as each microRNA can induce translational repression of hundreds of targets. Aim of our study was to identify a pattern of differentially expressed microRNAs in kidney biopsies of patients with DN and analyze the role of their putative targets in the pathogenesis and progression of the disease.

Methods: Using microarray technology we assayed microRNA expression in formalin fixed kidney tissues from 8 DN patients showing increased proteinuria and decreased glomerular filtration rate (GFR), and 4 control patients with no histological signs of nephropathy. Selected microRNAs were then validated using quantitative PCR.

Results: 76 miRNAs were differentially expressed in DN, of which 18 were further validated using quantitative PCR. The microRNA/mRNA joint target analysis revealed three proteins whose reduction could be crucial in the context of glomerular filtration: vasopressin, complement factor 9 and surfactant protein D.

Conclusions: To our knowledge there is no previous study reporting the microRNA profile of human DN kidney. The validation of these microRNAs in biomolecular fluids along with further functional studies in terms of mRNA target validation will soon allow the identification of novel disease biomarkers and untangle novel gene key players in DN progression.

SA-OR064

Systems Biology Approaches in Understanding Diabetic and Non-Diabetic Kidney Disease Risk Lori A. Nora Ledo, Yi-An Ko, Ae Seo Deck Park, Katalin Susztak. Perelman School of Medicine, Univ of Pennsylvania, Philadelphia, PA

Background: Recent genome-wide association studies (GWAS) have identified multiple loci associated with the risk of chronic kidney disease (CKD) development. The functional role of these loci and the nearby genes is largely unknown. The aim of our study was to map the expression of these genes in normal and disease human kidney samples using systems biology approaches.

Methods: We interrogated the expression and regulation of 86 different transcripts that was associated with 211 single nucleotide polymorphisms. Baseline transcript expression was examined by whole human kidney RNA-sequencing. In addition, expression arrays of 92 genes (glomeruli and tubules) control, diabetic and hypertensive human kidney samples were analyzed.

Results: Among the 86 different transcripts, 57 genes were expressed in the kidney based on the RNA-sequencing data. Only 6 genes showed significantly higher expression in glomeruli (p<0.05, fold change>1.5), while 8 genes were specific for tubules in normal human kidney samples. In hypertensive CKD 18 genes were down-regulated, 2 were up-regulated (p=0.01). In diabetic kidney disease (DKD) 13 transcripts were down-regulated and 2 were up-regulated (p=0.01). Down-regulation of SORT1, DACH1 and SETDB1 and up-regulation of ALMS1 and FBX2 were observed exclusively in DKD, not in hypertensive CKD. Furthermore, of the 57 kidney expressed transcripts, 27 showed strong statistically significant linear correlation with eGFR levels; these included UMOD, NAT8, LASS2, SLC34A1, SLC6A13, ANXA9, SLC7A9 (p<1E-04).

Conclusions: Our study adds new evidence to the post-GWAS functional characterization of the CKD risk loci is the analysis of the gene expression of nearby genes. We found that GWAS-associated genes are enriched for kidney developmental pathways. Our study did not find significant compartmental enrichment of these GWAS related genes. The expression of almost a third of these transcripts showed a strong association with renal function.

Funding: NIDDK Support

SA-OR067

Role of Sirtuin-1 in Deacetylation of Transcription Factors during Diabetic Nephropathy Yifei Zhong,1 Ruijie Liu,2 John C. He.3 1Nephropathy, Longhua Hospital, Shanghai Univ of Traditional Chinese Medicine, Shanghai, China; 2Medicine, Mount Sinai School of Medicine, James J. Peters VAMC, New York City, NY; 3Inst2.

Background: Acetylation and deacetylation of transcription factors such as NF-kB and STAT3 have been recognized as important events in pathogenesis of diabetic kidney disease (DKD). Sirtuin-1 (Sirt1) is an enzyme that mediates nicotinamide adenine dinucleotide-dependent deacetylation and can regulate several transcription factor’s activity through deacetylation.

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

86A
Methods: Diabetic db/db mice, podocyte-specific Sirt1 knockout diabetic db/db mice and human kidney biopsies were employed in the study. Kidney morphology and apoptosis were examined by PAS- and TUNEL stainings respectively. Expression of acetyl-NF-kB and acetyl-STAT3 were examined by immunostaining.

Results: Acetylation of NF-kB and STAT3 were increased in the kidneys of both db/db mice and patients. Moreover, when diabetic db/db mice were treated with pyridoxamine that restored Sirt1 expression, there was an increased level of Sirt1 and decreased acetylation of NF-kB and STAT3 in the kidney. In addition, pyridoxamine attenuated formation of proteinuria. It also improved kidney apoptosis. Furthermore, when Sirt1 was deleted in podocytes of db/db mice, there were aggravated proteinuria and kidney injury compared to type db/db mice. At the same time, acetylation of NF-kB and STAT3 was increased in podocyte-specific Sirt1 knockout diabetic db/db mice.

Conclusions: Sirt1 could regulate acetylation of NF-kB and STAT3, which makes Sirt1 as a new therapeutic target for treatment of diabetic nephropathy.

Funding: Government Support - Non-U.S.

SA-OR068

Gene Expression Differences in Skin Fibroblasts (SF) of Type 1 Diabetic (T1D) Patients (pts) with and without Diabetic Nephropathy (DN)

Maria Luisa A. Caramori,1 Youngki Kim,1 Jason H. Moore,2 Stephen Rich,3 Andrezj S. Krolewski,4 Allison B. Goldfime,4 Helen D. Nickerson,4 Michael Maurer,1 1 ‘U of MN: ‘Dartmouth College; ‘U of VA: ‘Joslin Diabetes Center; ‘JDRF.

Background: The in vitro behaviors of SF from pts with and without DN have been associated with DN risk.

Methods: We performed research skin biopsies in 100 former Genetics of Kidneys in Diabetes (GoKinD) pts. SF were grown in high glucose (HG, 25 mmol/L) for 3-4 passages until 90% confluence and gene expression determined by RNAseq in 40 DN controls (long-standing T1D duration and normoalbuminuria; C) and 60 DN cases (35 proteinuric [P] and 25 ESRD). Directional Exploratory Visual Analysis determined whether differentially expressed genes were over represented in KEGG pathways.

Results: Cases were older (56.7±17 years; p<0.001) and had longer T1D duration (44.4±8 vs. 35.5±7 years; p=0.001) than C. Cystolic blood pressure (BP) was higher in ESRD (137±20) than in P (127±17 mmHg; p<0.02) or C (121±14; p<0.001). There were no differences in sex distribution, HbA1c, or diastolic BP among groups. Spliceosome (p=8.4e-17), Cell cycle (p=3.7 e-15), DNA replication (p=1.8 e-14), Proteasome (p=8.9e-13), Pyrimidine metabolism (p=5.4e-7), Purine metabolism (p=9.1e-7), Mismatch repair (p=3.9e-9), DNA repair (p=2.1e-9), Base excision repair (p=5.1e-4), Ribosome (p=8.4e-4), Terpenoid backbone biosynthesis (p=8.6e-6), Proteasome metabolism (p=1.4e-4), Cysteine and methionine metabolism (p=2.4e-4), Fatty-acid metabolism (p=4.6e-7), Glycolysis-Gluconeogenesis (p=4.9e-9), Nucleotide excision repair (p=6.1e-7), Homologous recombination (p=7.2e-7), Pyruvate metabolism (p=7.2e-4), and TCA-citrate cycle (p=1.7e-8) were up-regulated in C vs. DN cases. The results were similar when C were compared to P or ESRD pts only.

Conclusions: There are robust differences in gene expression in SF grown in HG between pts with and without DN. T1D pts without DN despite long T1D duration show increased expression of genes in pathways predominantly related to cell cycle, cell cycle regulation and cell repair mechanisms. These findings are consistent with previous observations indicating protective mechanisms in T1D pts without DN.

Funding: Private Foundation Support

SA-OR069

Renal Outcomes with Aloskiren in Patients with Type 2 Diabetes: A Pre-Specified Analysis from ALTITUDE

Hiddo Jan Lambers Heerspink,1 Barry M. Brenner,1 Frederik I. Persson,2 Nish Chaturvedi,3 Scott D. Solomon,1 Marc A. Pfeffer,1 Hans-Henrik Parving,4 Dick de Zeeuw.1 1Clinical Pharmacology, Univ Medical Center Groningen, Netherlands; 2Brigham Woman Hospital, Boston; 3Steno Diabetes Center, Denmark; 4Imperial College London, United Kingdom; 4Aarhus Univ, Denmark.

Background: The ALTITUDE Trial (The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) trial showed no benefit of aloskiren on renal outcomes (doubling of serum creatinine, ESRD or renal death) as an adjunct to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. We performed a pre-specified analysis of the ALTITUDE trial analyzing the effects of aloskiren on intermediate renal outcomes.

Methods: In a double blind randomized controlled trial, 8561 patients were assigned to aloskiren 300 mg/day or placebo and followed for a median of 2.8 years. Intermediate renal endpoints were transitions in albuminuria-stages (i.e. normo-, micro, or macroalbuminuria) and rate of estimated glomerular filtration rate (eGFR) decline either calculated from baseline or from month 6, thus excluding the acute effect of aloskiren on eGFR.

Results: Aloskiren significantly decreased progression as well as increased regression of transitions in albuminuria classes by 14% (HR 0.86, 95%CI 0.77 – 0.95) and 27% (HR 0.73, 95%CI 0.67 – 0.80) respectively. Annual rate of eGFR decline was 3.1 ml/min/1.73m2/year in the aloskiren and 3.0 ml/min/1.73m2/year in the placebo group (p=0.52).

However, subjects assigned to aloskiren had a significantly greater fall in eGFR during the first 6 months compared to placebo (2.5 vs. 1.4 ml/min/1.73m2; p=0.001), but a slightly slower annual rate of eGFR decline thereafter (2.8 vs. 3.1 ml/min/1.73m2/year; p=0.068).

Conclusions: Although the ALTITUDE showed no beneficial effect of aloskiren on hard renal outcomes, aloskiren did delay progression to micro- and macroalbuminuria, and improved regression to micro- and normoalbuminuria. In addition, aloskiren attenuated the (chronic) eGFR decline. The lack of renoprotection with aloskiren, as measured on hard clinical outcomes requires further examination.

Funding: None
Conclusions: Lower physical activity, but not adipose tissue measures is associated with higher mortality in those with and without CKD in the representative US population. Future studies should study the effects of improving physical activity levels particularly in the CKD population.

Funding: Other NIH Support - National Center for Research Resources: RR024990

SA-OR074

Urinary Monocyte Chemotactic Protein-1 and Early Diabetic Nephropathy (DN) Lesions Michael Maurer,1 Brad H. Rovin,2 Jon B. Klein,3 Vasan S. Ramachandran,1 Harold I. Feldman,3 Paul L. Kimmel,3 John W. Kusek,3 Robert G. Nelson. 3

Background: MCP-1 is a key chemokine regulating monocytes/macrophages migration and infiltration. We asked whether urinary MCP-1 levels are associated with DN lesion severity or the rate of change in DN lesions over 5 yrs in a serial biopsy samples in normoalbuminuric normotensive, normal GFR patients (pts) with type 1 diabetes (T1D, duration 3-20 years) in the Renin Angiotensin System Study (RASS).

Methods: The progression of DN lesions was not slowed by RAS blockade in the trial. MCP-1 levels were measured by ELISA in baseline urines stored at -80°C and adjusted for urinary creatinine (MCP-1/Ucr) 166 of 246 pts had measurable MCP-1/Ucr levels. There was no statistically significant association between baseline MCP-1/Ucr and the baseline biopsy severity of DN lesions. Higher MCP-1/Ucr was associated with greater increases over 5 years in interstitial fractional volume (Vv[Int/cortex]) and glomerular basement membrane (GBM) width but not mesangial fractional volume (Vv[Mes/glon]) (Table 1). However, adjusted for T1D duration, HbA1c, age, and sex, only change in GBM width remained statistically significant.

Conclusions: We have previously shown that GBM width is a strong and independent predictor of progression from NA to proteinuria and ESRD in normoalbuminuric T1D patients (Cassorri et al, IASN, in press). In summary, MCP-1/Ucr may be an early biomarker of the progression of important DN lesions in normoalbuminuric, normotensive, normal GFR T1D patients consistent with the notion that inflammatory processes may be involved in the pathogenesis of early DN structural changes. FOR THE BIOMARKER CONSORTIUM

Funding: NIDDK Support, Veterans Affairs Support

SA-OR075

Clinical Significance of Linear Immunofluorescent IgG Staining in Patients with Diabetic Nephropathy Koki Mise, Junichi Hoshino, Yoshifumi Ubara, Masahiro Kawada, Rikako Hiramatsu, Toshiharu Ueno, Keiichi Sumida, Tatsuya Suvabe, Shigeko Haru, Kenmei Takaichi. Nephrology Center, Toranomon Hospital, Tokyo, Japan.

Background: The kidneys of diabetic patients usually exhibit a characteristic pattern of linear immunofluorescent staining for IgG along the glomerular and tubular basement membranes. However, the association between linear IgG staining and the clinical outcome remains unclear.

Methods: Among 233 patients with diabetes mellitus who underwent renal biopsy from 1985 to 2010 and were confirmed to have pure diabetic nephropathy according to the classification of Tervaert et al, 159 patients (glomerular class 1 to III) were enrolled in this study. Immunofluorescent staining was classified into three categories (0=none, 1=weakly positive, 2= positive) according to its intensity. Cox proportional hazards regression analysis was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for death-censored renal death, with each regression analysis examining two levels of multivariate adjustment. Renal death was defined as commencement of dialysis due to end-stage renal disease.

Results: After adjustment for age, gender, estimated glomerular filtration rate, type of diabetes, urinary protein excretion, systolic blood pressure, body mass index, HbA1c, diabetic retinopathy, and red blood cells in urinary sediment at the time of renal biopsy, the HRs for death-censored renal death of patients with IgG staining scores of 1 or 2 were 3.12 (95% CI: 1.08-9.14) and 4.50 (1.60-12.68), respectively, compared with patients whose staining score was 0.

Conclusions: More intense linear IgG staining is associated with higher HRs for renal death. This suggests that linear immunofluorescent staining for IgG may be a prognostic pathological finding in patients with diabetic nephropathy.
SA-OR076

Serum and Urinary Levels of TNFRs and Decreasing Renal Function in Type 1 Diabetes (T1D) Jung Eun Lee,1,2,3 Tomohito Gohda,1,2,4 Jan Skupien,1,2,5 William Walker,1 Kevin P. McDonnell,1 Rita H. Rolak,1 Adam Smiles,1 Andrzej S. Krolewski,1,2 Monika A. Niewczas,1,2 Research Div, Joslin Diabetes Center; Boston, MA; 3Harvard Medical School, Boston, MA; 4Dept of Medicine, Saumung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea; 5Dept of Internal Medicine, Juntendo Univ School of Medicine, Tokyo, Japan; 6Dept of Metabolic Disease, Jagiellonian Univ Medical College, Krakow, Poland.

Background: Increased circulating levels of soluble TNFR1 and TNFR2 are strong predictors of renal decline and progression to ESRD, however, the mechanism underlying this increase is unknown. This study aimed to determine serum and urinary patterns of TNFRs in subjects with T1D and various stages of diabetic nephropathy.

Methods: Study groups comprised T1D subjects with normo- or microalbuminuria (n=667), with proteinuria (n=412) and 78 healthy subjects. We determined serum and urinary concentrations of TNFR1 and TNFR2 and their respective fractional excretion (FE%) in the study group.

Results: Subjects with T1D and proteinuria had higher levels of serum and urinary TNFRs compared with subjects without proteinuria (P<0.001). In proteinuria group serum and urinary TNFRs concentrations and FE% increased progressively with advanced chronic kidney disease (CKD) stages (P<0.001 for trend). Findings for both TNFRs were similar, so TNFR1 data are shown.

Conclusions: Pattern of fractional excretion of TNFRs in our study suggests that increased levels of these receptors in serum and urine in T1D subjects at high risk of renal decline and rapid progression to ESRD result from their increased systemic production rather than being a simple reflection of impaired glomerular filtration.

Funding: NIDDK Support

SA-OR077

The Impact of Vitamin D Nuclear Receptor on Inflammation of Type 2 Diabetic Nephropathy Patients Bin Yi, Hao Zhang, Xiao-Fang Hu, Jing Huang, Wei Li. Dept of Nephrology, The Third Xiangya Hospital of Central South Univ, Changsha, Hunan, China.

Background: The development of chronic inflammation is closely related with the progress of diabetic nephropathy(DN). Studies in vitro have shown that nuclear vitamin D receptor(nVDR) has anti-inflammatory effect. In order to investigate the impact of VDR on the inflammatory state of DN patients, we will detect the nVDR and NF-κB expressions in diabetic groups.

Methods: 143 subjects were enrolled, including 113 diabetic patients and 30 healthy subjects (NC group). According to the uACR, diabetic patients were divided into normal albuminuria group(DN0 group), microalbuminuria group(DN1 group), and macroalbuminuria group(DN2 group). Urine MCP-1 and RANTES levels were measured by ELISA. VDR and NF-κB expressions were detected by realtime qPCR and western-blotting. One-way analysis of variance, Pearson correlation analysis and multiple stepwise regression analysis were used for statistical analysis.

Results: VDR mRNA and VDR protein expressions in diabetic groups were gradually decreased with the uACR increase, and significantly lower than those in NC group (P<0.05). However, NF-κB levels of diabetic patients were gradually increased with the uACR, and NF-κB expressions in DN2 group were significantly higher than those in DN0 and DN1 group (P<0.05). Urinary MCP-1/Cr and RANTES/Cr levels were significantly different between these groups, and those in DN2 group were higher than the other three groups. Multivariate linear regression analyses showed that nVDR was closed related with SBP, eGFR, VDR and NF-κB65 levels, and urinary MCP-1 and RANTES excretion rate; the urinary MCP-1/Cr and RANTES/Cr were independently associated with eGFR,SBP and VDR levels.

Conclusions: The expression of nVDR were decreased in type 2 DN patients, and negatively related with uACR and urinary MCP-1/RANTES excretion rate. The down-regulation of nVDR may induce inflammation by over-expressed NF-κB, which may play a role in DN pathogenesis.

Funding: Government Support - Non-U.S.

SA-OR078

Klotho Genomic Variants Impact on Serum Klotho and Patients Survival in Hemodialysis: The Aragonese Project Denis Fouque,1,2 Delphine Maucourt-Bouchel,1 Jocelyne Drau,3 Leslie Genet,1 Guillaume Jean,1 Christophe Marquis,4 Nephrology, Centre Hospitalier Lyon Sud, Pierre Benite, France; 5Carmen Cens, Univ de Lyon, Lyon, France; 6Bistatistics, Centre Hospitalier Lyon Sud, Pierre Benite, France; 7Biochimie, Centre Hospitalier Lyon Sud, Pierre Benite, France; 8Dialysis, Nephrocare, Ste Foy, France.

Background: Klotho (KL) is a recently discovered FGF23 cofactor involved in phosphorus metabolism. KL overexpression is associated with extended longevity, whereas KL-KO animals die prematurely.

Methods: We prospectively followed 769 hemodialysis (HD) pts between 2009 and 2012 and studied 3 KL genomic polymorphisms, serum KL protein and survival. KL polymorphisms (KL-VS, rs577912 and rs526906) were genotyped through dHPLC analysis and DNA sequencing. Serum α-KL was measured by Elisa (IBL, Japan, normal values 231-1269 pg/mL).

Results: Patients were 69±14 yr old, male (58%), diabetic (35%), smokers (37%), diabetes management was ≥6.0 yr, BMI 25.2. Serum phosphorus was 4.7±0.9 mg/dL, calcium 9.0±0.7 mg/dL, 25OHD vit D 56 nmol/L. Median serum a-KL was 127.4 pg/mL (IQ 117-272), significantly lower in controls. Overall mortality was 13.3% per year. Cox analyses adjusted on dialysis vintage showed that KL- VS homoyzogotes had a 12% better survival compared to patients without the KL-VS allele (nonsignificant trend). By contrast, homozgyotes for rs577912 minor allele had a survival reduced by 20% (p=0.05) compared to homoyzogotes for rs577912 major allele. There was no trend of rs526906 polymorphism on survival. Accordingly, KL-VS homoyzogotes was associated with a higher serum α-KL concentration (245±116 pg/mL), whereas the detrimental rs577912 minor allele homoyzogote was associated with a lower serum a-KL (116 vs 130 pg/mL).

Conclusions: This is the first long term study showing that KL polymorphisms may impact on HD patients survival. Furthermore, KL expression differed depending on KL-VS and rs577912 genotypes, and genotypes with better survival had higher serum α-KL. Whether attempts to increase serum α-KL will improve survival should be tested in future trials.

Funding: Government Support - Non-U.S.
Resistance Exercise Program Improves Protein-Energy Wasting and Inflammation in Hemodialysis Patients Cristiane Moraes, Sandra Mara Silva de Azevedo Marinho, Milena Barca Stockler-Pinto, Wellington Seguinhas da Silva, Maria Thereza Baptista Wady, Antonio Nobrega, Denise Mafra,\textsuperscript{1} Graduate Program in Cardiovascular Sciences, Fluminense Federal Univ, Niterói, RJ, Brazil; \textsuperscript{2} Graduate Program in Medical Sciences, Fluminense Federal Univ, Niterói, RJ, Brazil; \textsuperscript{3} Carlos Chagas Filho Biophysics Institute, Federal Univ of Rio de Janeiro, Rio de Janeiro, RJ, Brazil; \textsuperscript{4} Immunology Institute, Oswaldo Cruz Foundation, Rio de Janeiro, RJ, Brazil.

Background: Inflammation and protein-energy wasting (PEW) are highly prevalent in hemodialysis (HD) patients. We assessed the effects of resistance exercise (RE) on these conditions.

Methods: Patients (n=38, 45±9.14 years, 61% men, BMI 23.8±4 kg/m²) underwent 6 months of RE (3x/week, intradialytic) with elastic bands and bilateral ankle loads. Adhesion molecules (ICAM-1, VCAM-1) were measured by EIA and, interleukin-6 (IL-6), C-reactive protein (CRP) and Tumor Necrosis Factor-Alpha (TNF-α) by ELISA. PEW was diagnosed if patient had simultaneously: BMI <23 kg/m², albumin <4 g/dL and, reduced mid-arm muscle circumference area.

Results: Adhesion molecules, CRP and, PEW reduced and, physical capacity improved significantly.

Conclusions: RE improved PEW and inflammation of HD patients.

Bone Fracture and Mortality Risk Prediction Using FRAX® in Male Japanese Hemodialysis Patients Toshio Hashi, Nobuhiko Joki, Yuri Tanaka, Hiroyuki Hase, Div of Nephrology, Toho Univ Ohashi Medical Center, Tokyo, Japan.

Background: Individuals with bone fracture are at substantially increased risk of mortality. Recently, The World Health Organization Fracture Risk Assessment Tool (FRAX®) has been developed to estimate a 10-year absolute risk of major osteoporotic fracture (HR 1.14, 95% CI 1.05 to 1.23) and mortality (HR 1.11, 95% CI 1.04 to 1.18), and cumulative survival was 90.6 and 75.9% (p=0.045). The subgroup analysis examined the effect of FRAX® in patients with relative ESA resistance (baseline ESA doses ≥ 13,000 U/week) compared to those who were normo-responsive to ESA.

Results:

- Serum phosphorus (P) by use of oral binders.
- Oral iron in the form of ferric citrate (FC) can be used as an iron preparation in hemodialysis patients.
- The administration of oral iron reduces the need for intravenous iron infusions.
- The use of oral iron in hemodialysis patients has been associated with improved outcomes, including reduced rates of hospitalization and improved quality of life.

Conclusions: The use of oral iron in hemodialysis patients is a safe and effective alternative to intravenous iron infusions, with potential benefits in terms of reduced hospitalization rates and improved quality of life.

Funding: Government Support - Non-U.S.
Conclusions: Thus oral FC controls serum P concentrations and is associated with evidence of increased iron stores. However, FC is not associated with the appearance of markers of inflammation or malnutrition. These data suggest FC will not predispose to MICS in HD patients.

Funding: Pharmaceutical Company Support - Keryx

SA-OR084

Intravenous Iron for Functional Iron Deficiency Anemia in Hemodialysis Patients: A Meta-Analysis

Paweesa Susantitaphong,1 Fahad S. Alqahtani,1 Bertrand L. Jaber,1 Medicine, St. Elizabeth’s Medical Center, Boston, MA; 2 Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: Studies on benefits of intravenous iron therapy among hemodialysis patients with functional iron deficiency anemia have shown conflicting results. We conducted a meta-analysis to assess the efficacy and safety of intravenous iron in hemodialysis patients with functional iron deficiency anemia.

Methods: We searched MEDLINE (through December 2012), Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for single-arm studies and randomized controlled trials (RCTs) that examined the effect of intravenous iron for functional iron deficiency anemia in hemodialysis patients on anemia parameters and markers of oxidative stress and inflammation. Studies of absolute iron deficiency were excluded. Random-effect model meta-analyses were used to compute changes in outcomes of interest.

Results: We identified 41 studies (3,202 patients), representing 27 single-arm studies, and 2 crossover and 12 parallel-arm RCTs. The results of the single arm studies are shown in the Table.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>No. study arms</th>
<th>No. patients</th>
<th>Mean change (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>2</td>
<td>2,042</td>
<td>2 (0.1, 3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>7</td>
<td>679</td>
<td>1,380 (89, 2,460)</td>
<td>0.001</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>10</td>
<td>652</td>
<td>-0.01 (-0.02, 0.001)</td>
<td>0.06</td>
</tr>
<tr>
<td>Erythropoietin dose, units/week</td>
<td>29</td>
<td>2,404</td>
<td>-1506 (-2,360, -653)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>51</td>
<td>4,798</td>
<td>138 (89, 186)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SA-OR085

Uremic Toxicity Induces Erythropoiesis and Atypical Monocyte Transformation: Erythropagocytosis as a Novel Pathway to Renal Anemia

Natalia Borges Bonan,1 Thiago Maass Steiner,1 Peter Kotanko,2 Viktoriya Kuntsevich,2 Roberto Pecoot-Filho,1 Andrea Novais Moreno-Amaral.1 1PUCPR, Curitiba, Brazil; 2RRI, New York.

Background: Anemia is common in chronic kidney disease (CKD) and hemodialysis (HD). Uremia alters red blood cell (RBC) membrane resulting in increased phosphatidylserine (PS) exposure and increased RBC clearance (erythropoiesis). CD14+/CD16+ monocytes represent an atypical inflammatory phenotype that mimics a macrophage, potentially capable of erythropagocytosis. Here we investigate the effects of uremic serum and p-Cesol (pC) on erythropagocytosis, monocytes transformation and erythropagocytosis.

Methods: Cells from CKD and HD patients and healthy controls (HC) (3 subjects each) were pretreated with RPMI, pC (10 and 50 μg/ml) or uremic serum. Cells were stained with annexin V to detect PS expression, and anti-CD14+CD16 to detect monocyte transformation. Erythropagocytosis was evaluated using control monocytes and RBC stained with anti-CD14 and anti-Glycoporphin-A, previously co-incubated with control cells for 2 hours: control monocyes against pretreated RBC or control RBC against pretreated monocyes.

Results: The fraction of annexinV+ RBC was increased in CKD (6%) and HD (6%) when compared to HC (1.9%). Incubation of RBC with uremic serum or pC, 50 μg/ml, resulted in 5.9% and 8.5% annexin V+ cells. The fraction of CD14+CD16+ monocyes was greatly increased in CKD (40%) and HD (19%), when compared to controls (3.4%). We observed an increase in CD14+CD16+ cells following addition of pC at concentrations of 10 μg/ml (8%) and 50 μg/ml (18%). Erythropagocytosis was increased when RBC were pretreated with pC, 50 μg/ml, and uremic serum (62%), and co-incubated with monocytes. HC monocytes pretreated with 50 μg/ml uremic serum, and co-incubated with RBC showed increased erythropagocytosis (73% and 35%, respectively).

Conclusions: This is the first description that uremic serum and pC can (a) increase RBC PS expression (and thus erythropagocytosis); (b) transform monocyte phenotypes; and (c) increase erythropagocytosis. Taken together, our observations indicate a novel pathway in the pathogenesis of CKD anemia.

SA-OR086

Hypoxia Inducing Factor Prolyl Hydroxylase Inhibitor FG-4592 Corrects Anemia in Hemodialysis Patients: Results from an International Study

Lim Paik Seong,1 Len A. Usuyuk,2 Michael Eter,3 Peter Kotanko,4 Nephrocare and Tungs Taichung Metropolitan Hospital, Taiwan; 5 Fresenius Medical Care North America, Waltham, MA; 6 Fresenius Medical Care Asia Pacific, Hong Kong, Hong Kong; 7 Renal Research Institute, New York, NY.

Background: Recent basic research indicates that hepatitis C core+1/ARFP, a novel protein produced by a second functional open reading frame within the core gene, decreases hepcidin expression in hepatoma cells (Kotta-Loizou, 2013). As hepcidin is a key regulator of iron availability, we hypothesized that hepatitis C positive patients will have lower iron levels compared to patients without hepatitis C.

Methods: We analyzed data from 14,589 Taiwanese and 6,238 US patients. In the cohort from Taiwan 16.8% of patients were hepatitis C positive, in the US cohort 9.3%. Hepatitis C positive patients in both populations showed higher hemoglobin levels (Taiwan: 10.5 vs. 10.4 g/dL; US: 10.9 vs. 10.8 g/dL) and lower EPO doses (Taiwan: 3637 vs. 4532 U/HD; US: 4979 vs. 5199 U/HD). Compared to hepatitis C positive patients, EPO resistance was increased in hepatitis C negative patients by 5% in the US and by 20% in Taiwan. In the US cohort the average iron dose per HD was lower in hepatitis C positive patients (73.9 vs. 77.0 mg/HD).

Conclusions: In two large diverse dialysis populations a positive hepatitis C serostatus is associated with improved anemia control and EPO responsiveness. This observation is possibly related to the recently described interaction between hepatitis C virus and hepcidin expression.
Methods: A new ES cell line that is sensitized to FSGS, and express podocyte specific rTA. Laser assisted micro-injection that facilitates generation of 100% chimeric mice. Induction of knock down of candidate genes in podocytes by doxycycline.

Results: We developed a FSGS disease candidate gene list based on the statistical analysis of the sequences of 2500 podocyte genes that we sequenced in over 200 FSGS patients of European ethnicity. To efficiently validate these genes, we developed a mouse ES cell strategy to test individual genes. We first established a mouse ES cell line that is sensitized to the development of FSGS based on our previous finding that haplotypedeficiency in both Cldap and Synpo, leads to FSGS over 6-12 months. We designed a Mir30 based shRNA expression cassette that allows tetracycline inducible expression of the shRNA and facilitates efficient homologous recombinantion into the Hprt1 locus. The recombinant ES cells were then injected using a method that generates mice with near 100% chimerism. Chimeric mice were directly used for screening by doxycycline-induced shRNA expression. The method was validated by showing that a CD2AP shRNA can induce nephrotic syndrome. Using this method, we will test each of our candidate genes.

Conclusions: We established a mouse model to induce RNAi in podocyte in vivo, and validated that this method is applicable for screening candidate genes that were identified by the large-scale genomic analysis. Now we are screening for the genes that induces proteinuria when they are knocked down in the chimeric mice.

SA-OR098
Lack of Murine Double Minute (MDM)-2 in Podocytes Causes Dysregulation of Autophagy and Focal Segmental Glomerulosclerosis

Dana Tomaszewska, Hauke A. Bruns, Helen Liapis, Hans J. Anders.

Background: Podocytes are terminal differentiated epithelial cells of the glomerular filtration barrier that can hardly be replaced upon loss. Like neurons, they seem to survive many decades and manage to stand the hemodynamic, toxic, and immunologic insults that occur during lifetime. The E3-ubiquitin ligase murine double minute (MDM)-2 is a non-essential factor for the developmental process of podocytes. MDM2 has been speculated to play a role in glomerular development, including podocyte differentiation.

Methods: We generated and characterized podocyte-specific MDM2-knockout mice (Podocin-Cre/MDM2floX) in comparison with littermates with floX allele.

Results: Comparison of podo-MDM2-/- mice with their heterozygous +/- littermates revealed lack of MDM2 in podocytes in wildtype mice. Neprin/Wt-T1+ podocytes were identical in 3 weeks old mice of both groups. The podocyte/glomerulus ratio increased with aging in non-stressed podocytes, however, is unknown today. We hypothesized, that MDM2 would be required to prevent p53 overactivation, a state that may cause premature podocyte loss.

Conclusions: In contrast to the pathogenic role of MDM2 in podocyte injury, podocytes need MDM2 during homeostasis to avoid dysregulated autophagy and podocyte loss.

SA-OR099
Direction of Transdifferentiation between Podocytes and Parietal Epithelial Cells, and Its Role for Focal Segmental Glomerulosclerosis

Kazuo Sakamoto, Toshiharu Ueno, Namiko Kobayashi, Satoshi Hara, Taiji Matsusaka, Michio Nagata, Pathology, Univ of Tsukuba, Tsukuba, Ibaraki, Japan; Nephrology, Izuza Hospital, Izuza, Hukuoka, Japan; Medicine, Tokai Univ, Isehara, Kanagawa, Japan.

Background: Although transdifferentiation (TD) between podocytes and parietal epithelial cells (PEC) has been suggested in focal segmental glomerulosclerosis (FSGS), its role for FSGS is still unknown. Using genetic tagging system combined with cell-markers, we are able to determine the direction of TD between two cells and its frequency/localization.

Methods: Mouse model of FSGS (LMB2-treated NEP25 mouse) carrying genetic tagging on podocyte (FSGS mice; n = 9) and NEP25 without LMB2 (controls; n = 7) were analyzed. TD from podocyte to PEC was determined when cells expressed LacZ, a podocyte lineage-marker, and Pax8, a PEC marker, by double staining. TD from PEC to podocyte was estimated by comparison of frequency between Nestin, a podocyte marker, and Pax8 double positive (DP) cells, and that of LacZ-Pax8-PD cells. When frequency of each-DP cells was different, we considered TD to have occurred. When Nestin/Pax8 or Pax8 cells are more, some fraction of cells is supposed to be PEC to podocyte. We counted the number of DP cells per 100 glomeruli to examine the frequency. From localization of DP cells, we speculated role of epithelial TD in FSGS. Statistical analysis was done by Student’s T test.

Results: Totally 795 glomeruli in FSGS and 546 glomeruli in control were analyzed. 1. The frequency of DP cells for Nestin/Pax8 was significantly increased in FSGS mice (1.6 ± 0.4% vs. 5.8 ± 0.5%, control vs. FSGS, P < 0.01) and those of LacZ-Pax8 were also significantly higher in FSGS mice (1.5 ± 0.6% vs. 4.3 ± 0.6%, control vs. FSGS, P < 0.01).

Conclusions: Epithelial transdifferentiation in FSGS was much more likely from podocyte to PEC than PEC to podocyte in FSGS and its role is minimal in FSGS lesion.

SA-OR091
Paricalcitol Reduces Proteinuria and Improves Renal Function in Podocin Deficiency and Nephrotic Syndrome


Background: Mutations in the podocin gene, NPHS2, have been shown in familial and sporadic forms of steroid-resistant nephrotic syndrome with focal segmental glomerulosclerosis (FSGS). Studies indicate that the vitamin D analog paricalcitol ameliorates proteinuria and prevents kidney injury in acquired podocyte injury. So far the renoprotective effect of vitamin D in genetic nephrotic syndromes has not been addressed. We examined the effect of paricalcitol in a genetic FSGS model caused by inactivation of podocin in the mouse kidney using the Cre-fox technology.

Methods: Mature podocin knockout mice (Nphs2fl/fl; Cre+) and littermate controls (Nphs2fl/fl; Cre-) were induced by injection with tamoxifen. Subsequently, the knockout and control mice were receiving either paricalcitol (0.15 μg/kg BW) or vehicle using osmotic minipumps for 5 weeks. Plasma samples, 24-hour urine samples, and kidney tissue were collected.

Results: Paricalcitol attenuated weight-loss of the podocin knockout mice and reduced the uncorrected/creatinine ratio by 43 +/- 3% when compared to vehicle treated knockout mice. At 5 weeks creatinine clearance in vehicle treated podocin knockout mice was reduced to 29 +/- 8 μl/min or 13% of wildtype (211 +/- 22 μl/min, p<0.001). Paricalcitol treated knockouts sustained a creatinine clearance of 97 +/- 53 μl/min (p=0.02 compared to vehicle treated knockout mice), and had a reduced renal expression of the injury marker NGAL and the pro-inflammatory cytokine IL-6. No renal effects of paricalcitol treatment were observed in wildtype mice.

Conclusions: Paricalcitol protects renal function and reduces proteinuria in a mouse model of genetic nephrotic syndromes involving mutations of the podocin gene. This may be further explored in human disease.

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

SA-OR092
Induction of CCAAT/Enhancer-Binding Protein Delta (CEBPD) Links Inflammation and Hypoxia to Injury by Regulating Hypoxia-Inducible Factor 1 (HIF-1)

Junna Yamaguchi, Tetsuhiro Tanaka, Nobuki Eto, Masaomi Nangaku. Div of Nephropathy and Endocrinology, The Univ of Tokyo, Tokyo, Japan.

Background: Tubulointerstitial hypoxia is a critical determinant in the pathogenesis of ischemic kidney diseases. HIF-1 is a master regulator of defense against hypoxia, and we designed this study to identify novel HIF-1 regulators in kidney.

Methods: An shRNA library was created based on our microarray analysis of chronic kidney hypoxia model. The impact of candidate genes on HIF-1 was evaluated by predicting hypoxia-inducible reporter assays in vitro, leading to identification of a novel upregulator of HIF-1. Its canonical regulation of HIF-1 and the underlying mechanisms were investigated by real-time PCR, immunoblotting, HIF-1α promoter assay and chromatin immunoprepcipitation (ChIP) in human proximal tubular cells (HK-2).

Results: An shRNA library experiment consisting of 150 genes identified CEBPD, a transcription factor, as a novel HIF-1 regulator. CEBPD was induced in kidneys subjected to systemic hypoxia, as well as in models of various acute and chronic ischemic kidney injuries (ischemia reperfusion injury, cisplatin nephrotoxicity, renal artery stenosis and focal segmental glomerulosclerosis). CEBPD shRNA knockdown and overexpression mediated down- and upregulation of HIF-1α as well as its target genes, respectively. Mechanistically, CEBPD directly promoted the transcription of HIF-1α by binding to its promoter. Furthermore, we characterized the inflammatory nature of CEBPD and linked inflammation and the HIF response. CEBPD was rapidly inducible by inflammatory cytokines, such as interleukin-1β (IL-1β), in an NFκB-dependent manner, and was indispensable for the non-hypoxic induction of HIF-1α.
Cebpr as a novel HIF-1 regulator in kidney. Cebpr was up-regulated in tubular epithelial cells via NF-kB-dependent pathway and regulated HIF-1 expression and its transcriptional activity. Given the overall positive roles of HIF-1, modulation of CEBPb activity may offer a novel therapeutic strategy in kidney diseases characterized by co-existent hypoxia and inflammation.

Funding: Government Support - Non-U.S.

SA-OR093
mTORC1 and -2 Induced Signalling Pathways Regulate Renal Proximal Tubular Endocytosis Franziska Theil1, Patricia Matthey1, Brigitte Scolari, Florian Grahammer2, Tobias B. Huber2.

Background: Receptor-mediated endocytosis is a pivotal function of the renal proximal tubule (PT) to reabsorb proteins from the ultra filtrate. PT dysfunction occurring e.g. in nephropathic diseases results in an impairment of this process. The regulation of endocytic and signaling pathways involved remain unknown. The aim of the study was to identify possible kinase-induced signaling pathways involved in the regulation of endocytosis.

Methods: Therefore OK cells were incubated with various kinase inhibitors and endocytosis assays using rhodamine-coupled albumin were performed. Transgenic mutants of mTORC1 and -2 were used to elucidate their role in endocytosis.

Results: Inhibitors for mTORC1, mTORC2, PI3-kinase and PKC significantly inhibited receptor-mediated endocytosis, whereas Inhibitors for MAPK, JNK and ERK did not alter albumin uptake. To further elucidate the role of mTORC1 and -2, Raptor43 and Rictor44 PAXLTet2TetOre as well as double mutants were analyzed. Low molecular weight proteinuria was only observed in the double knockout. Injection of horse reddish peroxidase demonstrated a significantly reduced uptake in PT of transgenic mice compared to the respective controls. Electron microscopic analysis revealed a diminished content of endocytic vesicles which was mostly pronounced in the Raptor43/Rictor44 PAXLTet2TetOre. Silencing of S6-kinase 1 and rictor by adenoviral transduction strongly reduced early endosome formation, the actin cytoskeleton remained unaltered. Western blot analysis demonstrated a knockdown degree of approx. 65 ± 11 % and reduced clathrin, EEA1 and Rab11 expression for clathrin vesicles, early endosomes and recycling endosomes, respectively. However, PI3-kinase and PKC were unchanged between groups and may not be involved as a downstream target of mTORC1 and -2 to affect endocytosis.

Conclusions: In conclusion, mTORC1 and -2 are important regulators to alter PT endocytic functions.

Funding: Other NIH Support - SNF

SA-OR094
Anti-miR21 Protects Collagen 4A3 Deficient Mice from Progression of Alport Disease by Decreasing Oxidative Stress Ivan G. Gomez1, Deidre Mackenna1, Allie M. Roach2, Bruce Gordon Johnson3, Tai-Ha Xia1, Vivek Kaimal1, Dorin-Bogdan Borza4, Jie Zhang5, Shiguang Liu6, B. Nelson Chau7, Jeremy Stuart Duffield1.

Regulus Therapeutics, Medicine, Univ of Washington, Seattle, WA; Vanderbilt Univ, Vanderbilt University Center.

Background: Alport syndrome in humans is an inherited form of kidney disease characterized by the coding the collagen membrane collagen IV. The disorder is characterized by progressive glomerulosclerosis, leading to glomerulosclerosis, tubulo-interstitial disease and organ failure. Col4a3+/- mice also spontaneously develop severe kidney disease highly similar to human disease. Recent studies have shown that miR-21 promotes interstitial kidney disease with fibrosis by silencing metabolic pathways, particularly fatty acid metabolism, and by promoting ROS formation. We hypothesized that treating Col4a3+/- mice with silencing anti-miR21 oligonucleotides would prevent progression of disease.

Methods: Col4a3+/- mice were given anti-miR21 (25mg/kg qd) or control from wk3 to wk9. Urine, plasma and kidneys were harvested at the end of wk9. All samples were analyzed to determine changes in kidney function and fibrosis.

Results: Anti-miR21 treatment attenuated the loss of kidney function and development of albuminuria. Glomerulosclerosis and interstitial fibrosis were markedly attenuated, proximal tubules were preserved, and crescent formation reduced. Anti-miR21 reduced infiltrating macrophages, myofibroblast appearance, and tissue and urinary ROS production. Global transcriptional analysis confirms our previous observations implicating a role for PPARα in the mediation of anti-miR-21 in models of chronic kidney disease; additional analyses are ongoing and will be discussed.

Conclusions: Anti-miR21 prevents progressive loss of kidney function in the Col4a3+/- mouse, attenuates both glomerular and tubulo-interstitial disease by reducing oxidative stress as one of the potential mechanisms. Anti-miR21 is a potential new therapy for Alport Syndrome.

SA-OR095
APOL1 is an Innate Immunity Effector That Induces Stress Autophagy by Interacting with the SNARE Protein, VAMP8 John F. O’Toole1. Sethu M. Madhavan1, David B. Thomas2, L. Barisoni1, Leslie A. Bruggeman1, John R. Sedor1. 1Case Western Reserve Univ; 2Univ of Miami.

Background: Apolipoprotein L1 (APOL1) prevents African Sleeping Sickness, a trypanosomadal disease. However, some species express a serum resistance associated protein (SRA) that binds and blocks APOL1 function. Genetic variants in APOL1 (variant APOL1s) that occur in the SRA-binding domain of APOL1 circumvent parasitic resistance, but associate with non-diabetic kidney diseases in African Americans. The mechanisms by which variant APOL1s promote nephropathy are unknown. We hypothesized that the cognate receptor for an autophagosome SNARE protein, was the top hit, its interaction with wild type APOL1 was confirmed by pull-down and IP. APOL1 risk variants attenuated this interaction and deletion of the SRA-binding domain abolished it. APOL1 and VAMP8 colocalized in podocytes of normal kidney. Expression of wild-type APOL1 in cell lines stimulated autophagy, which was less when variant APOL1s were expressed. Expression of wild-type or variant APOL1s in VAMP8 knockdown cells also increased the appearance of LC3II on immunoblotting, but the small change with the addition of bafilomycin A with variant APOL1s suggests a block in autophagy maturation.

Conclusions: Wild-type APOL1 stimulates autophagy and interacts with VAMP8, a structural orthology of the trypanosomal SRA protein. Variant APOL1s attenuate the APOL1-stimulated autophagy, as well as, the APOL1 interaction with VAMP8. The interaction of VAMP8 with the SRA-domain of APOL1 may promote autophagic maturation as a defense against environmental stress.

Funding: NIDDK Support, Clinical Revenue Support

SA-OR096
Variants in Genes Encoding Complement Regulation Proteins CFH, CFHR3 and CFHR1 Affect the Complement Activation and Susceptibility of IgA Nephropathy Li Zhu1,2, Yangli Zhao1,2, Fengwei Wang1,2, Jicheng Lv1,2, Damin Xu1,2,3, Sufang Shi,1,2 Lijun Liu,1,2,3 Mengyu Zhao,1,2,3 Hong Zhang,1,2 Renal Div, Dept of Medicine, Peking Univ First Hospital; 2Peking Univ Institute of Nephrology; 3Key Laboratory of Renal Disease, Ministry of Health of China.

Background: Complement activation was common in patients with IgAN and further associated with disease severity. Our recent GWAS study identified 1q23 as an IgAN associated locus, containing complement regulatory protein genes CFH and the related CFHR3, CFHR1, CFHR4, CFHR2, CFHR5, with rs6677604 in CFH as the top signal SNP. Therefore OK cells were incubated with various kinase inhibitors and signaling pathways involved remain unknown. The aim of the study was to identify possible kinase-induced signaling pathways involved in the regulation of endocytosis.

Methods: Therefore OK cells were incubated with various kinase inhibitors and endocytosis assays using rhodamine-coupled albumin were performed. Transgenic mutants of mTORC1 and -2 were used to elucidate their role in endocytosis.

Results: Inhibitors for mTORC1, mTORC2, PI3-kinase and PKC significantly inhibited receptor-mediated endocytosis, whereas Inhibitors for MAPK, JNK and ERK did not alter albumin uptake. To further elucidate the role of mTORC1 and -2, Raptor43 and Rictor44 PAXLTet2TetOre as well as double mutants were analyzed. Low molecular weight proteinuria was only observed in the double knockout. Injection of horse reddish peroxidase demonstrated a significantly reduced uptake in PT of transgenic mice compared to the respective controls. Electron microscopic analysis revealed a diminished content of endocytic vesicles which was mostly pronounced in the Raptor43/Rictor44 PAXLTet2TetOre. Silencing of S6-kinase 1 and rictor by adenoviral transduction strongly reduced early endosome formation, the actin cytoskeleton remained unaltered. Western blot analysis demonstrated a knockdown degree of approx. 65 ± 11 % and reduced clathrin, EEA1 and Rab11 expression for clathrin vesicles, early endosomes and recycling endosomes, respectively. However, PI3-kinase and PKC were unchanged between groups and may not be involved as a downstream target of mTORC1 and -2 to affect endocytosis.

Conclusions: In conclusion, mTORC1 and -2 are important regulators to alter PT endocytic functions.

Funding: Other NIH Support - SNF

SA-OR097
Mesangial Cell Hypersensitivity to Galactose Deﬁcient IgA, a Key to the Development of IgA Nephropathy Kerstin Eberfors1, Peidi Liu1, Johannes Elvin2, Borje Haraldsson2, Jenny C. Nyström3. 1Physiology, Neuroscience and Physiology, Gothenburg, Sweden; 2Molecular and Clinical Medicine, Medicine, Gothenburg, Sweden.

Background: The key feature of IgA nephropathy (IgAN) is deposition of galactose-deﬁcient IgA (gd-IgA) in the mesangial matrix. These depositions can also be found in asymptomatic individuals. There are also individuals who have gd-IgA in their circulation without developing the disease. We therefore hypothesize that patients developing IgAN have mesangial hypersensitivity to gd-IgA. Since IgAN is a disease that can reoccur in the transplant (around 40% of cases), we also hypothesize that around half of the population have mesangial hypersensitivity. However, since most of us do not have gd-IgA in our circulation, we have no risk of developing the disease.

Methods: We developed a unique method for culturing mesangial cells from patients with IgAN and from controls. IgA was purified from serum from patients with IgAN and healthy controls using the method of jacknin purification. Mesangial cells were stimulated with purified IgA and the expression of matrix genes and release of cytokines were investigated.

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

Underline represents presenting author.

93A


Experimental Pathology of Kidney Disease

Oral Abstract/Saturday

93A
Results: First, we investigated the gene expression of selected matrix genes in cells from patients and controls, and found that untreated cells from patients had a different expression profile compared to cells from controls. Stimulation of cells with purified IgA1 did not affect the expression of selected matrix genes further. Second, we investigated the release of cytokines after stimulation with IgA from patients and controls. We found that the cells responded with release of several cytokines and cells from patients with IgAN released more PDGF-bb than most controls. Stimulation with IgG-A gave a significantly stronger response than control IgA. In line with our hypothesis we also found control cells (cells from 3 out of 8 control subjects) responding the same way as cells from patients with IgAN.

Conclusions: Mesangial cells from patients with IgAN are hypersensitive to IgG-A, likely depending on their matrix composition (as shown previously by our group). We believe that this hypersensitivity is necessary for the IgA depositions to be pathogenic.

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

SA-OR098

Toll Like Receptor 9 on Regulatory T Cells Regulates Acute Kidney Injury
Medicine and Nephrology, Monash Univ and Monash Health, Melbourne, Victoria, Australia.

Background: Acute kidney injury (AKI) is a significant cause of renal death. Cisplatin nephrotoxicity is mediated by leukocytes and cytokines. Toll like receptors (TLRs) are innate immune cells which actively control inflammation.

Methods: We treated C57BL/6 wild type (WT) and TLR9−/− mice with cisplatin and assessed renal inflammation and injury. CD25 negative (−), effectors, and CD4+CD25+ splenocytes were isolated by magnetic bead separation. For reconstitution experiments we used CD4−CD25−cells from WT or TLR9−/− mice. We observed that the expression of TRAIL and its receptors were highly upregulated in renal tubular cells in renal IRI. To clarify the function of TRAIL in renal IRI, we investigated the release of cytokines after stimulation with IgA1 from patients and controls. We found that the cells responded with release of several cytokines and cells from patients with IgAN released more PDGF-bb than most controls. Stimulation with IgG-A gave a significantly stronger response than control IgA. In line with our hypothesis we also found control cells (cells from 3 out of 8 control subjects) responding the same way as cells from patients with IgAN.

Conclusions: Mesangial cells from patients with IgAN are hypersensitive to IgG-A, likely depending on their matrix composition (as shown previously by our group). We believe that this hypersensitivity is necessary for the IgA depositions to be pathogenic.

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

SA-OR099

Blockade of Death Ligand TRAIL Inhibits Renal Ischemia Reperfusion Injury
Takao Adachi,†,‡ Nortiyuki Sugiyama,‡ Takahiko Yokoyama,† 1Dept of Nephrology, Kyoto Prefectural Univ of Medicine, Kyoto, Japan; 2Dept of Anatomy and Cell Biology, Osaka Medical College, Takatsuki, Osaka, Japan; 3Anatomy and Developmental Biology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

Background: Acute kidney injury (AKI) remains a significant clinical problem because of high mortality and morbidity rates. However, the mechanisms of AKI has not been fully understood. Here we report a novel finding that TLR9 regulates T cell-mediated suppression of cisplatin induced acute kidney injury.

Methods: We treated C57BL/6 wild type (WT) and TLR9−/− mice with cisplatin and assessed renal inflammation and injury. CD25 negative (−), effectors, and CD4+CD25+ splenocytes were isolated by magnetic bead separation. For reconstitution experiments we used CD4−CD25−cells from WT or TLR9−/− mice.

Results: Renal inflammation and injury was enhanced in the absence of TRAIL. Blood urea nitrogen (BUN) was increased (WT 43.6±11.1 vs. TLR9−/−: 99.8±15.0 mmol/L, P<0.01), as was histological injury, interstitial neutrophil recruitment and kidney CXCL1 and CXCL2 expression. Kidney mRNA expression of Fox9 was decreased in TLR9−/− mice. Renal injury was similar in RAG1−/− mice reconstituted with WT and TLR9−/− effectors and treated with cisplatin. However after reconstitution with whole splenocytes functional (BUN; WT rec 32.3±8.1 vs. TLR9−/− rec 63.6±11.6 mmol/L, P<0.05) and histological injury (Injury Score [0-4]; WT rec 2.3±0.3 vs. TLR9−/− rec 3.0±0.2, P<0.05) was increased in RAG1−/− mice reconstituted with TLR9−/− splenocytes. Finally, we depleted endogenous Tregs in DEREG mice and reconstituted them with CD4+CD25+ cells from WT or TLR9−/− mice, followed by cisplatin. Compared to DEREG reconstituted mice with WT CD4+CD25+ cells renal functional injury was enhanced after reconstitution with TRAIL−/−CD4+CD25+ splenocytes (BUN; WT rec 50.3±13.7 vs. TLR9−/− rec 93.8±11.3 mmol/L, P<0.05) as was histological injury (Injury Score [0-4]; WT rec 2.6±0.3 vs. TLR9−/− rec 3.7±0.1, P<0.01).

Conclusions: Endogenous TRAIL Tregs mediate suppression of cisplatin induced acute kidney injury.

Funding: Government Support - Non-U.S.

SA-OR100

Mesenchymal Stem Cells Ameliorates Rhabdomyolysis-Induced Acute Kidney Injury through Activation of M2 Macrophage
Xiang-Mei Chen, Li Zhang, Yanqiu Geng. Dept of Nephrology, State Key Laboratory of Kidney Disease, State Key Laboratory of Disease, Beijing, China.

Background: Acute kidney injury (AKI) associated with myoglobinuria is the most serious complication of rhabdomyolysis. The mortality of critical AKI is still high since there is no effective therapy. Several studies have shown that administration of bone marrow-derived mesenchymal stem cells (MSCs) leads to the amelioration of AKI, but the mechanisms are still unknown. It was showed that MSCs could induce macrophage both in vivo and in vitro, which mediates MSCs protection in other experimental inflammation related organ injury. However, whether macrophage is also involved in the protective effect of MSCs in rhabdomyolysis-induced AKI needs to be clarified. In this study, we investigated the effects of MSCs on macrophage activation in rhabdomyolysis-induced AKI.

Methods: Rhabdomyolysis-induced AKI was induced in male C57BL/6 mice by intramuscular injection with 50% glycerol solution following deprivation of water for 24 hours. We administered MSCs (10^6 per mouse) via intravenous injection. We found that intravenously delivered MSCs to Rhabdomyolysis-induced AKI may significantly decrease serum creatinine, creatinine and blood urea nitrogen levels, improve tubular injury and lowered acute tubular necrosis score. Serum proinflammatory cytokines TNF-α and IL-6 were decreased, and inflammatory cytokines IL-10 increased.

Results: First, we investigated the gene expression of selected matrix genes in cells from patients and controls, and found that untreated cells from patients had a different expression profile compared to cells from controls. Stimulation of cells with purified IgA1 did not affect the expression of selected matrix genes further. Second, we investigated the release of cytokines after stimulation with IgA from patients and controls. We found that the cells responded with release of several cytokines and cells from patients with IgAN released more PDGF-bb than most controls. Stimulation with IgG-A gave a significantly stronger response than control IgA. In line with our hypothesis we also found control cells (cells from 3 out of 8 control subjects) responding the same way as cells from patients with IgAN.

Conclusions: Mesangial cells from patients with IgAN are hypersensitive to IgG-A, likely depending on their matrix composition (as shown previously by our group). We believe that this hypersensitivity is necessary for the IgA depositions to be pathogenic.

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

SA-OR101

Myeloid Cells Are Essential Mediators of Renal Endotoxin Preconditioning
Takashi Hato, Rakesh Kumar, Pierre C. Dagher. Medicine, Indiana Univ, Indianapolis, IN.

Background: We have previously demonstrated that systemically administered endotoxin directly interacts with renal proximal tubule and results in severe tubular oxidative stress. Here we examined whether it is possible to precondition the kidney in vivo and curtail endotoxin-induced tubular injury.

Methods: We compared preconditioned (0.25 mg/kg followed by 5 mg/kg lipopolysaccharide ip) and non-preconditioned animals (single-dose 5 mg/kg ip). A combination of tools was used including mutant and bone marrow chimeric mice, qPCR, flow cytometry, and intratwial 2-photon microscopy.

Results: We found that preconditioning completely abolished tubular oxidative stress upon subsequent high-dose endotoxin challenges. Renal KIM-1 and NGAL mRNA expression levels were also markedly decreased in the preconditioned kidneys. While preconditioning did not affect the total number of infiltrating renal macrophages, it favored an M2 phenotypic switch. In addition, preconditioning upregulated cytoprotective heme oxygenase-1 and sirtuin-1 in infiltrating macrophages. In chimeric mice lacking hematopoietic TR4, preconditioning failed to prevent tubular oxidative stress indicating that hematopoietic cells are essential for preconditioning. Along with TR4, CD14 is a co-receptor for endotoxin that is primarily expressed on myeloid cells and is essential for TRF pathway signaling. Chimeric mice lacking hematopoietic CD14 also showed complete failure to exhibit tolerance after preconditioning suggesting that TRF4 pathway is involved in endotoxin tolerance. Indeed, the administration of poly (I:C), which stimulates exclusively the TRF pathway, significantly restored endotoxin tolerance in CD14KO/WT chimeras.

Conclusions: These data support a model in which myeloid cells are essential mediators of the protective effects of endotoxin preconditioning on the kidney. Understanding the mechanisms underlying endotoxin preconditioning can have important clinical applications in the prevention of sepsis-induced acute kidney injury.

Funding: NIDDK Support, Private Foundation Support

SA-OR102

Forskolin, a Potent Cyclic-AMP Pathway Activator, Protect Mice From Acute Pyelonephritis Induced by Uropathogenic Escherichia coli
Ke Li†, Yang Wei†, Wuding Zhou‡. †Core Research Laboratory; The Second Affiliated Hospital, Xi’an Jiaotong Univ, Xi’an, China; ‡MRC Center for Transplantation, King’s College London, London, United Kingdom.

Background: Pyelonephritis caused by uropathogenic Escherichia coli (UPEC) are very common infections that can cause severe kidney damage. Uncultured or dysregulated innate immune responses are well recognized as a contributor to the pathogenesis. In this study, we investigated the effect of forskolin (a potent activator of cyclic-AMP pathway) on susceptibility/severity of acute pyelonephritis and innate immune responses to pathogen using an established experimental model of ascending UTI and primary cell cultures (i.e. renal tubular epithelial cells[RTEC], monocytes/macrophages).

Methods: Forskolin (10mg/kg) was given before the induction of infection by i.p. injection. Kidney infection was assessed in forskolin or control reagent treated mice at 6, 12, and 24 hours after infection. We suggest that TRAIL plays a critical role in renal IRI, and that TRAIL blockade ameliorates renal IRI. Our findings may have clinical relevance and provide new insights into the pathogenesis of renal IRI. This study also suggests that targeting TRAIL may be a novel significant therapeutic approach to overcome renal IRI.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.

94A
SA-OR103
DNA Methylation in Acute Kidney Injury and Kidney Repair
Zheng Dong,1,2 GRU; VC
Background: To evaluate the changes of DNA methylation in acute kidney injury (AKI) and kidney repair by a global methylation analysis.
Methods: To examine DNA methylation during AKI, B6 mice were treated with cisplatin (1 mg/30 g body weight) and subjected to 30 minutes of bilateral renal ischemia followed by 48 hours of reperfusion. To study DNA methylation during kidney repair, B6 mice were subjected to 25 minutes of bilateral renal ischemia followed by 1 week or 1 month of reperfusion. Genomic DNA was purified from frozen cortex tissue for reduced representation bisulfite sequencing (RRBS) to evaluate DNA methylation changes during and after AKI.
Results: Totally 1,411-1,960 million of CpG sites in the sham and injured kidney genome were analyzed. Comparing the methylation profiles of sham control and AKI kidneys, there were 2,065-3,519 differentially methylated regions (DMRs). The numbers of hypermethylated DMRs and hypomethylated DMRs were similar between sham and cisplatin 3days, sham and 30 minutes ischemia/48 hours reperfusion, sham and 25 minutes ischemia/1week reperfusion groups., suggesting that the overall DNA methylation does not change under these conditions. In contrast, the 25 minutes ischemia/1month reperfusion group showed more hypermethylated DMRs than hypomethylated DMRs, indicating an increase of DNA methylation. The distribution of DMRs was very similar in the 4 AKI groups comparing these conditions. In contrast, the 25 minutes ischemia/1month reperfusion group showed more hypermethylated DMRs than hypomethylated DMRs, indicating an increase of DNA methylation. The distribution of DMRs was very similar in the 4 AKI groups comparing these conditions.
Conclusions: Collectively, the results demonstrate DNA methylation in specific genes during and after AKI.

SA-OR104
Telomerase Deficiency Delays Renal Recovery after Ischemia Reperfusion Injury (IR)
Huifang Cheng,1 Xiaofeng Fan,1 William E. Lawson,1 Paisit Pauksukanon,2 Raymond C. Harris,1 Medicine, Vanderbilt Univ Medical Center, Nashville, TN; 2Pathobiology, Microbiology and Immunology, Vanderbilt Univ Medical Center, Nashville, TN.
Background: Increasing morbidity and higher mortality of acute kidney injury (AKI) are reported in the aged populations. Aging may be directly linked to telomere shortening; both (TelT) and telomerase RNA (TelRC) are essential to maintain telomere length. 
Methods: To investigate molecular and genetic mechanisms underlying susceptibility of AKI in seniors, we induced renal IR in mice from three genotypes: wild type (Wt); and fourth generation (G4) mice with TelT or TelRC deletion (TelT KO and TelRC KO respectively) by clamping both renal pedicles for 25 mins., using sham operated mice each with genotype as control.
Results: Our results suggested that IR induced similar renal injury from day 1 in each genotype, indicated by plasma BUN (Wt: 112.9±2.6; TelT KO: 119.6±3.0; TelRC KO: 122.6±6.0 mg/dl), albuminuria and acute tubular injury score (ATIS) according to the percentage of damaged tubules (eg, loss of brush border, tubular dilation, “blebbing”, cast formation and epithelial cell lysis), injury predominantly in proximal tubules. Increased apoptotic tubular epithelial cells detected by TUNEL Assay and renal Ki-1 were found in all mice by day 1 after IR. However, compared to Wt, both TelT KO and TelRC KO mice had significantly delayed recovery, based on evaluation of BUN, albuminuria, ATIS score and calculation of tubular epithelial cell apoptosis / proliferation (measured by Ki 67). Electron microscopy demonstrated that IR stimulated autophagosome formation in renal tubular epithelial cells from each group, but the peak in Wt was at 3 post IR, while it was markedly delayed in TelT / TelRC KO mice (peak at day 14). Immunoblotting and immunohistochemistry also demonstrated that the ratio of LC III-2/1 significantly increased at day 3 in Wt, but only at day 14 in TelT / TelRC KO. Similar patterns were noted with up-regulation of PI3K and ubiquitin.
Conclusions: Our study suggested that deletion of either TelT or TelRC in mice led to delayed kidney recovery from IR, possibly via impairment of autophagy.
Funding: NIDDK Support, Veterans Affairs Support

SA-OR105
Proximal Tubule Specific Deletion of p53 Reduces Ischemic Renal Injury in Mice
Yuan Ying, Babu J. Padanilam. Cellular & Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE.
Background: The key features of ischemic renal injury (IRI) are vascular damage, inflammation and proximal tubular cell apoptosis and necrosis, particularly in the outer medulla. The transcription factor p53 plays an important role in conducting cell cycle arrest, apoptosis, and even necrosis after various types of cell stress. Although a key role for p53 is implicated in IRI, there are conflicting reports on its benevolent and malevolent effects. We hypothesize that specific deletion of p53 in the proximal tubule protects kidneys from ischemic injury.
Methods: Mice with the p53 gene specifically deleted in the proximal tubule underwent either sham surgery or clamping of the renal pedicle for 30 min followed by reperfusion for different time periods. Renal function was assessed by creatinine and blood urea nitrogen (BUN) assays, histological damage by Periodic acid-Schiff staining, inflammation by neutrophil and macrophage (F4/80) staining, and fibrosis by Sirius red staining. Apoptosis was measured by TUNEL staining and Western blot analysis.
Results: Plasma levels of creatinine and BUN were significantly decreased 24 h after reperfusion in p53 knockout mice compared with wild type. Knockout mice had less renal histological damage, infiltration of leukocytes and apoptosis. Deletion of p53 attenuated the expression of its target gene, the cyclin-dependent kinase inhibitor p21. Consistently, renal fibrosis was significantly reduced in p53 knockout mice 16 d after reperfusion.
Conclusions: Specific knockout of p53 in the proximal tubule protects kidneys from functional and histological deterioration after IR by decreasing apoptosis, inflammation, and fibrosis.
Funding: NIDDK Support

SA-OR106
Primary Cilia-Dependent Nos1 in the Macula Densa (MD) Protects against Ischemia-Reperfusion-Induced Acute Kidney Injury (IR-AKI)
Yan Lu, Luis A. Juncos, Ying Ge, Yiling Fu, Jin Wei, Richard J. Roman, Ruisheng Liu. Univ of Mississippi Medical Center, MS.
Background: Our study suggested that deletion of either TerC or TerT in mice led to impaired kidney recovery from IR, possibly via impairment of autophagy. To investigate molecular and genetic mechanisms underlying susceptibility of AKI in seniors, we induced renal IR in mice from three genotypes: wild type (Wt); and fourth generation (G4) mice with TerC or TerT deletion (TerC KO and TerT KO respectively) by clamping both renal pedicles for 18 min at 37oC. NO measurement: fluorescent TGF was measured with microperfusion and microperfusion AKI marker: Serum Creatinine; Urine KIM-1; Histology (fluorescent H&E staining).
Results: Increasing flow across a MD cell-line increased NO (from 175 ± 22 to 276 ± 24) in the presence of intact primary cilia, but had no effect when the cilia were removed by siRNA (48.6 ± 17.5 vs. 62.7 ± 15.2). Similarly, increasing tubular flow in isolated IGA obtained from control mice, increased NO in the MD from 20±22 to 164±14. Subjecting C57BL/6 mice (WT) to 18 minutes of bilateral IR-AKI decreased the number and length of primary cilia and prevented flow-induced increases in NO in isolated JGA (72±16 vs. 86±15). We then tested whether specifically inhibiting primary cilia-dependent NO production in the MD would exacerbate I/R-AKI. For this we developed 2 strains of NKCC2- ciliopathy, knock-out (KO) mouse strains: KCNQ1-tert (PT-SSAT-Cko) mice. Administration of forskolin significantly reduced bacterial load in kidneys of sham control and AKI kidneys, there were 296-359 differentially methylated regions (DMRs). The numbers of hypermethylated DMRs were analyzed. Comparing the methylation profile ...

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

95A
important role in the mediation of renal I/R injury. In order to assess the basis of SSAT-mediated cell injury, we examined the effect of its expression on HEK cells. Our results indicated that SSAT expression leads to the loss of mitochondrial integrity, activation of caspase 3, cleavage of poly (ADP-ribose) polymerase 1 and apoptosis. In addition, SSAT expression leads to increased expression of high mobility group B 1 (HMGB1) protein.

Based on our in vivo and in vitro results we examined the effect of SSAT ablation on the onset of ischemic injury in cilia and skeletal abnormalities. Our results indicate that, compared to wt mice, PT-SSAT-Cko animals had: 1) lower HMGB1, toll-like receptor-2 and -4 levels; 2) increased serum 657 phospholipidic dynamin-related protein 1 levels, indicative of reduced mitochondrial fission; and 3) reduced cleaved caspase 3 levels.

Cilia expression of PTC plays a maladaptive role in kidney I/R injury; 2) reduced tissue damage in PT-SSAT-Cko mice is in part due to the modulation of innate immune and apoptotic responses; 3) Enzymes involved in polyamine catabolism can be targets for the treatment of renal I/R injury.

**Funding:** NIDDK Support, Veterans Affairs Support

---

**SA-OR108**

**The Cystic Kidney Disease Protein ANKS6 is a Novel Binding Partner and Substrate of the NEK8 Kinase**

Peter G. Czarniecki,1, 2 Danielle K. Manning,3 Mikhail Sergeev,4 Marja Garnaas,5 Wolfram Goessler,6 David Beier,7 Jagesh V. Shah,8 1 Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; 2 Renal Div, Brigham and Women’s Hospital, Boston, MA; 3 Genetics Div, Brigham and Women’s Hospital, Boston, MA; 4 Center for Developmental Biology and Regenerative Medicine, Children’s Research Institute, Seattle, WA; 5 Dept of Systems Biology, Harvard Medical School, Boston, MA.

**Background:** Cystic kidney disease is a consequence of mutations and knockouts of many ciliary genes. How these gene products exert their effect on kidney epithelium to promote cystogenesis remains unknown. Here we investigated the cystic kidney disease gene NEK8, which is mutated in the juvenile cystic kidney (jck) mouse and in a subset of patients with nephropathy (NPHP). ANKS6 is a new gene identified in zebrafish that is expressed in the kidney and cilia. Characterization of this gene will allow us to understand its function in the ciliary compartment and the kidney.

**Results:** Analysis of NEK8 co-immunoprecipitates by mass spectrometry revealed ANKS6 to be a novel binding partner of NEK8. The ANKS6-NEK8 interaction is mediated by the binding of the ankyrin domain of ANKS6 to the kinase domain of NEK8. The ankyrin domain of ANKS6 is also required for its localization to the Inversin compartment in ciliated cells. Morpholino-mediated inhibition of ANKS6 resulted in the formation of pronephric cysts and pericardial edema, a phenotype that is characteristic of many ciliopathy genes. However, unlike loss of function mutations in NEK8, ANKS6 and NPHP3, three other core constituents of the Inversin compartment, defects in LR asymmetry were not observed. We found ANKS6 to be readily phosphorylated by NEK8 and identified a number of phosphorylation sites in the C-terminal region including the SAM-domain. Deletion of the SAM domain results in enhanced oligomerization of ANKS6 and NEK8, and hyperaccumulation of these proteins in the Inversin compartment.

**Conclusions:** Our work reveals a novel interaction network between cysitic kidney disease proteins that may represent the basis of a new cystogenic pathway.

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

---

**SA-OR109**

**Defects in the IFT-B Component IFT172 Cause Neophosphorinopathy with Skeletal Abnormalities**


**Background:** Intraflagellar transport (IFT) is an evolutionarily conserved mechanism, essential for cilia assembly and maintenance. All components of IFT subcomplex A, have been implicated in human skeletal ciliopathies including Sotos, and Meckel- Saldino syndrome (MSS). Additionally, the IFT-B component IFT80 and the IFT-A motor cilia dysfunction is linked to polycystic kidney disease (PKD). We previously demonstrated that the exocyst, a conserved eight-protein trafficking complex, is required for ciliogenesis and cystogenesis, most likely due to its role in trafficking ciliary proteins. We also showed, in culture, that Cdc42, a small GTPase, co-localizes with the exocyst at primary cilia, and biochemically interacts with Sec10, a crucial exocyst component. Knockdown of Cdc42 and Tuba, a Cdc42 GEF, inhibited ciliogenesis and resulted in MAPK pathway activation, something observed in cells with dysfunctional cilia.

**Methods:** Given the importance of Cdc42 for cell function, to study how cdc42 affects ciliogenesis and cystogenesis in vivo, we used two different animal models and techniques: anti-sense morpholinos (MOs) to knockdown cdc42 in zebrafish, and the Cre-Lox system to knockout Cdc42 in a kidney-specific manner in mice. Zebrafish embryos were injected with cdc42 start-site MOs. Cdc42 renal tubule specific knockout mice were generated by breeding Cdc42 floxed and Ksp-cadherin Cre mice.

**Results:** We show cdc42 knockdown in zebrafish phenocopies many aspects of sec10 knockdown—including tail curvature, glomerular expansion, and MAPK activation. Other ciliary phenotypes include hydrocephalus and loss of photoreceptor cilia. We also observe a synergistic genetic interaction between zebrafish cdc42 and sec 10, suggesting that cdc42 and sec10 function in the same pathway. Cdc42 kidney-specific knockout mice died within weeks of birth of renal failure. Histology revealed cystogenesis in distal tubules and collecting ducts, decreased ciliogenesis in cyst cells, increased tubule cell proliferation, increased apoptosis, increased fibrosis, and MAPK activation, all features of PKD, especially nephrophthisis.

**Conclusions:** These data support a model in which Cdc42 localizes the exocyst to primary cilia, whereupon the exocyst targets and docks vesicles carrying ciliary proteins, and, if this does not occur, the result is abnormal ciliogenesis and PKD.

**Funding:** Other NIH Support - DK069909 and DK047757 to J.H., and DK093625 to L.H., Veterans Affairs Support

---

**SA-OR111**

**Deletion of S6 Phosphorylation Exacerbates Renal Cystogenesis in Conditional Tsc Knockout Mice**

Huijuan Wu,1 Jianchun Chen,2 Jian-Kang Chen.1 Experimental Medicine, Georgia Regents Univ, Augusta, GA; 2 Medicine, Vanderbilt Univ, Nashville, TN.

**Background:** Tuberous sclerosis (TSC) is caused by Tsc1 or Tsc2 gene mutations and characterized by proliferative lesions in many organs, with kidney involvement being the leading cause of death in adult TSC patients. Phosphorylation of the40S ribosomal protein S6 (S6P) is a major catabolism can be targets for the treatment of renal I/R injury; 2) reduced tissue damage in PT-SSAT-Cko mice is in part due to the modulation of innate immune and apoptotic responses; 3) Enzymes involved in polyamine catabolism can be targets for the treatment of renal I/R injury.

**Funding:** NIDDK Support, Veterans Affairs Support

---

**SA-OR110**

**Cdc42 Knockdown/Knockout Results in Ciliary Abnormalities and Cystic Kidneys**

Sooyoung Cheh,1 Maria F. Chacon-Heszele,1 Liwei Huang,1 Sarah McKenna,1 Francis P. Wilson,1 Xiaofeng Zuo,1 Joshua H. Lipschutz.1, 2 Dept of Medicine, Univ of Pennsylvania; 1 Philadelphia VAMC, Philadelphia, PA.

**Background:** Primary cilia are found on renal tubule cells, and cilia dysfunction is linked to polycystic kidney disease (PKD). We previously demonstrated that the exocyst, a conserved eight-protein trafficking complex, is required for ciliogenesis and cystogenesis, most likely due to its role in trafficking ciliary proteins. We also showed, in culture, that Cdc42, a small GTPase, co-localizes with the exocyst at primary cilia, and biochemically interacts with Sec10, a crucial exocyst component. Knockdown of Cdc42 and Tuba, a Cdc42 GEF, inhibited ciliogenesis and resulted in MAPK pathway activation, something observed in cells with dysfunctional cilia.

**Methods:** Given the importance of Cdc42 for cell function, to study how cdc42 affects ciliogenesis and cystogenesis in vivo, we used two different animal models and techniques: anti-sense morpholinos (MOs) to knockdown cdc42 in zebrafish, and the Cre-Lox system to knockout Cdc42 in a kidney-specific manner in mice. Zebrafish embryos were injected with cdc42 start-site MOs. Cdc42 renal tubule specific knockout mice were generated by breeding Cdc42 floxed and Ksp-cadherin Cre mice.

**Results:** We show cdc42 knockdown in zebrafish phenocopies many aspects of sec10 knockdown—including tail curvature, glomerular expansion, and MAPK activation. Other ciliary phenotypes include hydrocephalus and loss of photoreceptor cilia. We also observe a synergistic genetic interaction between zebrafish cdc42 and sec 10, suggesting that cdc42 and sec10 function in the same pathway. Cdc42 kidney-specific knockout mice died within weeks of birth of renal failure. Histology revealed cystogenesis in distal tubules and collecting ducts, decreased ciliogenesis in cyst cells, increased tubule cell proliferation, increased apoptosis, increased fibrosis, and MAPK activation, all features of PKD, especially nephrophthisis.

**Conclusions:** These data support a model in which Cdc42 localizes the exocyst to primary cilia, whereupon the exocyst targets and docks vesicles carrying ciliary proteins, and, if this does not occur, the result is abnormal ciliogenesis and PKD.

**Funding:** Other NIH Support - DK069909 and DK047757 to J.H., and DK093625 to L.H., Veterans Affairs Support

---

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

96A
SA-OR112
Loss of Cilia Suppresses Cyst Growth in Genetic Models of Autosomal Dominant Polycystic Kidney Disease

Ming Ma,1 Xin Tian,1 Mingfeng Li,1 Christopher Y. Chen,1 Yiqiang Cai,1 Peter Igarashi,2 Gregory J. Pazour,3 Stefan Somlo.1,4
1Dept of Internal Medicine, Yale Medical School, New Haven, CT; 2Dept of Medicine, Univ of Texas Southwestern Med School, Dallas, TX; 3Program in Molecular Medicine, UMass Medical School, Worcester, MA; 4Dept of Genetics, Yale Medical School, New Haven, CT; 5Dept of Neurobiology, Yale Medical School, New Haven, CT.

Background: Inactivation of a single cilia membrane component protein, polycystin, in ADPKD is complemented by renal malv of cilia by inactivation of intracellular transport-related proteins in ciliopathies both give rise to kidney cysts, yet the interrelationship of these two mechanisms of cyst formation is not understood.

Methods: We combined inactivation of Pkd1 and Pkd2 with loss of Kif3a and Jil20 in kidney and liver to investigate the role of cilia in ADPKD. We examined epithelial cell proliferation and activation of several known ADPKD associated pathways in polycystin-only and cilia/polycystin double mutants. We also defined genotype dependent changes in the transcriptome at the pre-cystic stage of inducible adult onset ADPKD models using RNASeq with loss of polycystin alone or of cilia/polycystin together.

Results: We found that loss of intact cilia suppresses cyst growth following inactivation of polycystins. The severity of cystic disease and the associated epithelial proliferation was improved in single Pkd1 or Pkd2 mutants compared to both wild type and Pkd1/Jil20 double mutants. In contrast, inactivation of ciliary proteins with loss of Kif3a or Jil20 failed to affect cyst formation.

Conclusions: The data establish the existence of a novel signaling pathway showing polycystin-dependent inhibition and cilia-dependent activation that is central to the pathogenesis of ADPKD. Alterations in the transcriptome of polycystin-only mutants compared to cilia/polycystin double mutants should identify transcriptional targets which will help in defining these pathways and in identifying therapeutic targets.

Funding: NIDDK Support

SA-OR113
Pkd1extra, Transgenic Mice Implicate P2E Gene Dosage as a Pathogenic Mechanism

Marie Trudel, Almina Kurbegovic. Molecular Genetics and Development, Institut de Recherches Cliniques de Montreal, Montreal, Canada.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by slow progression of multiple cysts in both kidneys that lead to renal insufficiency in mid-life or later. ADPKD is associated with mutations mainly in the PKD1 gene (encoding polycystin-1 or PCK1) and less frequently in the PKD2 gene (encoding polycystin-2 or PCK2).

Methods: To mimick naturally occurring human PKD1 mutations and gain insight into the Pck1 extracellular domain function, four transgenic mouse lines were established with exogenously the extracellular domain of the Pkd1 gene (Pkd1extra) under endogenous transcriptional regulation.

Results: Expression of the Pkd1extra transgene was 2- to 80-fold above endogenous levels. Strikingly, the Pck1extra protein was more abundant than expected based on proportion to the mouse endogenous lines. All four transgenic mouse lines consistently displayed progressive renal cystic phenotype. Consequently, these transgenic mice reproducibly distinguish between wild-type and Pkd1/Jil20 double mutants.

Conclusions: Our data provide evidence for cystic disease is influenced by Pck1 dosage and suggest that the Pck1 extracellular domain play a critical role in the pathologic mechanism in ADPKD.

Funding: NIDDK Support

SA-OR114
Scattered Single-Cell Deletion of Pkd1 in Mouse Kidneys Recapitulates Human Polycystic Kidney Disease and Refines the Model of Cystogenesis

Wouter N. Leonard,1 Malu Zandberg,1 Kimberley Veraar,1 Emile De Heer,1 Martijn H. Breuning,1 Dorien J.M. Peters.1
1Dept of Human Genetics, Pathology, Leiden Univ Medical Center, Netherlands.

Background: ADPKD patients carry a germline mutation in PKD1 or PKD2 which leads to the formation of thousands of kidney cysts. The relatively rapid progression of the disease is preceded by a lag-phase of several decades. Although the cause of this rapid progression is poorly understood, extensive research led to the presumption that somatic inactivation of the remaining allele initiates the formation of cysts, and the progression is further accelerated by renal injury. This hypothesis is based primarily on animal studies in which the gene is inactivated in large percentages of kidney cells. In this study we lowered this percentage to mimic human ADPKD more precisely.

Methods: To inactivate Pkd1 in fewer renal cells in adult tamoxifen-inducible kidney-specific Pkd1-deletion mice, we lowered the tamoxifen dose. Quantification and visualization of Pkd1*LS cells was done by qELISA and by crossbreeding to LacZ reporter mice. Renal injury was applied by nephrotoxic (DCV) injection, unilateral nephrectomy, or combinations. Western blot and IHC analysis was used to assess the expression of several PKD-related proteins.

Results: Interestingly, no pathological changes occurred for six months after scattered single-cell Pkd1 deletion in adult mice and additional renal injury did not trigger rapid PKD. However, in the next few months (i.e. 6-10 months following Pkd1-disruption) the mice developed rapidly progressing PKD that was remarkably similar to human ADPKD.

Conclusions: This shift was not caused by aging but was preceded by increased PSTAT3, Kii-67 and LCN2 expression in the vicinity of the initial cysts.

Funding: This work was supported by a grant from the Dutch Kidney Foundation.

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

97A
Conclusions: Our data suggest the intriguing possibility that changes in O₂ concentration alter the channel properties of the PC1-PC2 complex, leading to changes in ER calcium release that in turn affect mitochondrial function. This study also suggests that PDH may be a possible novel target for PKD pharmacotherapy.

Funding: NIDDK Support, Other U.S. Government Support

SA-OR117

Transcriptional Targets of STAT6 in Polycystic Kidney Disease

Erin E. Olsen, Nicholas Doerr, Thomas Weimbs. Molecular, Cellular and Developmental Biology, Univ of California, Santa Barbara, CA.

Background: The majority of ADPKD patients have mutations in the PKD1 gene, encoding the large, multi-pass transmembrane protein polycystin-1 (PC-1). Previously, we showed that a soluble fragment of PC-1, consisting of the c-terminal cytoplasmic tail, interacts with STAT6 and activates STAT6-dependent reporter transcription. Additionally, we reported increased phosphorylated STAT6 in several PKD mouse models, and showed that genetic removal or pharmacological inhibition of STAT6 decreases disease severity. To understand how STAT6 activation may contribute to renal cyst growth we identified several potential transcriptional targets of STAT6 signaling in PKD including IL24, periostin and galectin-3. IL24 is an IL10 family cytokine that functions in wound healing and inflammation in the skin and has been shown to be transcriptionally regulated by STAT6 in immune cells. Periostin, an extracellular matrix protein, and galectin-3, a β-galactoside binding lectin, both have previously been implicated in PKD.

Methods: Kidney cell lines treated with IL4 or IL13 or transfected with the PK-1 cytoplasmic tail were analyzed by RT-PCR. Microarray analysis was performed on cells overexpressing the PK-1 cytoplasmic tail. Total RNA or protein extracts from normal or cystic mouse kidneys were analyzed using RT-PCR or Western blot.

Results: We found that treatment of human and mouse kidney epithelial cells with IL4 or IL13, cytokines that signal through STAT6, increases IL24 gene expression. Overexpression of the PK-1 cytoplasmic tail also increases IL24 transcript levels. Importantly, we show that IL24 is upregulated in kidneys from several cystic mouse models. As predicted, we found increased levels of periostin and galectin-3 in cystic mouse kidneys compared to normal, and their expression levels are diminished in STAT6 KO cystic kidneys, suggesting that gene regulation is dependent on STAT6. Overexpression of the PK-1 cytoplasmic tail increased transcript levels of a related protein, galectin-8.

Conclusions: STAT6 has been shown to be an important signaling molecule in PKD. Here we identify several genes involved in the pathogenesis of PKD that can be transcriptionally regulated by STAT6.

SA-OR118

Evidence for Abnormal Glucose Homeostasis in Idiopathic Calcium Stone Formers

Kristin J. Bergsland, Elaine M. Worcester, Fredric L. Coe. Dept of Medicine, Nephrology Section, Univ of Chicago, Chicago, IL.

Background: Calcium (Ca) stone formers with idiopathic hypercalciuria (IHSF) have an exaggerated calciuric response to glucose administration. We and others have found that glucose homeostasis in both male and female IHSF is markedly different than in C. Higher glucose in all IHSF, and higher insulin in ICSF after eating, cannot be explained by differences in diet or body size, since subjects were non-diabetic, ate the same meals, and analyses were corrected for BMI. Alterations in insulin sensitivity or pancreatic function in IHSF may contribute to Ca stone disease, and possibly to differences in stone type, and will be the subject of future research.

Funding: NIDDK Support

SA-OR119

Distinguishing Characteristics of Idiopathic Calcium Oxalate Kidney Stone Formers with Low Amounts of Randall's Plaque

Xiangling Wang, Amy E. Krambeck, James Williams, Andrew D. Rule, Eric J. Bergstrahl, Loren Paula Herrera Hernandez, John C. Lieske. Mayo Clinic, Rochester, MN; Indiana Univ School of Medicine, Indianapolis, IN.

Background: Overgrowth of calcium oxalate on Randall’s plaque, composed of apatite that extends from the medullary interstitium to the papillary surface, has been hypothesized to be the main mechanism of stone formation among idiopathic CaOx stone formers (ICSF). However, it is less clear how stones form in ICSF that have little or no plaque.

Methods: In the current study a cohort of ICSF who underwent percutaneous nephroscopic papillary mapping and papillary tip biopsy during a stone removal procedure were divided into those with high (≥5%; mean 10.5%) versus low (<5%; mean 1.5%) amounts of Randall’s plaque coverage per papilium. Demographic and laboratory features were compared between these two groups.

Results: Low plaque ICSF were more likely to be female and obese and had a significantly lower 24-hr urine calcium excretion (Table). Their stones were more likely to have a positive bacterial culture and to have an atypical morphology by micro CT (lacked a CaP core consistent with origin upon plaque). Papillary biopsies of low plaque patients had less severe interstitial and basement membrane punctate crystallization (P<0.05).

Conclusions: These findings suggest that the pathogenesis of CaOx stone formation differs in patients with low amounts of Randall’s plaque. Those ICSF with low plaque lack hypercalciuria, more commonly have stones with atypical morphology, and appear to have distinct clinical features (more likely to be female, obese, and have infected stones). Thus, there may be different pathways to stone formation amongst ICSF with and without abundant plaque.

Funding: NIDDK Support

SA-OR120

Modulators of Urinary Stone Formation: Transcriptional Study in an Animal Model of Hyperoxaluria

Saeed R. Khan, Sanil Joshi, Wei Wang, Amnon B. Peck. Pathology, Univ of Florida, Gainesville, FL.

Background: Role of macromolecular modulators (MMs) in stone formation has been investigated in animal models, one MM at a time. We used an unbiased approach to identify genes transcriptionally regulated by STAT6 in the cortex and medulla of hyperoxaluric kidneys. It appears that NADPH oxidase inhibitor apocynin.

Methods: Male Sprague-Dawley rats were fed rat chow or chow supplemented with 5% w/w hydroxy-L-proline (HLP) with or without apocynin-supplemented water. After 28 days, rats were euthanized, kidneys explanted and dissected to separate cortex and medulla. Total RNA was isolated and microarray analysis was conducted on the renal cortical and medullary tissues using the Illumina bead array reader™. Immunohistochemistry Visualization of Integrated Discovery) enrichment analysis tool. Immunohistochemistry was used to confirm expressions of selected gene products.

Results: Administration of HLP led to crystal deposition in the kidneys. Deposits ranged from few scattered crystals to heavy deposit in the cortical tubules. Apocynin treatment resulted in near complete absence of crystals, despite showing similar levels of hyperoxaluria. Genes encoding for alpha-Iand alpha-2-microglobulin, fibronecin, CD 44, osteoconnection, fetuin, osteopontin, and matrix-gla protein, were up-regulated in both cortex and medulla. On the other hand, genes encoding for inter-alpha-inhibitor 1, 3 and 4, calgranulin B, prothrombin, and Tamm-Horsfall protein were down-regulated in both cortex and medulla. HLP-fed rats receiving apocynin had a significantly lower 24-hr urine calcium excretion (Table). Their stones were more likely to have a positive bacterial culture and to have an atypical morphology by micro CT (lacked a CaP core consistent with origin upon plaque). Papillary biopsies of low plaque patients had less severe interstitial and basement membrane punctate crystallization (P<0.05).

Conclusions: These findings suggest that the pathogenesis of CaOx stone formation differs in patients with low amounts of Randall’s plaque. Those ICSF with low plaque lack hypercalciuria, more commonly have stones with atypical morphology, and appear to have distinct clinical features (more likely to be female, obese, and have infected stones). Thus, there may be different pathways to stone formation amongst ICSF with and without abundant plaque.

Funding: NIDDK Support
High Prevalence of CKD among Genetic Stone Formers

Lada Beraa Lasic, Vidar O. Edvardsson, Runolfur Palsson, David S. Goldfarb, Eric J. Bergstralh, Ramila A. Mehta, John C. Lieske, Dawn S. Milliner, New York Harbor VAMC, New York, NY; Landspital Univ Hospital, Reykjavik, Iceland; Mayo Clinic, Rochester, MN.

Background: Kidney stone disease is a multisystem disease associated with reduced kidney function. Patients with primary hyperoxaluria (PH), cystinuria (Cys), APRT deficiency (APRTd), and Dent disease (DD) have lifelong recurrences of stones. Due to their rarity, understanding of the impact of these disorders on kidney function is limited. We performed a cross-sectional study of estimated glomerular filtration rate (eGFR) in patients with each of these disorders.

Methods: A total of 380 patients with PH, 223 with Cys, 46 with APRTd, and 108 with DD were enrolled in the observational registries of the Rare Kidney Stone Consortium. Serum creatinine at first presentation was used for calculation of first eGFR by the MDRD equation in adults and modified Schwartz equation in children. The prevalence of CKD at presentation and end stage renal disease (ESRD) ever was compared between diagnoses.

Results: Stage 3 CKD was common at presentation, in 21-35% of patients. Stage 4 CKD was also common at presentation in PH, APRTd and DD (14-19%), but less so in Cys (3%). ESRD was documented in 0% (Cys) to 42% (PH) of the patients.

Conclusions: Stage 3 and 4 CKD is common at presentation of patients with PH, Cys, APRTd, and DD. Development of ESRD at any time during registry follow up is common in all but Cys. Whether kidney damage is related to crystal nephropathy, stone burden or to other factors remains to be determined.

<table>
<thead>
<tr>
<th></th>
<th>APRT deficiency (n=46)</th>
<th>Cystinuria (n=223)</th>
<th>Dent disease (n=108)</th>
<th>Cys (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first eGFR (yr)</td>
<td>37.2 (18.9)</td>
<td>32.6 (19.4)</td>
<td>47.5 (22.1)</td>
<td>37.4 (18.1)</td>
</tr>
<tr>
<td>Age at last follow up (yr)</td>
<td>56.6 (18.1)</td>
<td>59.1 (20.4)</td>
<td>54.1 (22.9)</td>
<td>50.7 (17.1)</td>
</tr>
<tr>
<td>Stones at diagnosis</td>
<td>6.6 (3.2)</td>
<td>6.6 (3.4)</td>
<td>6.7 (3.5)</td>
<td>6.7 (3.5)</td>
</tr>
<tr>
<td>Stones at ESRD</td>
<td>8.0 (5.2)</td>
<td>8.2 (5.4)</td>
<td>9.0 (4.3)</td>
<td>7.3 (4.5)</td>
</tr>
</tbody>
</table>

Funding: NIDDK Support, Other NIH Support - National Center For Advancing Translational Sciences (NCATS)

Proximal Tubule Is a Site of Injury in Oxalate Nephropathy


Background: Loss of kidney function leading to kidney failure occurs in most patients with primary hyperoxaluria (PH). Oxalate (ox)-induced parenchymal kidney injury is felt responsible. Plasma oxalate (Pox) is freely filtered, concentrated in tubular fluid, and may also be secreted by the proximal tubule (PT), leading to high levels in the S3 fluid, which contribute to calcium oxalate (CaOx) crystal formation in the collecting duct.

Methods: 110/276 patients enrolled in the PH Registry of the Rare Kidney Stone Consortium had Pox prior to ESKD and were included for study. eGFR was estimated assuming an average 75% PT site-related differences.

Results: Age at PH diagnosis was 12.8 (3.3,16.7) yrs, mean (25%, 75% Sd), eGFR 88 (66,105) ml/min/BSA, Pox 6.7 (2.1, 8.2) umol/L, PT ox 47 (29,72) umol/L, and Uox 1.56 (0.94, 2.06) mmol/24 hrs/BSA.

Conclusions: Overall, CaOx stones are the most common, as is generally accepted. However, age and gender have marked influence on the type of stone formed. The change in composition amongst the elderly favoring UA has not previously been appreciated. These data also suggest a summer effect of increased stone risk, although this is restricted to CaOx and UA stones.

Funding: NIDDK Support

Urolithiasis and Fracture Risk over the Lifespan: A Population-Based Study Using the Health Improvement Network (THIN)

Lawrence A. Copelovitch,1,2 Kevin Haynes,1 Shamir Tuchman,3 Gregory Edward Tasian,1 Mary B. Leonard.1,2 Perelman School of Medicine at the Univ of Pennsylvania; 3Children’s Hospital of Philadelphia; 4Children’s National Medical Center.

Background: Studies have shown decreased bone mineral density in patients with urolithiasis, but the fracture (FX) burden is unclear. The objectives of this study were to determine if urolithiasis is associated with increased FX risk and to explore age, sex and site-related differences.

Methods: In a retrospective cohort study using THIN, a primary care electronic medical records database, we identified 60,629 subjects with urolithiasis and randomly selected 605,264 age, sex, and practice-matched subjects (10:1). Cox regression analysis was used to estimate the hazard ratio (HR) for first FX. Median age was 51 yrs, and 68% were male confirming their 2-fold greater urolithiasis burden. Over a median follow-up of 5 yrs (IQR 2-10), 4321 first FX events occurred in those with urolithiasis (113/10,000 person-yrs) vs. 36,367 FX events (98/10,000 person-yrs) in those without urolithiasis. Distribution of FX site was comparable between groups with forearm/wrist, hand, and lower leg/ankle being the most common sites in both.

Results: Over a median follow-up of 5 yrs (IQR 2-10), 4321 first FX events occurred in those with urolithiasis (113/10,000 person-yrs) vs. 36,367 FX events (98/10,000 person-yrs) in those without urolithiasis. Distribution of FX site was comparable between groups with forearm/wrist, hand, and lower leg/ankle being the most common sites in both.

Conclusions: Urolithiasis was associated with significantly increased FX risk in women after age 30 and in young, middle-aged and elderly men, with the greatest risk in the 3rd decade for females and late adolescence for males.

Funding: NIDDK Support, Other NIH Support - National Center For Advancing Translational Sciences (NCATS)
Conclusions: Urolithiasis was associated with increased FX risk, and the distribution of FX sites did not differ from that of the general population. While the HR was greatest in young adults, the significantly increased risk in the elderly has important public health implications.

Funding: NIDDK Support, Other NIH Support - This work was supported by the National Institutes of Health Clinical Translational Service Award: UL1-RR024134, Private Foundation Support

SA-OR125

Metabolic Acidosis as a Risk Factor for Mortality in Peritoneal Dialysis Patients

Methods: This prospective observational study included a total of 441 incident ESRD patients who started PD from Jan 2000 to Dec 2005. Using time-averaged serum bicarbonate levels (TA-Bic), we elucidated whether metabolic acidosis could predict all-cause mortality among patients with end-stage renal disease (ESRD) and its associated with increased mortality in hemodialysis (HD) patients. Given the continuous provision of dialysis treatment with PD, PD is more effective in correcting metabolic acidosis than HD, and thus the impact of metabolic acidosis on clinical outcomes may differ between the two dialysis modalities. However, there have been few studies on the relationship between serum bicarbonate levels and the risk of death in PD patients.

Methods: This prospective observational study included a total of 441 incident ESRD patients who started PD from Jan 2000 to Dec 2005. Using time-averaged serum bicarbonate levels (TA-Bic), we elucidated whether metabolic acidosis could predict all-cause mortality in these patients.

Results: Multivariable linear regression analysis revealed that serum bicarbonate concentrations were positively associated with hemoglobin levels ($\beta = 0.187$, $P = 0.001$) and residual renal function (RRF) ($\beta = 2.038$; $P = 0.042$), while they were negatively associated with serum albumin ($\beta = -0.235$; $P < 0.001$) and C-reactive protein (CRP) levels ($\beta = -2.804$; $P = 0.005$). During a median follow-up duration of 34.8 months, 149 deaths were recorded. After adjustment for age, diabetes, coronary artery disease, serum albumin, ferritin, CRP, RRF, normalized protein catabolic rate, and percentage of lean body mass, TA-Bic levels were associated with a significantly lower risk for mortality (HR per 1 mEq/L increase, 0.83; 95% CI, 0.76–0.90; $P < 0.001$). In addition, compared to patients with TA-Bic concentrations of 24–26 mEq/L, TA-Bic levels <22 and 22–24 mEq/L groups conferred 15.9- and 2.1-folds increased risk of death, respectively. Similar findings were observed for cardiovascular mortality.

Conclusions: Metabolic acidosis was an independent risk factor for mortality in incident PD patients. This relationship between low bicarbonate levels and adverse outcome might be partly related to enhanced inflammation associated with metabolic acidosis.

SA-OR126

The PD-Biosensor: A New, Quick and Easy Method to Assess the Functions of the Peritoneal Membrane

Background: During peritoneal dialysis (PD) glucose (G) is absorbed from dialysate (D) to blood (B) and the others solutes as urea, creatinine (Cr), etc. diffuse from B to D. During a dwell with a high osmolality PD solution (S) a marked reduction in the D sodium concentration (Na) may occur. To evaluate the functions of peritoneal membrane (PM) we use the peritoneal equilibration test (PET). The PET is complicated and requires a considerable expenditure of time and resources.

Methods: The PD-Biosensor (PD-B) is based on the ionic conductivity (Cd). Since the Cd of a S is a function of electrolytes concentration and of viscosity, due the G concentration, it is possible to evaluate changes in the Cd of the PD S during a dwell with a 3.86% G concentration, during which there is a dilution of the electrolytes and G absorption present in PD S. This difference in Cd are measured by the PD-B and can be used to evaluate the functions of PM. We evaluate the functions of PM during a 3.86%-modified-PET by the PD-B and the classical PET parameters in 69 PD pts (38 M, 31 F).

Results: The values of Cd, in the D at 240’ of dwell, was well correlated with transport of G (D/D, $r^2=0.62$), small solutes transport (D/PCr) ($r^2=0.72$) and Na ($r^2=0.63$). Two of the 67% of UFF had ultrafiltration failure (UFF). All the pts with UFF had a Cd in D at 240’ of the dwell, more then 12.5 mS/cm. The ROC curve for UFF of Cd measured by PD-B at 240’ had an area under curve (AUC) of 0.907 (chiSquare=10.20, $p<0.002$), the AUC of D/Pcr was 0.879 (chiSquare=10.87, $p<0.001$) and the AUC of D/W was 0.810 (chiSquare=8.50, $p<0.001$). The changes of Cd, measured by PD-B, during the dwell were greater in the 3.86%-modified-PET, are expression of changes in the peritoneal transport of G, small solutes (Cr) and Na: all these parameters can be measured together and with a single numeric parameter. The changes of Cd, measured by PD-B, are predictive of UFF.

Conclusions: The PD-B is a new, inexpensive and easy method to evaluate the functions of PM in real time without laboratory assay, calculation and interpretation of data. The PD-B can be used to evaluate the functions of PM more frequently, also at home, and may open new perspectives in PD.

SA-OR127

Spironolactone Prevents Cardiac Hypertrophy in Peritoneal Dialysis Patients without Significant Adverse Effects

Background: End-stage renal diseases treated by dialysis are associated with a high prevalence of increased left ventricular hypertrophy, which is associated with high mortality. Mineralocorticoid receptor antagonists are reported to improve the survival of patients with chronic heart failure (NEJM 1999, 2003, 2011); however, these effects remain uncertain in patients on dialysis.

Methods: We conducted a multicenter, open-label, prospective randomized trial in 158 patients under treatment with either angiotensin converting enzyme inhibitor or angiotensin type 1 receptor antagonist and on peritoneal dialysis and with or without spironolactone (control group) for 2 years.

Results: Left ventricular mass index (LVMI) was significantly suppressed in patients taking spironolactone after 18 months. As normal values of LVMI differ between males and females, we separately analyzed the effects. LVMI for males with a normal LVMI of ≤115 g/m² at baseline did not change in the group given spironolactone, but significantly increased in the control group. The LVMI for males with a higher LVMI at baseline did not change in the control group but was significantly reduced in the spironolactone group. These effects were unclear in females. The effects of spironolactone were obvious in patients with reduced residual renal function. Effects on ejection fraction were also confirmed in patients with reduced residual renal function. Renal K/Na and diastole/plasma creatinine ratio did not significantly differ between the groups during the observation period. Serious adverse effects such as hyperkalemia were not observed.

Conclusions: Spironolactone may help to prevent cardiac hypertrophy in patients on peritoneal dialysis without significant adverse effects, particularly in males.

SA-OR128

Urgent-Start Peritoneal Dialysis versus Other Modalities of Dialysis: A Prospective Cohort Study

Background: Several reports have described the feasibility of urgent initiation of peritoneal dialysis (PD) in unplanned end-stage renal disease (ESRD) patients using low-volume recumbent PD soon after PD catheter placement. While short-term clinical outcomes are similar in other dialysis modalities, there is a lack of data about longer-term outcomes.

Methods: This is a single-center prospective cohort study comparing hospitalizations, central venous catheter (CVC) exposure and infectious complications amongst 111 incident ESRD patients (17 planned HD, 13 planned PD, 53 urgent HD, 28 urgent-start PD) at our dialysis center between Jan 1, 2010 and December 31, 2011 with a median followup of 365 days (range 90-365 days).

Results: The differences in hospitalization rates (planned PD 0.92 ± 1.16; urgent-start PD 0.89 ± 1.17; planned HD 1.2 ± 2.1; urgent HD 1.6 ± 1.8) and length of stay (planned PD 5.7 ± 8.17 days; urgent-start PD 4.39 ± 6.06; planned HD 9.4 ± 17.6; urgent HD 9.6 ± 11.5) were not significantly different amongst different dialysis modalities ($p=0.05$). As compared to the urgent HD group, the average duration of CVC use was significantly lower in all other groups (planned HD 53.4 ± 64.1 days; planned PD 31.9 ± 85.3; urgent-start PD 19.1 ± 44.13; urgent HD 248.3 ± 99.4, $p<0.001$). The bacteremia rates were significantly
higher in the urgent HD group as compared to all other groups (planned HD 0, planned PD 0, urgent HD 0.39 ±0.77, urgent PD 0.07± 0.26, (p<0.01). Peritonitis rates were comparable between the urgent-start PD and planned PD groups at 1 to 100.9 patient-months versus 1 to 25.4 patient-months respectively. There were 2 deaths in the urgent HD group while no deaths occurred in the other groups.

Conclusions: Our study demonstrates that patients urgently started on PD have significantly higher CVC exposure and bacteremia rates than patients urgently started on HD, while having comparable rates to planned PD and HD. Our study suggests that urgent-start PD is feasible in late presenting patients with outcomes that warrant more widespread adoption of this modality in clinical practice.

SA-OR129
Peritoneal Dialysis Start and Mortality Arsh Jain, Jessica M. Sontrop, Jeffrey Perl, Peter G. Blake, William F. Clark, Louise M. Moist.

Background: Several observational studies of hemodialysis patients show an association between early dialysis initiation and increased mortality. Few studies have examined this association among peritoneal dialysis patients.

Methods: We analyzed a cohort of 8,047 peritoneal dialysis patients and evaluated the association between timing of dialysis initiation and mortality (Canada, 2001-2009). We used multivariable piece-wise Cox regression to evaluate mortality (overall and annually).

Results: Between 2001 and 2009, the proportion of patients starting peritoneal dialysis as early starts increased from 29% (95% CI: 26% to 32%) to 44% (95% CI: 41% to 47%). Compared with late starts, the overall mortality rate was not higher among early starts (adjusted HR 1.08; 95% CI: 0.96, 1.23) nor mid starts (adjusted HR 0.96; 95% CI: 0.86-1.09). However, when examined annually, early starts were significantly more likely to die within the first year of starting dialysis compared with late starts (adjusted HR 1.38; 95% CI: 1.10, 1.72), but not in subsequent years.

Conclusions: In Canada, patients are initiating peritoneal dialysis at increasingly higher levels of eGFR. Contrary to most observational studies assessing hemodialysis, the early initiation of peritoneal dialysis, at an eGFR above 10.5 mL/min per 1.73 m2, is not associated with increased mortality.

SA-OR130
Chondroitin Sulfate Attenuates Peritoneal Fibrosis Induced by Chlorhexidine Gluconate in Mice Shinichi Ake, Tomoya Nishino, Kimiko Ito, Yoko Ohata, Takechio Koji, Shigeru Kohno.

Background: Long-term peritoneal dialysis causes peritoneal fibrosis in submesothelial areas. Previous reports suggest that the angiogenesis and inflammation play crucial roles in peritoneal fibrosis. Chondroitin sulfate (CS) is a typical glycosaminoglycan distributed in a wide variety of tissues, and recent studies suggest the effect of various inflammatory diseases by suppressing NF-κB activation. Therefore, we examined the effect of chondroitin sulfate on the progression of peritoneal fibrosis in mice.

Methods: 10 week-old male ICR mice were divided into three groups, chlorhexidine gluconate (CG) + saline, CG + CS, and control group. Peritoneal fibrosis was induced by the injection of CG into peritoneal cavity in mice every other day for 3 weeks. The mice were sacrificed on the fifth day after CG injection and peritoneal tissues were dissected out. Morphologic peritoneal changes were assessed by Masson’s Trichrome staining. Inflammation and fibrosis associated factors were assessed by immunohistochemically.

Results: In CG-injected mice, the marked thickening of the submesothelial compact zone was shown. In contrast, the administration of CS suppressed the progression of peritoneal fibrosis. The median concentrations of patients cDNA with and without peritonitis in the last 3mo were 16025 vs 1518.37 pg/ul, respectively (p<0.01). A significant negative correlation was observed between cDNA concentration and days from the start of peritonitis (p<0.01). Each one-unit increase in days from the start of peritonitis was associated with a 402% decrease in cDNA level.

Conclusions: Our data have demonstrated that cDNA subsequent to peritonitis is increased in PD patients as index of tissue damage. Decreasing levels of cDNA were observed in patients with a longer peritonitis-free period. cDNA could be a marker of peritoneal membrane repair. Our results indicate the potential future role of cDNA in the prognosis of tissue recovery from peritonitis.
SA-OR133

The Development of In Vivo Small Interfering RNA Delivery System with Nanoparticles to Peritoneum for the Treatment of Peritoneal Fibrosis

Hiromichi Yoshizawa,1 Yoshiyuki Morishita,1 Akira Onishi,1 Shigeaki Muto,1 Eiji Kusano.2 1Div of Nephrology, Dept of Medicine, Jichi Medical Univ, Shimotsuke, Tochigi, Japan; 2Utsunomiya Social Insurance Hospital, Utsunomiya, Tochigi, Japan.

Background: Peritoneal fibrosis is an intractable complication without any established therapies in peritoneal dialysis (PD). Gene therapies would be a potentially good strategy for treatment of peritoneal fibrosis; however, the delivery methods of treatment genes to peritoneum remain to be established. We attempted to develop in vivo small interfering RNA (siRNA) delivery system with non-viral nanoparticles (NPs) to peritoneum for treatment of peritoneal fibrosis.

Methods: Peritoneal fibrosis mice were produced by intraperitoneally injection of PD fluid containing 40mM of methylglyoxal to C57BL/6 mice every day for 2 weeks. For delivery of anti-fibrotic (TGFβ1) siRNA to peritoneum, 500nmol of lyophilized NPs composed with phospholipids were rehydrated by 100 μl of water containing TGFβ1-siRNA (5nmol) and TGFβ1-siRNA encapsulated with NPs (TGFβ1-siRNA-NPs) were dissolved in 1000 μl of PD fluid and injected intraperitoneally to peritoneal fibrosis mice 3 times a week for 2 weeks. Peritoneal fibrosis mice those were injected with TGFβ1-siRNA alone or non-targeted-siRNA encapsulated with NPs served as controls. Finally, the peritoneal tissues were obtained after peritoneal equilibrium test. to investigate the expression of TGFβ1, epithelial cell markers (E-cadherin and occludin) and mesenchymal cell markers (α-SMA and vimentin) by qRT-PCR and/or immunohistocmestory, and morphological changes by light microscopy.

Results: TGFβ1-siRNA-NPs significantly knock downed TGFβ1 expression in peritoneum compared with those of other groups. TGFβ1-siRNA-NPs also inhibited peritoneal fibrous thickening with decreases expression of epithelial cell markers and increases expression of mesenchymal cell markers in peritoneum compared with those of other groups. Furthermore, TGFβ1-siRNA-NPs maintained better peritoneal functions than those of other groups.

Conclusions: We developed in vivo anti-fibrotic siRNA delivery system with NPs to peritoneum in the therapeutic setting for peritoneal fibrosis in PD.

SA-OR134

Mediators of Inflammation and Fibrosis in Peritoneal Dialysis

Michael E. Ullian, Thomas Mortinelli, Linda Walker, Megan Hicks. Medical Univ of South Carolina.

Background: Fibrosis of the peritoneal membrane limits the efficacy of peritoneal dialysis (PD), and angiotensin II (AngII) and glucose, the osmotic agent in PD fluid, appear to cause cycles of inflammation and fibrosis. We examined AngII-glucose interactions on the intracellular signals that mediate inflammation [cyclooxygenase 2 (Cox2)] and fibrosis [fibronectin (FN)] in cultured peritoneal mesothelial cells (PMC) and experimental PD.

Methods: Cells harvested from rat peritoneum were studied in culture passages 0 and 1, when characteristic cobblestone appearance was maintained. Cox2 and FN protein content (b-actin content for normalization) were quantitated by immunoblotting. Experimental PD in rats consisted of injection of glucose (2.5%), mannitol (4.25%), or AngII (100 nM, 6 hr) for 5 weeks, followed by parietal mesothelium fixation and Masson’s Trichrome staining.

Results: In PMC, 10nM AngII increased Cox2 expression 9.8-fold at 6 hr and 2.1-fold at 24 hr (n = 4); in contrast, FN expression occurred more slowly: 0.6-fold increase at 6 hr and 1.3-fold increase at 24 hr (n = 2). Glucose (2.5%) increased Cox2 expression 9.4-fold at 6 hr and 24.1-fold at 24 hr, and the addition of 10 nM AngII to the glucose increased Cox2 expression 33.9-fold at 6 hrs but did not increase it at 24 hr. Exposure of PMC to maximal stimulation of glucose (4.25%, 24 hr), the osmotic control mannitol (4.25%, 24 hr), or AngII (100 nM, 6 hr) resulted in 17- to 26-fold increases in Cox2 expression that were 90% prevented by inclusion of 5 μM Ro-10-69920, an inhibitor of NF-κB, which is a well-described mediator of inflammation (n = 2-4). Experimental PD in rats resulted in thickening of the mesothelium: [13 μm (saline) vs 24 μm (4.25% glucose-containing PD fluid), n = 8], which was completely prevented by inclusion of 10 μM losartan (AngII type 1 receptor antagonist), p < 0.05.

Conclusions: Glucose in PD fluid appears to cause cycles of inflammation and fibrosis of the peritoneal membrane, via mechanisms that include AngII and osmotic stress. The AngII type 1 receptor and NF-κB may be loci whose inhibitors could limit inflammation/fibrosis of the peritoneum and prolong PD as a renal replacement modality.

Funding: Pharmaceutical Company Support - Dialysis Clinic Incorporated
RIFLE Classification in Geriatric Patients with Acute Kidney Injury in the Intensive Care Unit

**Background:** The RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) classification is widely used to gauge the severity of acute kidney injury (AKI), but its efficacy has not been formally tested in geriatric patients. We studied 236 elderly patients who developed AKI in the intensive care unit (ICU) in accordance with the RIFLE criteria.

**Methods:** Patients were eligible if they were ≥65 years and developed AKI in ICU between January 2009 and April 2013. Exclusion criteria included patients on maintenance dialysis and stayed in ICU for <48 hours. We used the sRIFLE classification between January 2009 and April 2013. Exclusion criteria included patients on maintenance dialysis and stayed in ICU for <48 hours. We used the sRIFLE classification criteria in which only three levels are used to classify patients.

**Results:** A total of 606 samples were identified as having AKI between April-Nov 2012. 72 were removed as they were either repeat flag samples during the same AKI episode, did not meet the criteria or were not from GP locations. This left a total of 534 separate AKI episodes, identified on 528 patients. For the same period there were 159,280 samples received from 103,362 patients giving an incidence of 0.3% of samples in 0.5% of patients. AKI stage, age/sex split and follow up data are shown below.

**Conclusions:** The incidence of cAKI was low; however, these patients had a high mortality and high rate of hospital admission. The absence of repeat blood tests within 4 weeks in 28% of patients raises the possibility of under-recognition of the importance of AKI and a need for ongoing education.
Conclusions: Taking a RAS blocker prior to AKI does not appear to impact on the severity of AKI or its outcomes. The known clinical benefits of RASB, particularly in people with CKD, are denied to many patients following AKI.

Funding: Private Foundation Support

TH-PO006
Community and Hospital Acquired Acute Kidney Injury in the General Hospital Population
Mark Dominic Uniacke,1,2 Robert Lewis,1 Scott Harris,1 Paul J. Roderick.2
1Wesses Renal and Transplantation Service, Portsmouth, United Kingdom; 2Univ of Southampton, United Kingdom.

Background: Little is known about the natural history of AKI initiated in the community compared to AKI acquired in hospital. This is a study of hospitalized patients comparing the characteristics, natural history and outcomes of hospital and community acquired AKI.

Methods: A single-center prospective observational study of unselected hospital admissions between Nov 2009 and Apr 2011. The cohort consisted of two groups who sustained an AKI: Group 1 without pre-existing CKD and Group 2 with pre-existing CKD. Each group was further subdivided into those who had community acquired AKI evident on hospital admission and those who acquired an AKI in hospital. Historic records of eGFR were used to identify baseline renal function. AKIN criteria were used to identify cases of AKI. 6 months later, mortality and residual functional loss (eGFR >25% fall from baseline) was ascertained.

Results: 375 patients with AKI were recruited (Group 1 n = 190, Group 2 n = 185). AKI was community acquired in 62% of cases (n=118) in Group 1 and 39% of cases (n=72) in Group 2. In Group 1 community cases had a higher Charlson Comorbidity Score, were more likely to be medical admissions, to have underlying sepsis and to be of greater severity by AKIN staging. Hospital and 6 month mortality was higher in community cases while hospital acquired cases had a longer length of hospital stay. The odds of death within six months of AKI was increased in community AKI (OR 3.5, 95% C.I. 1.135 – 10.6, p=.03) but this was attenuated with adjustment for AKIN stage. No influence was found on recovery of renal function. In Group 2, community acquired AKI had higher AKIN stages and shorter hospital stay than hospital acquired AKI. There were no differences in AKI cause, mortality or in recovery of function.

Conclusions: Peak severity by AKIN staging was higher in community acquired AKI. In community cases without pre-existing CKD, sepsis was the most frequent cause of AKI and follow up mortality was higher. Sepsis in the community should be a target for preventive strategies.

Funding: Private Foundation Support

TH-PO007
Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Risk of Contrast Induced Acute Kidney Injury: Systematic Review and Meta-Analysis
Jeffrey Ma,1 Jesse Heyland,1 Birgida Hemmelgarn,3 Pietro Ravani,1 Neesh I. Panu,1 Merrill Knudson,1 Matthew T. James,1 Divo of Nephrology, Univ of Calgary, Calgary, Canada; 2Divo of Nephrology, Univ of Alberta, Edmonton, Canada; 3Labin Cardiovascular Institute, Univ of Calgary, Calgary, Canada.

Background: Contrast induced acute kidney injury (CI-AKI) is associated with adverse short and long-term outcomes. The effect of concurrent use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) on the risk of CI-AKI is uncertain. The purpose of this study is to determine the risk of CI-AKI associated with ACE-I/ARB use at the time of coronary angiography.

Methods: Electronic databases (MEDLINE and Embase from inception to September 2011) were searched for eligible studies. Two reviewers independently identified eligible articles and extracted data from randomized controlled trials (RCTs) and cohort studies. The random effects model of DerSimonian and Laird was used to obtain pooled estimates.

Results: A total of eight studies (5 RCTs and 3 cohort studies) including 1699 patients undergoing coronary angiography were identified. The mean age of participants ranged from 53.5 to 71.8 years, and mean baseline serum creatinine ranged from 0.8 to 1.4 mg/dL. Among 5 RCTs identified, allocation concealment and blinding were reported in only one trial, and none reported an intention-to-treat analysis. All 3 cohort studies reported results following multivariable adjustment. Significant differences in the risk of CI-AKI associated with ACE-I/ARB use were identified based on study design (meta-regression p=0.04). Based on pooled results from cohort studies, ACE-I/ARB use was associated with an increased risk of CI-AKI (Relative Risk [RR] 2.84, 95% CI 1.71 – 4.69, I² 0%). Results from RCTs were heterogeneous, with no significant effect of ACE-I/ARB use on CI-AKI (Pooled RR 0.82, 95% CI 0.33 – 2.02, I² 48.9%).

Conclusions: Estimates of the risk of CI-AKI associated with concurrent use of ACE-I/ARB use differ significantly by study design, suggesting confounding effects among observational studies. The effects of ACE-I/ARB use on the risk of CI-AKI remain uncertain.

TH-PO008
Albumin for Fluid Resuscitation Is Independently Associated with Acute Kidney Injury in Patients Undergoing Cardiac Surgery
Josee Bouchard,1 Anne Julie Fenrette,2 Pascaline Bernier,2 Annie Charbonneau,2 Jean-Philippe Rioux,1 David R. Williamson,2 Stephen Troyanov.1 1Medicine, Hôpital du Sacré-Coeur de Montréal, Canada; 2Pharmacy, Hôpital du Sacré-Coeur de Montréal, Canada.

Background: The risk of acute kidney injury (AKI) with the use of albumin-containing fluids in the intensive care setting is not well characterized. We evaluated the risk of AKI associated with albumin (5 and/or 25%) following cardiac surgery.

Methods: We performed a retrospective cohort study including patients undergoing cardiac surgery in a tertiary care center from 2008 to 2010. AKI was defined by the RIFLE creatinine criterion. We performed a multivariable logistic regression (LR) to predict AKI and a propensity score predicting the likelihood to receive albumin. Our LR model included reduced left ventricular ejection fraction (LVEF), duration of extracorporeal circulation (ECC), hemodynamic instability, and use of pentastarch (HES 10%), red blood cells (RBC) or albumin.

Results: Our cohort included 984 patients, with a majority of Caucasian men, and a baseline eGFR of 72±19 mL/min. Twenty-three percent had a reduced LVEF and 23% underwent valvular surgery. Sixteen percent of patients received albumin, with a median dose of 1.4 g/kg (IQR 1.1-2.2). The incidence of AKI was 5.3% and was independently associated with a reduced LVEF, duration of ECC, hemodynamic instability, use of albumin and HES 10%, and transfusion of RBCs. In our model, albumin administration was associated with the highest odds ratio (OR), 2.43 (95% CI 1.28-4.61). We obtained a propensity score, matching 141 cases to 141 controls. In this analysis, albumin was still associated with an increased risk (adjusted OR 1.94 95% CI 1.21-3.11). The risk for AKI was higher as the albumin dose increased.

Conclusions: In our study, albumin administration was an independent risk factor of AKI after multivariable adjustment and remained significant in a propensity score model. We also identified a dose-relationship between albumin administration and the risk for AKI. Future studies should address the safety of albumin-containing fluids on kidney function in patients undergoing cardiac surgery.

TH-PO009
Assessment of Nephrotoxic Medications in ICU Patients with Acute Kidney Injury
Kyle Gillis, Linda Awdishu, Ravindra L. Mehta. Medicine, UCSD Medical Center, San Diego, CA.

Background: AKI complicates up to 25% of ICU admissions and is associated with a high hospital and long-term mortality and adverse outcomes. Critically ill patients are exposed to multiple medications that can contribute to drug induced kidney injury. Improperly dosed medications may contribute to nephrotoxicity and further worsen underlying kidney function. We evaluated the prevalence of nephrotoxic agent exposure to test the hypothesis that nephrotoxic agent exposure would be present in greater than 25% of ICU patients who develop AKI.

Methods: We reviewed medical records of 94 patients enrolled in a prospective study of patients who developed AKI within the first 7 days of ICU admission. We examined exposure of nephrotoxic agents classified as antibiotics, NSAIDS, chemotherapy, ACE/ARB, immunosuppressive medications and contrast agents. Outcomes included AKI severity stage (AKI criteria), duration, renal functional recovery and mortality.

Results: Nephrotoxic agent exposure was seen in >65% of patients with over 25.27% of patients receiving multiple agents. Nephrotoxic antibiotics (58%), immunosuppressive agents (19%) and ACE/ARB agents (18%) were the commonest contributors. Patients with nephrotoxic exposure had a greater dialysis requirement, higher hospital mortality and were more likely to be dialysis dependent at hospital discharge. Patients with underlying CKD had similar hospital outcomes as those with de novo AKI. A multivariate regression model showed renal recovery was predicted by AKI severity stage and nephrotoxic exposure.

Conclusions: Nephrotoxic agents are important contributors to the development and resolution of AKI in critically ill patients. Additional studies are required to determine the susceptibility for drug induced kidney injury and establish the best techniques for medication dose adjustment.

Funding: NIDDK Support

TH-PO100
Validation of Three Clinical Scores to Predict Renal Replacement Therapy and Severe Acute Kidney after Cardiac Surgery
Cesar Flores-Gama, Maribel Merino, Armando Vazquez-Rangel. Nephrology, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico.

Background: Different scores to predict acute kidney injury requiring renal replacement therapy (AKI-RRT) after cardiac surgery (CS) have been developed, different criteria for starting RRT suggest that predicting severe AKI could be more useful. The aim of this study was to validate three clinical scores (Mehta, Thakar and Wijeysundera) to predict AKI-RRT and severe AKI.

Methods: Prospectively all patients over 17 years old undergoing CS with cardiopulmonary bypass at the Instituto Nacional de Cardiología Ignacio Chávez in Mexico City from March 2010 to June 2012 were included. RRT onset was not standardized. Severe AKI was defined as KDIGO stage ≥2 using urinary output and SC criteria. Discrimination analysis was described using area under curve (AUC), and Hosmer-Lemeshow statistic. For calibration, logistic regression models were developed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Results: A total of 752 patients (55 [42-65] years; eGFR 87±22 ml/min/1.73 m²) were analyzed for Thakar and Wijeysundera scores, only 499 patients with valvular and/or coronary arterial bypass surgeries for Methe score. Forty five percent patients developed AKI, 16% severe AKI and 6.9% requiring RRT. AUCs for RRT for Mehta, Thakar and Wijeysundera scores were 0.85 (0.78-0.92), 0.75 (0.66-0.83) and 0.77 (0.70-0.83) respectively. For severe AKI AUCs were 0.68, 0.64 and 0.66 respectively. Observed vs predicted incidences were not different.

Conclusions: Clinical scores evaluated tend to underestimate the risk of RRT and severe AKI in our cohort. Result can be explained by a higher prevalence of RRT and severe AKI in our cohort, due to differences between cohorts. It is advisable to evaluate and calibrate scores in any population where they are meant to be used.

TH-PO011
Risk Factors for Acute Kidney Injury in Mechanically Ventilated Patients
Raul Lombardi, 1 Nicolas Nin, 2 Alejandro Ferreiro. 3
1 Dept of Critical Care Medicine, SMI, Montevideo, Uruguay; 2 CIBERES, Hospital Universitario de Torrejon, Madrid, Spain; 3 Dept of Nephrology, CASMU, Montevideo, Uruguay.

Background: Few clinical studies have explored risk factors (RF) for AKI in patients under mechanical ventilation (MV). Therefore we carried out a study with the hypothesis that respiratory and ventilators variables, among others, are implicated in AKI in this setting.

Methods: The database of the 3th International Study of MV was used. Inclusion criteria: MV >24 hrs; two or more serum creatinine (SCr); a SCr ≥1.2 mg/dl at start of MV. AKI was diagnosed according to AKIN criteria. Variables known to be associated to AKI were included for the analysis. The study was divided in two periods: EARLY: first 48 hrs of MV; and LATE: day 5 to day 7. Accordingly, early AKI (AKI1), and late AKI (AKI2) were investigated. Demographic, reason for MV, physiological variables and ventilator parameters were recorded. Continuous variables are presented as mean (SD) or median (IQR). Categorical variables as proportions. Comparison between groups was made by U-Mann-Whitney or t test, or Fisher Exact test where appropriate. RF were assessed by a conditional logistic regression model. Variables with p<0.10 were retained in the model.

Results: 3520 pts were included. Mean age 58.4 (17.7). Male 58.5%. SAPS II 40 (30.52). GCS 10 (5,15). Main reasons for MV: coma and postoperative (PO). ICU mortality 21.8%. Total cases of AKI699 (19.8%). AKI, 575 and AKI2, 124. AKI1 pts; were older: 61.5 (17.2) vs. 58.7 (19.1); with more frequent PO reason for MV and less frequent pneumonia and coma; also higher proportion of cardiovascular (CV) SOFA ≥3; greater fluid balance; lower pH at admission. AKI was independently associated to age, SAPS II, COPD, PO and cardiac arrest as reason for MV, CV SOFA, PaFiO2, peak pressure, VT/kg, pH, SCr, platelet count at admission and ≥24 hrs fluid balance. AKI, to pneumonia pre-ICU, and CV, SOFA, pH, PaFiO2, PEEP, plateau and platelet count all of them 24 hrs pre/AKI.

Conclusions: AKI is frequent in MV and the RF pattern is different according to the onset of AKI.AKI was related to age, severity of illness, MODS at admission and injurious MV, while AKI, to MODS and injurious MV in ICU but not at admission.

TH-PO012
Early Predictors of Hemolytic Uremic Syndrome (HUS) in Patients with Shiga Toxin Producing Escherichia coli (STEC) O157 Infection
Van Nguyen, Magdalena Kendall, Rajal K. Modly. Centers for Disease Control and Prevention, Atlanta, GA.

Background: Most studies examining risk factors for STEC-related HUS focus on childhood; information applicable to patients of all ages is limited.

Methods: We assessed 46 candidate predictors of HUS among a cohort of patients of all age groups with STEC O157 infection from 10 states during 2006–10. Confirmed HUS was defined as anemia, thrombocytopenia, serum creatinine ≥1.0 mg/dL if <13 years old (≥1.5 mg/dL if ≥13), and hemolytic urticaria. Probable HUS met the first 3 criteria. We built a classification tree for HUS using recursive partitioning; splitting criterion was the level of Bonferroni-adjusted significance of a permutation-based test.

Results: Among 1315 patients, 137 (10%) developed HUS (102 confirmed). The tree separated patients into 10 groups. Predictors identified were, in order, initial white blood cell count (WBC) (>21,400 cells/μL, regardless of age and ≥12,800 cells/μL in patients >5.2 years old) and age ≤5.2 years. Among patients ≤5.2 years old, other predictors were any documented WBC, female sex, and emesis during the first 3 days of illness. Among patients >5.2 years old, other predictors were >30 emesis episodes in 24 h, use of non-prescription analgesics, and illness during September–November. The probability of HUS varied from 6–71% across groups. The tree’s sensitivity was 54%; specificity was 91%.

Conclusions: Distinct clinical profiles which varied by age, were associated with risk of HUS in STEC O157 infection. Profiles may help guide early clinical management of STEC O157 infection.

Funding: Other U.S. Government Support

TH-PO013
The Incidence and Risk Factors of Kidney Injury after Hepatobiliary Surgery
Won-Yong Cho,1 So-Young Lee,2 Eunjung Cho,1 Myung-Gyu Kim,1 Sang-Kyung Jo,1 Hyoung-Kyu Kim.1 Korea Univ Anam Hospital, Republic of Korea; Eulji Univ Hospital, Republic of Korea.

Background: Although intraperitoneal procedure is known to be one of major operations associated with postoperative acute kidney injury (AKI), the incidence, risk factors or its long-term renal outcome have not been well known. This study aimed to determine the risk factors and six month renal outcome after hepatobiliary surgery along with evaluating the role of urine neutrophil gelatinase-associated lipocalin (NGAL) in early detection of AKI.

Methods: Data were collected from 135 consecutive liver surgery. Urine samples for NGAL determination were collected before, 6, 12, and 24 h after surgery. AKI was defined according to the AKIN criteria. Outcome was defined as the decrease of eGFR at 6 month after surgery.

Results: AKI was developed in 9% after hepatobiliary surgery. Renal replacement therapy was required in only one patient. Urine NGAL at 12 h post surgery was most predictive for the development of AKI (AUROC 0.769, p=0.003). Subclinical AKI (urine NGAL+, AKIN-) was diagnosed by the highest urine NGAL level (cutoff value, 92.85 ng/ml) during the first 24 hr after surgery, and additional 42 patients were included in AKI group. AKI group showed higher level of urine NGAL at all time points, SOFA score, prothrombin time (INR), lower albumin, and had longer operation time than those of non-AKI group. Older age and higher preoperative SOFA score were risk factors for the development of postoperative AKI. AKI group had longer hospital stay after surgery, but there was no difference in in-hospital mortality. AKI group showed significantly decreased eGFR at 6 month after surgery. Liver transplantation, baseline eGFR, maximum value of urine NGAL, and intraoperative fluid balance were associated with the decrease of 6 month eGFR.

Conclusions: In hepatobiliary surgery, urine NGAL was useful to diagnose AKI early and to predict 6 month renal outcome. To assess the impact of postop AKI or subclinical AKI on progressive decline of renal function, longer term follow up is needed.

TH-PO014
Acute Kidney Injury – What Happens after Discharge?
Simon Sawhney, Nick Fluck. Renal Unit, Aberdeen Royal Infirmary, United Kingdom.

Background: Acute Kidney Injury (AKI) affects 1 in 5 hospital admissions. Mortality is high, but most survive to discharge although some recover incompletely. Severe AKI is linked with future CKD and mortality. KDIGO guidelines recommend outpatient surveillance. In practice, there is little data, but one study suggested as few as 10% receive outpatient review. Following AKI, nephrologists seem to prioritize by renal function but not AKI severity. Future studies should assess whether practice is consistent and supported by prognostic models.

Methods: We audited outpatient referral in Northeast Scotland (population 500,000) over 6 months (July 2011-January 2012). Data collected included demographics, clinical context, renal function, dialysis, renal recovery (UK Renal Association criteria), mortality and follow-up.

Results: 333 referred patients had severe AKI with 26% hospital mortality. Of survivors, 58.1% recovered to within 20% baseline at discharge. Half of those with incomplete recovery improved over 90 days. Of hospital survivors, 36.8% received outpatient review. This was greater in young patients, those with incomplete recovery or renal impairment at discharge (all p<0.001). Follow up was not related to AKI severity, acute dialysis or ITU stay.

Conclusions: Only a minority of AKI is followed up. Nephrologists seem to prioritize by renal function but not AKI severity. Future studies should assess whether practice is consistent and supported by prognostic models.
Incidence, Risk Factors, and Outcomes of Pregnancy-Related Acute Kidney Injury Treated with Dialysis

Ainslie M. Hildebrand,1 Kuan Liu,2 Salimah Z. Sharifi,3 Joel G. Ray,1 Michelle A. Hladunewich,1 William F. Clark,2 Amit X. Garg,1,2 Div of Nephrology, Western Univ, London, Canada; Institute for Clinical Evaluative Sciences at Western, London, Canada; Dept of Medicine, Univ of Toronto, Toronto, Canada; Div of Nephrology, Univ of Toronto, Toronto, Canada.

Background: Acute kidney injury is a rare complication of pregnancy, but may be associated with significant morbidity and mortality in young and often otherwise healthy women. As renal dysfunction in pregnancy may be missed or miscategorized using serum creatinine based definitions of acute kidney injury, we report the incidence of acute kidney injury treated with dialysis and describe the associated risk factors and maternal and fetal outcomes.

Methods: We used data from universal health care databases to study all consecutive pregnancies in Ontario over a 15-year period. Maternal outcomes included acute kidney injury during the peripartum period, 90-day mortality, and dialysis dependence among women who survived beyond 90 days. Fetal outcomes included low birthweight, small for gestational age or intrauterine growth restriction, premature birth, stillbirth, neonatal death, and perinatal mortality.

Results: There were a total of 1,918,789 pregnancies in Ontario between 1997 and 2011. The cumulative incidence of acute kidney injury during pregnancy was 1:10,000 over the study period. Among women who received acute dialysis, 4.3% died within the 90-day postpartum period and 3.9% of survivors were dialysis dependent. Adverse fetal outcomes associated with acute kidney injury treated during pregnancy included low birthweight (unadjusted relative risk [RR] 4.7, 95% confidence interval [CI] 3.6–6.0), small for gestational age (RR 3.2, 95% CI 1.9–5.3), and premature birth (RR 2.5, 95% CI 2.0–3.1).

Conclusions: The incidence of acute kidney injury treated with dialysis is low, but adverse maternal and fetal outcomes exist. These results provide important prognostic information for patients and reinforce the role of the nephrologist in pre-conception counseling, risk factor reduction, and monitoring during pregnancy for women at risk.

Iloprost: As an AKI Triggering Agent in Severe Atherosclerotic Patients Mehtap Erkmen Uyar,1 Piril Yucel,2 Zeynep Bal,3 Salihha Yildirim,2 Emre Tutul,2 Tankut Akay,1 Siren Sezer.1 Dept of Nephrology, Baskent Univ Medical School, Ankara, Turkey; 2Dept of Internal Medicine, Baskent Univ Medical School, Ankara, Turkey; 3Dept of Cardiovascular Surgery, Baskent Univ Medical School, Ankara, Turkey.

Background: Iloprost, a stable prostacyclin analog, is used as a rescue therapy for severe peripheral arterial disease (PAD). Prostacyclin has important effects on microvascular blood flow, inhibition of platelet aggregation, leukocyte-vessel interaction and it is used frequently in the treatment of obstructive PAD. It has systemic vasodilatation and antiaggregant influence while severe vasodilatation might cause organ ischemia when severe atherosclerosis is the underlying cause. In this study we retrospectively analysed the renal outcome after iloprost infusion therapy in 87 patients.

Methods: 87 patients with PAD who received iloprost infusion with 1 ng/kg/min dosage for the last 6 months were retrospectively analyzed. All patients’ clinical and biochemical parameters before (baseline, C1), during (third day, C2) and after (2 weeks after infusion, C3) the iloprost treatment were recorded. Acute kidney injury (AKI) was defined as ≥0.3 mg/dL increase in creatinine levels from baseline within 48 hours according to KDIGO guidelines.

Results: C2 (1.46±0.1 mg/dL) and C3 (1.53±0.12 mg/dL) levels were significantly higher from baseline C1 (1.15±0.6 mg/dL) values. AKI was observed in 36 patients (41.37%) on the third day of iloprost infusion. Binary logistic regression analysis revealed that smoking and no ASA use were the primary predictors (p: 0.02 and p:0.008 respectively) of acute kidney injury during iloprost treatment. In the third day of the infusion urinary output of patients was significantly increased from the initiation of therapy (1813.30±1123.46 cc vs. 1545.17±873.00 cc), 74.14±9.42 mm Hg vs. 70.07±15.50 mm Hg.

Conclusions: Even though the iloprost treatment is effective in peripheral arterial disease patients who are not suitable for surgery, severe systemic vasodilatation might cause renal ischemia ending up with non-oliguric acute kidney injury. Smoking, no ASA use and lower diastolic BP are the clinical risk factors for AKI during iloprost treatment.

Low 25-Hydroxyvitamin D Level at Continuous Renal Replacement Therapy Initiation Predicts In-Hospital Mortality

Kyung Don Yoo, Hajeong Lee, Seung Seok Han, Jung Nam An, Yon Su Kim, Dong Ki Kim. Internal Medicine, Seoul National Univ Hospital, Seoul, Jongno-gu, Korea.

Background: The low 25-hydroxyvitamin D (25(OH)D) level has been known to be associated with the development and prognosis of acute kidney injury (AKI) in critically ill patients. However, the association between serum 25(OH)D level and outcome of AKI remains unspecified in patients initiating continuous renal replacement therapy (CRRT).

Methods: This prospective observational cohort study included patients with severe AKI requiring CRRT, from Nov. 2011 to Nov. 2012. Patients with end-stage renal disease were excluded. Biochemical data including 25(OH)D were measured at the time of CRRT initiation. Patients with 25(OH)D level below the median were included in the Low group.
acute kidney injury (AKI).

and to predict clinical outcome in patients with cardiovascular disease. However, the 5-30% risk of developing AKI The aim was to investigate the prognostic value of small, mortality, end-stage renal disease and heart failure in patients with coronary heart disease. curve revealed that all-cause mortality was signi-

K-M score (r = 0.135, P = 0.010). During the study period, 239 deaths (66.2%) occurred. K-M platelet count (r = -0.315, P < 0.001), whereas it was positively associated with APACHE II, SOFA score, c-reactive protein, hemoglobin, BUN and serum albumin (Hazard Ratio 1.63, 95% confidence interval 1.08-2.45; P<0.01).

Conclusions: In this study, we demonstrated that critically ill patients with AKI requiring CRRT showed severe 25(OH)D deficiency. Moreover, low 25(OH)D level at the start of CRRT was negatively correlated with platelet size and mortality in AKI patients requiring CRRT.

TP-PO019

Mean Platelet Volume Is a Prognostic Factor in Patients with Acute Kidney Injury Requiring Continuous Renal Replacement Therapy

Ji Suk Han,1 Jhi Sun Paeng,2 Hye-Young Kang,2 Sung Jin Moon,2 Taey-Hyun Yoo,2 Shin-Wook Kang,2 Dae-Suk Han,1 Hyung Jung Oh.3

Background: Increased platelet size has been demonstrated to reflect platelet activity and to predict clinical outcome in patients with cardiovascular disease. However, the prognostic value of platelet size for mortality has never been explored in patients with acute kidney injury (AKI).

Methods: This study investigated the relationship between platelet size and mortality in 361 AKI patients who received continuous renal replacement therapy (CRRT) in an intensive care unit between August 2009 and October 2011. We retrospectively collected the data for mean platelet volume (MPV) representing platelet size, platelet count, and other laboratory parameters at the time of CRRT initiation. Kaplan-Meier (K-M) plots were constructed to determine and to compare 28-day mortality rates and multivariate Cox analyses were conducted to elucidate the independent prognostic value of MPV for mortality.

Results: The mean age was 61.1 years and 224 patients (62.0%) were male. The median MPV was 0.12 fl. At the start of CRRT, MPV was negatively correlated with platelet count (r = -0.315, P < 0.001), whereas it was positively associated with APACHE II score (r = 0.135, P = 0.010). During the study period, 239 deaths (66.2%) occurred. K-M curve revealed that all-cause mortality was significantly higher in patients with MPV ≥ 0.12 fl compared to those with MPV < 0.12 fl (P < 0.001). In addition, Cox regression analysis found that MPV was an independent predictor for mortality after adjustment of age, gender, platelet count, serum albumin, APACHE II score, and the cause of AKI (HR, 1.093; 95% CI, 1.023-1.167; P = 0.008).

Conclusions: MPV at the time of CRRT initiation might be a simple and useful predictor for mortality in AKI patients requiring CRRT.

TP-PO020

Minimal Changes in Postoperative Creatinine Values for Prediction of Mortality and Cardiovascular Events after CABG

Daniel Olsson, Marcus Liotta, Ulrik Sartipy, Martin Holzmann.

Background: Acute kidney injury (AKI) is related to an increased risk of long-term mortality, end-stage renal disease and heart failure in patients with coronary heart disease. Coronary artery bypass grafting (CABG) is one of the most common surgeries and performed as often as 1,000,000 times annually worldwide. CABG is associated with a 5-30% risk of developing AKI. The aim of this study was to investigate the prognostic value of small, subclinical increases in postoperative serum creatinine (SCr), in patients undergoing CABG.

Methods: From the SWEDEHEART registry all 25.686 patients who underwent primary, isolated, non-emergent CABG in Sweden between 2000 and 2008 were included. Postoperative support and follow-up was offered to all patients. The CABG patient cohort was divided into 3 stages: stage 1, 0-3 mg/dL; stage 2, 0.3-5.0 mg/dL and stage 3, > 5.0 mg/dL. No AKI (reference group) was defined as no increase or decrease in postoperative SCr. Hazard ratios were calculated using logistic and Cox proportional hazard regression for 30-day mortality, long-term mortality and a composite of death, myocardial infarction, stroke and heart failure by AKI stage.

Results: During a mean follow-up of 4.5 years there were 4.520 (17%) deaths and 7.095 (28%) hospitalizations for MI, stroke, heart failure or death combined. The adjusted odds ratios with 95% confidence intervals (CI) in AKI stages 1, 2 and 3 for 30-day mortality were 1.37 (0.82-2.21), 3.64 (2.07-6.38) and 15.4 (8.96-23.9), respectively. The adjusted hazard ratios for long-term mortality in AKI stages 1, 2 and 3 were 1.07 (95% CI 1.00 to 1.15), 1.33 (95% CI 1.19 to 1.48) and 2.11 (95% CI 1.92 to 2.32), respectively. The corresponding results for the composite end-point were 1.09 (95% CI 1.03-1.15), 1.39 (95% CI 1.22-1.52) and 1.99 (95% CI 1.84-2.16), respectively.

Conclusions: Already subclinical increases in postoperative creatinine values are related to long-term mortality and cardiovascular events in patients undergoing CABG.

TP-PO021

Impact of Acute Kidney Injury Requiring Renal Replacement Therapy on Mortality and Renal Survival

Silvia Gonzalez S, Pedro J. Labrador, Jesús P. Marin, Claudio Javier Cebrian Andrade, Maria C. Jimenez, Ines Castellano, Sandra Gallego, Vanesa Garcia-Bernal, Juan R. Gómez-Martino.

Background: The aim was to assess characteristics, renal survival and mortality of patients who developed acute kidney injury (AKI) stage 3, according to KDIGO guidelines, and needed renal replacement therapy (RRT).

Methods: All patients who required RRT due to AKI stage 3 along one year were included, excluding patients in intensive care unit. Demographic and personal history data, previous renal function, cause of AKI, renal function, renal survival, and mortality at one, three and six months after AKI were recorded.

Results: Total of 60 patients were enrolled (incidence 150 patients/10 population/ year). Mean age 73.6±13.6 (range 25-91), 53.3% men. Patient’s characteristics: 80% hypertensive, 32% diabetics, 42% dyslipemics, 43% obese, 23% smokers, and 58% with chronic renal failure (28.7% stage 3, 21.1% stage 4, and 8.8% stage 5). Cause of AKI: renal disease 60%, prerenal 32%, obstructive causes 8%.

Renal function (RF): Serum creatinine before AKI 1.78±1.2mg/dL; maximum serum creatinine during AKI hospitalization 7.48±4.04mg/dL; at discharge, 2.88±1.63mg/dL; one month later, 2.25±1.49mg/dL; three months later, 2.62±1.73mg/dL; and six months later, 2.53±0.99mg/dL.

Conclusion: During hospitalization, 20% died, 15% kept on RRT at discharge, and 65% recovered partial or completely RF. One month after AKI, 28.3% had died, 11.7% kept on RRT, and 60% preserved RF. Three months later, 41.7% died, 13.5% kept on RRT, and 45% preserved RF, 6.7% was missing. Six months later, 48.3% had died, 10% kept on RRT, 33.3% preserved RF, 8.3% were missing.

Conclusion: In our health area AKI stage 3 requiring RRT has an incidence similar to other studies. Mortality in AKI patients increase in time, near to 50% six months after AKI episode, while renal survival decreases in this period. So nephrology follow-up must be established in these patients.

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

Underline represents presenting author/disclosure.

107A
Conclusions: In a large, diverse community-based population, incidence of hospitalized AKI increased between 2004 and 2007 but decreased through 2011, which was not explained by population demographic and clinical factors. Studies are needed to evaluate how changes in targeted management practices may explain recent favorable trends in AKI. Funding: NIDDK Support

TH-PO023
Urine Output Criteria for Defining Acute Kidney Injury: Association with Length of Stay and 5-Year Mortality in Critically Ill Children
Rami Ali, Jacques R. Lacroix, Veronique Phan, Philippe Jouvet, Jean-Philippe Lafrance, Ronald Gottesman, Shari Ann Segal, Ana Palijan, Michael Pizzii, Mariana Dumitrascu, Nikki J. Rink, Susan M. Samuel, Michael Zappitelli, Montreal, Montreal, Canada; McGill U., Montreal, Canada; U. Calgary, Calgary, Canada.

Background: The relevance of acute kidney injury (AKI) urine output (UO) criteria in children is unclear. We determined impact of UO criteria on AKI incidence and outcome associations.

Methods: Retrospective cohort study (chart, administrative data) of children in to 2 intensive cares units (PICU) (excluding no health number, serum creatinine (SCr), outcome data; dialysis, renal transplant). We compared AKI by Kidney Disease Improving Global Outcomes (KDIGO) SCr (AKI-SCr), UO (AKI-UO) and both (AKI-full) criteria for associations with outcomes: hospital (Hospital-LOS); PICU length of stay (PICU-LOS) (multiple linear regression); 5-year mortality (multiple logistic regression). We evaluated cardiac surgery (CS) subgroups (a priori).

Results: 580 children were included: (median [interquartile range, IQR]) 4.5 [11.3] yrs, 54% male, 16% CS, 8% death, 31% AKI-SCr, 8% AKI-UO, 36% AKI-full. AKI-SCr and AKI-UO were associated with Hospital-LOS (AKI-SCr: 14 ± 22 d, p < 0.001) and PICU-LOS (AKI-UO: 5 ± 7 d, p < 0.001); these remained significant after adjustment. The LOS associations were only significant in non-CS (not shown). All AKI methods predicted 5-year mortality; this was strongest using AKI-UO in non-CS (Table).

Conclusions: AKI-UO was more strongly associated with 5-year mortality, but more weakly associated with LOS than AKI-SCr was. Studies should elucidate how this may impact AKI definition in future research.

TH-PO024
Defining Renal Angina for the Prediction of Acute Kidney Injury in Patients with Septic Shock
David D. Leedahl, Erin N. Frazez, Garrett E. Schramm, Lakhmir S. Chawla, Kianoush Banaei-Kashani, Pharmacy Services, Mayo Clinic, Rochester, MN; Renal Diseases and Hypertension, George Washington Univ Medical Center, Washington, DC; Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: The concept of renal angina (RA) has been recently proposed to enhance early identification of critically ill patients at high risk for acute kidney injury (AKI). The primary objective of this study was to define RA in a cohort of patients with septic shock.

Methods: This was a retrospective analysis of 390 adult patients admitted to the medical intensive care unit (ICU) of a tertiary, academic medical center with septic shock. We collected hourly urine output from septic shock recognition (hour 0) to the earlier of hour 96, urine catheter removal, or ICU discharge. Serum creatinine (SCr) measurements were collected until hour 96. The definition of RA was determined during the first 12 hours of resuscitation by evaluating the initial episode of oliguria, increase from baseline to peak SCr level, and Acute Physiology and Chronic Heath Evaluation (APACHE) III score in a multivariable receiver operator characteristic (ROC) analysis. The primary outcome was incidence of moderate to severe AKI according to Acute Kidney Injury Network (AKIN) criteria. Secondary outcomes included the need for renal replacement therapy and 28-day mortality.

Results: Ninety eight (25%) patients developed moderate to severe AKI after septic shock recognition. APACHE III score and SCr level increase in the first 12 hours were not statistically associated with moderate to severe AKI in multivariable ROC analysis. Consecutive oliguria for 3 hours had fair predictive ability for moderate to severe AKI (area under ROC curve = 0.73), and five hours of consecutive oliguria demonstrated optimal accuracy (82%, 95% CI 79%–86%).

Conclusions: The novel concept of RA, defined as 3 to 5 hours of consecutive oliguria in septic shock patients, may provide a valuable measure of AKI risk. Further validation to support this definition is needed.

Funding: Private Foundation Support

TH-PO025
Racial Disparity in Acute Kidney Injury: The Atherosclerosis Risk in Community Study
M. Grams, Kunihito Matsushita, Yingyang Sang, Michelle M. Estrella, Adrienne Tin, Meredith C. Foster, Wen Hong Linda Kao, Josef Coresh, Johns Hopkins Univ.

Background: African-Americans face higher risk of acute kidney injury than Caucasians. The extent to which this increased risk is due to differences in clinical, socioeconomic, or genetic risk factors is not known.

Methods: We evaluated 10,589 African-American and Caucasian participants in the Atherosclerosis Risk in Community (ARIC) study, a community-based prospective cohort of middle-aged individuals. Participants were followed from baseline study visit (1996–1999) until first hospitalized AKI (defined by bilirubin code), end-stage renal disease (ESRD), death, or December 31, 2010, whichever came first.

Results: African-American participants were slightly younger (61.8 years vs. 63.1 years, p = 0.001), more often female (63.9% vs. 53.5%, p = 0.001), and had higher baseline eGFR and prevalence of microalbuminuria. Annual family income, presence of health insurance, and education level were lower among African-Americans compared with Caucasians. The unadjusted incidence of hospitalized AKI was 8.1 cases per 1000 person-years among African-Americans and 6.2 cases per 1000 person-years among Caucasians. The elevated risk of AKI persisted after adjustment for demographics, cardiovascular risk factors, kidney markers, and time-averaging number of hospitalizations (adjusted hazard ratio (HR) for African-American race: 1.27, 95% CI 1.07–1.50, p = 0.007); however, after accounting for differences in income and/or insurance by race, the association was no longer significant. High risk variants of APOL1 were not significantly associated with AKI among African-Americans (demographic-adjusted HR 1.21, 95% CI 0.80–1.82, p = 0.4) even after accounting for the competing risk of ESRD.

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

108A
discharge were excluded. Post-hospitalization renal evaluation was defined 3 ways: (1) sCr testing, (2) urine albumin testing, and (3) nephrology clinic visit. Post-AKI evaluation was assessed at 6 months and stratified by eGFR from the last inpatient sCr.

**Results:** The study found 72,465 hospitalizations with AKI where the patient was alive at 6 months after discharge. 84% of these hospitalizations had sCr, 14.5% had urine albumin and 17.5% had nephrology visits within 6 months of discharge. 15% of hospitalizations had no patient sCr or urine albumin testing and 82.5% had no nephrology follow-up. Follow-up evaluation increased with decreasing eGFR estimated by the last inpatient sCr (see Figure).

Follow-up Renal Evaluation Stratified by Estimated GFR from Last Serum Creatinine Testing Reporting Hospitalization

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73m²)</th>
<th>% of Hospitalizations</th>
<th>% with sCr</th>
<th>% with Urine Albumin</th>
<th>% with Nephrology Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>95%</td>
<td>84%</td>
<td>14.5%</td>
<td>82.5%</td>
</tr>
<tr>
<td>60-89</td>
<td>80%</td>
<td>90%</td>
<td>17%</td>
<td>80%</td>
</tr>
<tr>
<td>30-59</td>
<td>50%</td>
<td>95%</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>≤29</td>
<td>30%</td>
<td>100%</td>
<td>30%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Conclusions: The vast majority of US VA patients underwent sCr testing during the 6 months after an AKI hospitalization. The proportion with nephrology follow-up visits was higher among those with poorer kidney function at discharge. Additional studies may determine the impact of renal follow-up on outcomes and cost-effectiveness.

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

TH-PO027

Evaluation of a Clinical Risk Assessment Scoring System for Acute Kidney Injury in Critically Ill Patients

Jane S. Kim, Ravindra L. Mehta. School of Medicine, Univ of California, San Diego, San Diego, CA.

**Background:** Acute kidney injury (AKI) is a major complication of hospitalization and is an independent risk factor for in-hospital mortality. Because clinical manifestations can vary widely, AKI is under-recognized. Several studies have evaluated risk scores for AKI in specific settings (e.g. cardiac surgery, contrast exposure). However, few studies identified the clinical risk factors for developing AKI in the intensive care unit (ICU). We evaluated the performance of a clinical risk score based on clinical and demographic factors to predict AKI in an ICU population.

**Methods:** Medical records of 327 patients who were admitted to the ICU at UCSD Hillcrest Medical Center and were screened for enrollment in a prospective registry for AKI were reviewed. Patient information within the first 48 hours of ICU admission was recorded, and AKI risk scores were calculated based on the presence of 5 co-morbidities (CXR, kidney disease, CHF, hypertension, atherosclerotic CVD) and 5 acute clinical events (arterial pH, nphetoxy in exposure, sepsis, mechanical ventilation, and anemia). Point scores were applied to each variable, and multivariable analyses were performed to evaluate how well the risk factors in the model could predict AKI. Area under the curve (AUC) and Hosmer-Lemeshow test of p = 0.334. The mean age was 67 ± 10 y, 57% male, 85% solid tumors, 15% hematological tumors, 67% on vasopressors, 61±15 y, 57% male, 85% solid tumors, 15% hematological tumors, 67% on vasopressors, 61±15 y, 57% male, 85% solid tumors, 15% hematological tumors, 67% on vasopressors, 61±15 y, 57% male, 85% solid tumors, 15% hematological tumors, 67% on vasopressors.

Conclusions: A clinical risk score combining clinical co-morbidities and acute events within the first 48 hrs after ICU admission has a good performance in predicting development of AKI in critically ill patients. This score can allow physicians to identify patients at high risk AKI at mortality of 9.8%. Development of AKI in the ICU was associated with higher scores for the variables included in the AKI risk score. Length of stay, dialysis requirements, and in-hospital mortality were also greater among patients with AKI. Higher scores predicted the development of AKI with an ROC curve with AUC of 0.778 (p < 0.001) and with Hosmer-Lemeshow test of p = 0.334.

**Funding:** NIDDK Support

TH-PO028

Association between Perioperative Blood Transfusions and Acute Kidney Injury in Patients Undergoing Joint Replacement Surgeries: A Retrospective Cohort Study

Ghanshyam Palamander Subash Shantha, Ravi Gurusamy, Robert M. Corey, Himanshu Sharma, Jayakrishna Chintanaboina, John E. Prior. Internal Medicine, The Wright Center For Graduate Medical Education, Scranton, PA.

**Background:** Blood transfusions (BT) increase risk for perioperative acute kidney injury (AKI) in cardiac surgeries. This association has not been well studied in patients undergoing surgeries that involve minimal hemodynamic changes like joint replacement surgeries. In this retrospective cohort study, we assessed the association between BT and AKI among patients undergoing joint replacement surgeries.

**Methods:** Case records of 425 consecutive adult patients who underwent joint replacement surgeries, in 2 community hospitals in Scranton, Pennsylvania, from January 2012 to December 2011 were reviewed. Peri-operative (pre, during and post operative) red cell transfusions (BT) was considered exposure. Acute kidney injury (AKI) was defined by Acute Kidney Injury Network Criteria (AKIN). Cox proportional hazards regression was performed to assess the association between BT (coded as categorical variable) and AKI, after adjusting for age, gender, pre-operative hemoglobin (PH), eGFR, diabetes diagnosis, hypertension diagnosis, NSAIDS use, type of anesthesia, average intraoperative mean arterial pressure (MAP) and the type of joint replaced.

**Results:** The mean age was 68.7 years. The population was 58% male and 8% black. Baseline creatinine was 0.9 ± 0.5 mg/dL. Mean PH was 12.1 ± 1.2 g/dl. Three hundred and twelve (73%) , 97 (23%) and 16 (4%) had knee, hip and shoulder replacements respectively. MAP was 93 ± 6 mmHg. Forty seven (11%) developed AKI. AKI developed 24 ± 6 hours post surgery. Of these, 39 (83%), 6 (13%) and 2 (4%) had stages 1, 2 and 3 AKI respectively. None of these AKI's was dialysis requiring. Sixty three (15%) received BT. BT was independently associated with AKI (Hazard ratio: 1.39, 95% C.I: 1.07 – 1.62, P = 0.032).

Conclusions: BT is associated with increased risk of AKI in patients undergoing joint replacement surgeries, independent of MAP and PH. AKI was predominantly stage I and non-dialysis requiring. Randomized trials are required to confirm our observational data.

TH-PO029

Association of Vitamin D and Acute Kidney Injury in Patients with Hematological Malignancies: A Retrospective Cohort Study

Gurusamy, Robert M. Corey, Himanshu Sharma, Jayakrishna Chintanaboina, James Hung, TaniaRubia Flores Rocha, Elbio Antonio D’amico, Luis Yu, Pavan Kumar Irukkula, Lawrence J. Cheskin. 1Hematology/Oncology, The Wright Center For Graduate Medical Education, Scranton, PA; 2Health Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

**Background:** Association of vitamin D and acute kidney injury (AKI) in patients with hematological malignancies (HM) has not been well studied. In addition to inflammation, vitamin D deficiency has been associated with increased cell survival and poor outcomes in HM. In this retrospective cohort study, we assessed the association between vitamin D and AKI in HM.

**Methods:** Case records of 346 consecutive adult patients with HM from hematology/oncology divisions of 5 community hospitals in Scranton, Pennsylvania, from 2007 - 2012 were reviewed. Vitamin D levels (25-hydroxy cholecalciferol) at cancer diagnosis were considered exposure. AKI was defined by Acute Kidney Injury Network Criteria (AKIN). Cox proportional hazards regression was performed to assess the association between vitamin D levels and AKI, after adjusting for age, gender, eGFR, diabetes diagnosis, NSAIDS use, HOCRP, cancer stage, cancer type and type of chemotherapy.

**Results:** Mean age was 67.5 years. The population was 64% male and 27% black. Baseline creatinine was 1.0 ± 0.2 mg/dl. One hundred seven (31%), 57 (16%), 55 (16%), 43 (12%), 39 (11%), 38 (11%) and 7 (3%) had a diagnosis of chronic myeloid leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, B cell lymphoma, T cell lymphoma, multiple myeloma and miscellaneous HM respectively. Mean follow-up period was 8 ± 4 months. Seventy six (22%) developed AKI [stage 1: 34 (45%), stage 2: 20 (26%), stage 3: 22 (29%)] within a mean of 4 ± 2 months. Six (8%) required dialysis. The unadjusted cumulative AKI incidence across quartiles 1-4 (10, 11, 20 – 21, 30 – 30 mg/dl) of vitamin D concentration was 31, 30.5, 25.5, and 15% respectively. After adjustment, 1st vitamin D quartile had a 1.53 times the hazard of the fourth quartile (95% CI: 1.10, 1.72; P-trend = 0.022) for AKI.

Conclusions: Low vitamin D at cancer diagnosis is associated with incident AKI in patients with HM. Further studies are needed to elucidate the underlying mechanism.

TH-PO030

Severe AKI Increases Platelet Adhesion and Aggregation in Cancer Patients

James Hung1, Tania Rubia Flores Rocha2, Elbio Antonio D’amico, Luis Yu,1 Pavan Kumar Irukkula,1 Lawrence J. Cheskin. 1Hematology/Oncology, The Wright Center For Graduate Medical Education, Scranton, PA; 2Hospital das Clinicas, Universidade de Sao Paulo, Brazil; 3Hospital de Clinicas, Universidade de Sao Paulo.

**Background:** The association between renal dysfunction (uremia) and bleeding due to impaired platelet function has been previously described in AKI patients. However, patients with cancer usually present hypercoagulable state. Thus, we sought to evaluate the effect of uremia on platelet function in cancer patients.

**Methods:** We prospectively enrolled patients admitted to the Intensive Care Unit of a Cancer University Hospital with sepsis. Renal dysfunction was classified according to the AKIN criteria. DaMed Impact R was used to evaluate platelet function under near physiological flow conditions using cone and plate technology. In this test, an image analyser quantifies the adhered platelets and results are expressed as percentage of well surface covered by aggregates (SC %) as an index of adhesion and average size of the aggregates (AS microm2) as an index of aggregation.

**Results:** From August 2012 to February 2013, 103 patients were included: mean age 61±15 y, 85% solid tumors, 15% hematological tumors, 67% on vasopressors, 68% developed AKI (AKIN 1 - 19 patients, AKIN 2 - 20 patients, AKIN 3 - 31 patients).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Acute Kidney Injury (AKI) is one of the major adverse effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which restricts the prescription of NSAIDs in patients with chronic kidney disease (CKD). Studies have shown that NSAIDs can induce acute kidney injury (AKI) in patients with CKD. The incidence of AKI caused by NSAIDs in CKD patients is significant, and the risk of AKI is higher in patients with severe renal impairment. Therefore, it is crucial to understand the risk factors for NSAIDs-induced AKI in CKD patients to propose appropriate NSAIDs use in this group.

Methods: In a retrospective cohort study, we identified 770 patients with CKD (eGFR (estimated glomerular filtration rate) ≤60 ml/min/1.73 m²) who received flurbiprofen axetil (Robigan® between December 2006 and December 2011. The AKI criteria from the Kidney Disease: Improving Global Outcomes (KDIGO) were applied to identify AKI cases.

Results: Mean (Standard Deviation) of age was 69.3 ± 13.1 years old. In the analysis (N = 125), 81 patients (25.0%) developed AKI. Diuretic use (Odds ratio/OR) 1.91, P = 0.03), diabetes mellitus (OR 1.83, P = 0.05), low eGFR (OR 1 (30–60eGFR) ≤60), and 2.83, P = 0.02 (eGFR ≤30) were risk factors for AKI. We also found that AKI itself was a risk factor for CKD worsening (more than 50% of serum Cr increase in later than 3 months after NSAIDs prescription) (OR 3.02, P = 0.04).

Conclusions: Our study suggests that NSAIDs should be used with caution in CKD patients with diuretic use, diabetes mellitus and low eGFR. NSAIDs-induced AKI might be irreversible disease resulting in CKD worsening.

TH-PO033
Risk Factors and Predictive Score of Acute Kidney Injury in Patients with Acute Myocardial Infarction
Yong Yue, Hong Cheng, Yi-Pu Chen. Div of Nephrology, Beijing Anzhen Hospital, Capital Medical Univ, Beijing, China.

Background: Although an acute kidney injury (AKI) commonly occurs among patients hospitalized for acute myocardial infarction (AMI), its risk factors is unknown. The article aims to develop a clinical predictive score in order to predict the AKI after AMI. The early identification of patients with risks of developing AKI can reduce its incidence.

Methods: We analyzed data on consecutive patients with AMI from January, 2010 to July 31, 2011 at Beijing Anzhen Hospital. All the patients were divided into two groups, AKI group and non-AKI group, with the definition of AKI by Acute Kidney Injury Network. The univariable analysis and logistic regression model were used to establish the predictive score.

Results: The total cohort consisted of 1429 patients. The derivation cohort consisted of 106 patients, and the validation cohort consisted of 396 patients. In the derivation cohort, the rate of AKI was 14.3%. Mortality was significantly higher in the AKI group (10.1% vs 6.6% in those without AKI, P = 0.000). In the validation cohort, the rate of AKI was 15.7%. A lot of in-patients occurs AKI within a week, patients with AKI stay longer than AKI.Univariable analysis disclosed age, hypertension, diabetes mellitus, chronic kidney disease(CKD), heart rate, lower estimated glomerular filtration rate (eGFR), anaemia, severe Killip class, extensive anterior myocardial infarction, troponin I(TNI) ≤50ng/ml, left ventricular ejection fraction (LVEF) ≤30%, shock, Ventricular fibrillation, β-blocker non-use and longer time before admission to hospital as risk factors to develop AKI. After adjusting for other factors associated with AKI, reduced GFR at presentation, Killip class ≥3, extensive anterior myocardial infarction, hypertension, β-blocker non-use and longer time before admission to hospital were independently associated with AKI.

Conclusions: we developed a clinical predictive score for AKI after AMI. This predictive score presented good discrimination and calibration. It would help the clinicians to make decision for preventive intervention. Further studies on interventions to minimize AKI or to more aggressively treat patients developing AKI should be tested.

Funding: Government Support - Non-U.S.

TH-PO034
Cardiorenal Syndrome in Hospitalized Patients with Mild versus Moderate-to-Severe Concomitant Hyponatremia on Admission: A Retrospective Study
Rainer U. Plaguet, Katrin Schlump, Matthias Gündt. Clinic of Internal Medicine, Nephrology, Martin-Luther-Universität Halle-Wittenberg, Halle, Germany.

Background: Hyponatremia on admission has been related to a worse outcome among different co-morbidities including chronic heart failure. Regarding cardiorenal syndrome (CRS), a detrimental role for hyponatremia has been extrapolated from chronic heart failure studies (CJASN 2009;4:2013). Here, the degree of (acute) cardiac failure, (acute) cardiac failure on admission, duration of hospital stay, and 1-year mortality were determined for hospitalized CRS patients with mild or moderate-to-severe hyponatremia on admission.

Methods: Retrospective study of consecutive patients hospitalized for CRS in “University Hospital Halle” of Martin-Luther University Halle-Wittenberg from 01/01/2007 to 12/31/2011. Diagnosis was derived from diagnosis information using hospital documentation software. Among all CRS patients, patients with mild hyponatremia (<135 mmol/l; ≤130 mmol/l) and moderate-severe hyponatremia patients (<130 mmol/l) were analyzed and entered this study. Information on plasma laboratory values including sodium, creatinine, brain-natriuretic peptide (BNP) on admission, duration of hospitalization and 1-year mortality (city-council inquiry) was gathered. Results were given as median with 25% and 75% quartile.

Results: Over a 5-year period, 386 CRS patients were admitted. In 262 patients, CRS diagnosis was confirmed. Hyponatremia occurred in 90 or 34.4% of CRS patients. Thereof, mild hyponatremia occurred in 59 (22.5%) patients, moderate-severe hyponatremia in 31 (11.8%). BNP was significantly higher in CRS patients with mild hyponatremia (754.5 μg/ml vs 107.5 μg/ml) versus moderate-severe hyponatremia (401.5 μg/ml; Cr 2 - 1934; p < 0.0001). Creatinine on admission was not different between groups (moderate-severe hyponatremia: Crea=226 μmol/l; mild hyponatremia: Crea=256 μmol/l; p ns). Likewise, duration of hospital stay (14.8 vs. 14.9 days) and 1-year mortality (25 of 56 patients or 44.6% vs. 14 of 30 patients or 46.7 % in mild vs. moderate-severe hyponatremia) were not different. In a subgroup, 9 CRS patients with severe hyponatremia (Na ≤ 125 mmol/l) had a 1-year mortality of 66.7%.

Conclusions: mild and moderate hyponatremia were associated with worse outcome compared to normonatremia. These findings could not be explained by increased age, gender, comorbidity or medication use pattern. More research is necessary to clarify the different outcomes related to CRS and hyponatremia.
Conclusions: CRS patients with hyponatremia on admission had a considerably poor outcome (1-year mortality). Interestingly, irrespective of volume state, mild hyponatremia associates with worse cardiac function than moderate-severe hyponatremia on admission in CRS patients. The role of arginine vasopressin peptide (AVP) release as a compensatory mechanism and the role of renal failure for AVP action need to be further investigated.

Funding: Clinical Revenue Support

TH-PO035

Incidence of Acute Kidney Injury following Left Ventricular Assist Device Placement: A Meta-Analysis of Prospective Cohort Studies

Reegis Stephen,1 Chandrashekar Kashyap,2 Sevg Demirjian,2 Sankar D. Navaneetham,3 Medicine, Bridgeport Hospital, Bridgeport, CT; 4Nephrology, Cleveland Clinic, Cleveland, OH.

Background: Left Ventricular Assist Device (LVAD) placement is an increasingly common therapy for bridge-to-transplant or destination therapy for patients with heart failure. Although some reports noted improvement in renal function following LVAD, it is associated with a high risk of acute kidney injury (AKI). We conducted a meta-analysis to determine the incidence of AKI with LVAD and whether this risk differs based on the type of the device.

Methods: We searched MEDLINE and Scopus (April 2013) for relevant prospective cohort studies and trials of LVAD therapy. Incidence rates for AKI reported in individual studies were pooled using an inverse of variance method. AKI was defined as rise in serum creatinine or requirement of dialysis as defined by individual studies. A random effects model was used, and subgroup analyses were performed to explore the influence of type of LVAD device (continuous vs. pulsatile) on the incidence of AKI.

Results: 15 prospective studies including 2586 patients were included in this meta-analysis. Mean follow-up of these studies varied from 28 days to 657 days. The incidence of AKI after LVAD was 21% (15 studies, 2586 patients, 95% CI 15%-30% p<0.001) with significant heterogeneity between the studies (I²=92%) and the device type accounted for 40% of this heterogeneity. The incidence of AKI was higher in patients receiving pulsatile LVAD device placement at 23% (7 studies, 1217 patients, 95% CI 15%-38%, p=0.001) compared to 15.6% when continuous-flow devices were used (7 studies, 983 patients, 95% CI 10%-23%, p<0.001).

Conclusions: The incidence of AKI has varied widely in patients receiving LVAD therapy. Newer continuous-flow devices have reduced this risk which still remains substantial. Studies focused on renal function and potential risk factors are needed to better understand this phenomenon.

TH-PO036

Acute Kidney Injury and Mortality following Ventricular Assist Device Implantation


Background: Ventricular assist devices (VADs) are increasingly common and their surgical implantation predispose patients to acute kidney injury (AKI). We sought to evaluate the incidence, risk factors and short and long term mortality of patients with AKI following VAD implantation.

Methods: We identified all patients who underwent VAD implantation at the University of Chicago from Jan. 2008 to Jan. 2012. Using demographic and lab data we evaluated the prevalence of AKI, defined as a ≥50% increase in serum creatinine over the first 7 post-op days (RIFLE Risk). Using a cox proportional hazards model (model: age, gender, race, preoperative eGFR, AKI, Diabetes Mellitus (DM), Body Mass Index (BMI), cardiopulmonary bypass time and intra-operative blood transfusion) we examined the factors that were associated with 30 and 365 day mortality.

Results: A total of 157 eligible patients had VADs, with 44 (28%) developing post-implantation AKI. There was no difference between baseline serum creatinine or eGFR for those with and without AKI (p=0.57 and 0.87 respectively). In a multivariate analysis only DM (OR=2.283) were independent factors associated with 30-day mortality. At 365 days, 21(48%) of those with AKI had died compared to 34(30%) without AKI (p=0.037).

Conclusions: AKI is common following VAD implantation. AKI and DM are independent predictors of 30 and 365 day mortality following VAD implantation.

Funding: NIDDK Support

TH-PO037

Independent Risk Factors in Common for Elderly Patients of Cardiorenal Syndrome Type I by Different Criteria

Lu Cai, Xinling Liang, Zhilian Li. Div of Nephrology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China.

Background: Cardiorenal syndrome type I reflects an abrupt worsening of cardiac function (eg. Acute heart failure) leading to acute kidney injury and is associated with substantial morbidity and mortality, especially in elderly patients. But there are no consensus diagnostic criteria for it. Thus, the objective of present study was to explore independent risk factors in common for elderly patients of cardiorenal syndrome type I by RIFLE, AKIN and KDIGO criteria of acute kidney injury.

Methods: Data was retrospectively collected from elderly patients (age ≥60 years old) with acute heart failure in Guangdong General Hospital between July 2002 and July 2012. The primary outcome was regarded as AKI defined as RIFLE, AKIN and KDIGO criteria, and baseline serum creatinine was defined as the lowest serum creatinine in the three months before admission.

Results: Among 808 elderly participants, more patients were diagnosed as AKI by KDIGO (46.2%) than RIFLE (37.9%) and AKIN (48.6%). Logistic regression indicates that albumin<30g/L (OR 1.74), uric acid<436umoL/L (OR 1.62), use of low-dose dopamine (2-3ug/kg/min) (OR 2.283) within 48 hours after admission were independent factors for cardiorenal syndrome type I by RIFLE and so were albumin<30g/L (AKIN-OR 1.798; KDIGO-OR 1.745), uric acid<436umoL/L (AKIN-OR 2.658; KDIGO-OR 2.464), use of diuretics, angiotensin-converting enzyme inhibitor/Angiotensin receptor inhibitor/ACEI/ARB and low-dose dopamine(AKIN-OR 2.010; KDIGO-OR 2.173) within 48 hours after admission by AKIN and KDIGO.

Conclusions: Albumin<30g/L, uric acid<436umoL/L and use of low-dose dopamine within 48 hours after admission were independent risk factors in common for elderly patient of cardiorenal syndrome type I by RIFLE, AKIN and KDIGO criteria.

Funding: Government Support - Non-U.S.

TH-PO038

Relationship of the Time Interval between Coronary Angiography and Elective Off-Pump Coronary Artery Bypass Surgery with Postoperative Acute Kidney Injury

Yan Zhang, Nan Ye, Hong Cheng, Yi-Pu Chen. Div of Nephrology, Beijing Anzhen Hospital, Capital Medical Univ, Beijing, China.

Background: To investigate whether there are effects of time intervals between coronary angiography (CAG) and elective off-pump coronary artery bypass graft (OPCABG) on postoperative acute kidney injury (AKI).

Methods: Clinical data of patients undergoing CAG and OPCABG from June, 2010 to December, 2011 in Beijing Anzhen Hospital were retrospectively analyzed. All the patients were divided into AKI group and non-AKI group Univariate analysis was performed to find possible factors associated with AKI. Multivariate logistic regression analysis was used to identify whether the short time interval was one of the independent risk factors of AKI after adjusting for potential confounding variables.

Results: Of the 1513 patients, 436 patients (28.8%) developed AKI. The mortality rate in AKI group (5.7%) was 6 times higher than that in non-AKI group (0.9%). The incidence of AKI was highest (48.8%) in patients in whom OPCABG was performed ≤24h after CAG. Multivariate logistic regression analysis showed that the time interval less that 24h between CAG and OPCABG did increase the risk of AKI (OR=2.44, 95%CI 2.0026,1.19, 4.99) after adjusting for the following confounding variables: male, advanced age, hypertension,
diabetes, NYHA heart function class III and IV, lower estimated glomerular filtration rate, numbers of coronary artery bypass grafts, intraoperative or postoperative intra aortic balloon pump, postoperative hypotension time ≥30min, dosage of furosemide ≥60mg/d.

Conclusions: It was one of the independent risk factors of postoperative AKI that the OPCABG was performed ≤24h after CAG.

Funding: Government Support - Non-U.S.

TH-P0039
Risk Factors and Clinical Predictive Score for Acute Kidney Injury after Off-Pump Coronary Artery Bypass Surgery
Yan Zhang, Nan Ye, Hong Cheng, Yi-Pu Chen. Div. of Nephrology, Beijing Anzhen Hospital, Capital Medical Univ, Beijing, China.

Background: To investigate the risk factors of acute kidney injury (AKI) after off-pump coronary artery bypass graft (OPCAB), develop a clinical predictive score and validate its discrimination and calibration.

Methods: Clinical data of 1513 patients undergoing coronary angiography(CAG) and OPCAB from June, 2010 to December, 2011 at Beijing Anzhen Hospital were retrospectively analyzed. All the patients were divided into AKI group and non-AKI group. Univariable analysis and multivariable logistic regression analysis were used to establish the predictive score.

Results: 436 patients (28.8%) developed AKI. In a multivariable model about AKI included: increased age, male, hypertension, diabetes, New York Heart Association class III or IV, lower estimated glomerular filtration rate (eGFR), shorter time interval between CAG and elective OPCAB, much numbers of grafts, intraoperative or postoperative intra aortic balloon pump, longer postoperative hypotension time, larger dosage of loop diuretics. The predictive model was discriminated well (ROC=0.71) and had well calibrated according to the Hosmer-Lemensh test (P=0.30).

Conclusions: We developed a clinical predictive score for AKI after CAG and OPCAB. This predictive score presented good discrimination and calibration.

Funding: Government Support - Non-U.S.

TH-P0040
Serum Hepcidin – A Protective and Inverse Biomarker of CI-AKI in Patients Undergoing Percutaneous Coronary Interventions-PCI
Jolanta Malyczyk,1 Jacek S. Malyczyk,1 Hanna Gajewska,2 Ewa Koc-Zorawska,1 Slawomir Dobrzycki. 2

Methods: Hepcidin, serum and urinary NGAL, cystatin C, eGFR serum and urinary creatinine in these patients.

Results: In this study we tested the hypothesis whether serum hepcidin could represent an early protective biomarker of CI-AKI in 26 patients with normal serum creatinine undergoing PCI. In addition, we assessed serum and urinary NGAL, cystatin C, eGFR serum and urinary creatinine in these patients.

Conclusions: Serum hepcidin was significantly higher 8 and 24 hours after PCI.

Funding: Government Support - Non-U.S.

TH-P0041
Risk Factors of Non-Early Recovery after an Episode of Acute Kidney Injury

Background: Acute kidney injury (AKI) might be a risk factor for the future development or accelerated progression of chronic kidney disease (CKD).

The aim is to determine risk factors are related to non-recovery after an AKI episode.

Methods: Retrospective observational cohort study during a follow-up period of 9 years. Potential subjects were identified and enrolled by systematic chart review using the hospital coding system (ICD-9). Patients were included after exclusion of pre-renal and obstructive etiologies or known CKD. We used the ADQI definition and classification.

Results: We included 228 patients, 64% men, age 84±19 years. Background revealed hypertension (53%), diabetes (28%), ischemic heart disease (17%) and peripheral vascular disease (23%). The most common etiology was ischemic AKI (42.5%), followed by septic (22.8%). Distribution of cases was: Risk 22.3%, Injury 25.9%, Failure 51.8%. Median duration of AKI episode was 32±44 days, and 30 (13.2%) patients needed renal replacement therapy during hospitalization. In our study, 185 patients (81.1%) recovered renal function during the first 4 weeks after diagnosis, compared with 43 (18.9%) patients who did not.

In univariate analysis, the predictors of non-recovery of renal function after an episode of AKI were: age>64 years (OR 2.5, 95%CI 1.17-5.40), hypertension (4.6, 95%CI 1.04-22), AKI secondary to nephrotoxicity (5.18, 1.68-16.0), and serum creatinine at admission >4mg/dl (OR 2.70, 1.37-5.3). In multivariate analysis, independent risk factors for lack of recovery of renal function in four weeks were: age>64 years (OR 2.54, 1.01-6.37), AKI secondary to nephrotoxicity (OR 3.58, 1.07-11.93) and serum creatinine during hospitalization >4mg/dl (OR 3.58, 1.07-11.93).

Conclusions: Age older than 64 years, serum creatinine >4mg/dl and that the AKI was related to nephrotoxicity were the independent risk factors for lack of recovery of renal function during the first 4 weeks after an episode of AKI.

TH-P0042
Retrospective Analysis of 30 Years’ Data Base, over 68000 Patients Using IMIS (Integrated Medical Information System in Kochi University) to Search Risk Factor of Acute Kidney Injury
Taro Horino,1 Kazunori Otomo,2 Kazu Hamada,2 Yoshiko Shimamura,2 Koji Ogiata,2 Kosuke Inoue,2 Yoshinori Taniguchi,2 Yoshio Terada,1 Yoshiyasu Okuhara,2 1Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi Univ; Nankoku, Kochi, Japan; 2Center of Medical Information Science, Kochi Medical School, Kochi Univ, Nankoku, Kochi, Japan.

Background: In Japan, the etiology of acute kidney injury (AKI) remains unclear. Therefore, we estimated risk factors of acute kidney injury by using large medical data base in Kochi University, or Integrated Medical Information System (IMIS) data base for 30 years.

Methods: 68504 patients who had hospitalized and were more 18 years old in Kochi Medical School from 1981 to 2010 were enrolled. AKI was diagnosed according to AKIN criteria. Our study evaluated odds ratio for AKI of underlying diseases which developed within 30 days from AKI onset and continued during AKI course. All data were estimated by analysis software, Retrieval xStream for Open Medical Analysis (RYSMA2).

Results: AKI patients were 8879 (13.1%); male 5541 (61.7%). In elderly patients especially over 70years, the risk of AKI up to 15.5%. The odds ratios of classical risk factors; septic shock, cardiacogenic shock, liver failure, acute respiratory distress syndrome, pulmonary edema and acute lung injury were 16.45 (95%CI, 12.21-22.17), 9.76 (3.31-13.58), 9.36 (7.70-11.39), 9.12 (6.86-12.13), 7.97 (6.21-10.23), and 7.93 (5.94-10.58), respectively. Noteworthy, we detected also novel risk factors; the odds ratios of hemorrhagic gastric ulcer and hyperuricemia were 2.50 (2.15-2.90) and 1.76 (1.60-1.95), respectively. Furthermore, the incidence of AKI was elevated in patients, especially in female, with hyperuricemia (more 7.0 mg/dl in male and more 5.5 mg/dl in female) at dose-dependent manner. Interestingly, the risk of AKI is also increased hyperuricemia (less than 3.0 mg/dl), so the curve of odds ratio for AKI shows “J-shaped” curve.

Conclusions: This is the first data investigated about the risk factors for AKI with using large scale medical data base in Japan. Our data revealed that hyperuricemia might be an important risk factor for AKI in addition to classical risk factors.

TH-P0043
Association between Mortality Risk and Severity of Acute Kidney Injury among Critical-Care Patients from Remote Islands: A Single Center Prospective Cohort Study
Junichi Ishigami,1 Masato Tajima,1 Ayako Motomura,1 Tatemitsu Rai,2 Shinichi Uchida,2 Sei Sasaki.2 1Dept of Nephrology, Tokyo Metropolitan Hiroo Hospital, Tokyo, Japan; 2Dept of Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: The prevalence of acute kidney injury (AKI) is high among critical-care patients in emergency department and their outcome remains poor. Tokyo Metropolitan Hiroo Hospital plays a major role to provide emergency medical care for people in the remote islands and patients are transferred to the hospital if immediate intensive care is required. We conducted a prospective observational cohort study to assess the prevalence of AKI and the outcome of the patients transferred from the islands.

Methods: 476 patients who were transferred from 10 remote islands to the hospital between December 1st 2010 and November 31st 2012 were included to the study. Patients were classified according to the severity of AKI using AKIN (Acute Kidney Injury Network) definitions: Stage 1, 2 and 3. Kaplan-Meier survival curve was used to assess the longitudinal risk of mortality. Logistic regression analysis was used to assess the multiple factors affecting the outcome.

Results: Among 476 patients, 54(11.3%), 17(3.6%) and 32(6.7%) developed AKIN 1, 2 and 3 respectively. 34 patients (7.1%) died within 30 days from ICU admission. Patients who developed AKI had longer length of ICU stay compared to patients who did not (6.4 versus 3.5 days; p<0.001). Patients who developed AKI 2 or 3 had higher mortality risk compared to patients who did not develop AKI (HR 5.66, 95%CI 1.79 to 17.93; p<0.001).

In logistic regression model, development of AKI was not associated with age, sex, use of radiodensity agent, history of diabetes mellitus, hypertension, dyslipemia, cardiovascular disease, ischemic heart disease and congestive heart disease.

Conclusions: The patients developed AKI had longer length of ICU stay compared to those without AKI. Since AKI 2 and 3 patients had highest mortality risk among the cohort, these patients should be transferred preferentially to a hospital with adequate emergency medical service.

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

112A

Background: Non-tunneled hemodialysis (HD) catheter was known to be used safely without infectious complication up to 1 month, but recent trend is to recommend using tunneled catheter in the patients requiring renal replacement therapy (RRT) for more than one week. Nevertheless, there exist difficulties following such recommendation in ICU because the patients in ICU have poor survival so that it is difficult to predict RRT duration, so we investigated the propriety of current recommendation for catheter choice in ICU.

Methods: Forty-five ICU patients receiving tunneled HD catheter insertion and 105 ESRD patients were respectively assigned to ICU and ordinary ESRD groups. Patient survival and tunneled catheter survival, in addition to duration of catheter use and immediate and long term complication rates were compared.

Results: Immediate complication rate including exit site bleeding, bruise and hematoma was rather higher in ordinary ESRD group (32.9% vs. 8.1%; p=0.003). Long term complication rates including catheter dysfunction and catheter related infection were comparable (5.4% in ICU group vs. 12.7% in ordinary ESRD group; p=0.33). Duration of catheter use was significantly shorter in ICU group (39 ± 53 days vs. 73 ± 50 days; p<0.001), although catheter survival were comparable between 2 groups (p = 0.8). Patient survival in ICU group was significantly poor, compared with ordinary ESRD group (p = 0.002).

Conclusions: ICU patients receiving tunneled catheter insertion for RRT showed poor life survival rate with short span in catheter use, compared with ordinary ESRD group, although catheter survival was not inferior and its insertion was safely performed in ICU setting. Therefore, considering patient survival and span of catheter use besides infection risk, separate guideline for catheter choice in ICU setting is required.


Background: Considering contrast is excreted through kidneys, use of estimated glomerular filtration rate (eGFR) without body surface area (BSA) normalization is expected to be an effective rate for evaluating the risk of contrast-induced acute kidney injury (CI-AKI). No studies have thus far suggested use of eGFR without BSA normalization for predicting CI-AKI. We aimed to demonstrate eGFR without BSA normalization is more appropriate than CI-AKI with BSA normalization for predicting CI-AKI.

Methods: This study included 433 myocardial infarction patients treated with primary percutaneous coronary intervention. Demographic data and clinical findings were compared between groups with and without CI-AKI. Logistic regression analysis was performed to identify independent risk factors. We used receiver-operating characteristic curves to compare the prediction of CI-AKI between eGFRs with and without BSA normalization.

Results: The ratio of contrast volume to raw MDRD eGFR, which is the value of ratio of contrast volume to eGFR without BSA normalization better predicted CI-AKI than does ratio of contrast volume to eGFR with BSA normalization.

Conclusions: As both patient groups were balanced for age and number of co-morbidities one would expect better outcomes with lower severity of AKI. Although outcomes were not statistically significant, the trend suggests possible assessment & management of less severe AKI at our centre. This has led to the local introduction of an AKI risk assessment tool and AKI care pathway.
Conclusions: Patients with AKI did not receive optimal care on a daily basis. However, care did not significantly deteriorate on subsequent days when compared to Day 1 of AKI. More work and education of all members of staff is necessary to achieve full compliance with the AKI bundle on a daily basis.

TH-PO049
Exertional Acute Kidney Injury in U.S. Military Personnel Is Not Always due to Rhabdomyolysis
John S. Hanness, Matthew J. Wauson, Joseph D. Hebro, Daniel J. Dean. Medicine, Naval Medical Center San Diego, San Diego, CA.

Background: Exertion leading to acute kidney injury (AKI) is well described. It may be due to rhabdomyolysis (AKI-R) or patchy ischemia (AKI-ALPE) or exertional heat illness (AKI-EHI). We sought to determine why AKI-ALPE is appearing in U.S. military personnel (ADSM). The U.S. Marine Corps instituted a Combat Fitness Test (CFT) which involves intense bursts of exertion in 2008.

Methods: We reviewed inpatient and outpatient electronic health records of all ADSM’s hospitalized with discharge diagnosis of AKI from 2008-2012. We evaluated demographic, clinical and laboratory parameters of patients (pts) for cases of AKI-R, AKI-ALPE, and AKI-EHI. AKI-ALPE was defined as AKI occurring after exertion, accompanied by loin or abdominal pain, and with a creatine kinase (CK) value less than 3000 UI/L which did not resolve with 24 hours of volume repletion.

Results: There were 15 cases of AKI-ALPE, 9 cases of AKI-R, and 11 cases of AKI-EHI. AKI-ALPE cases had similar peak Scr (3.7±4.2 vs 4.2±7.0) to AKI-R. There was no difference in the need for dialysis between groups (7% vs 33%, p=1.39). The mean number of days till recovery of kidney function (10.4±13.3 vs 6) did not differ between AKI-ALPE and AKI-R. Of 15 AKI-ALPE cases, 9 had recently completed a Combat Fitness Test (CFT) compared with 0 of 20 non AKI-ALPE cases. Pts with AKI-EHI were quickly identified, cooled, and had lower severity of illness (mean peak Scr 1.6, 0 pts diazylized). No patients died.

Conclusions: AKI-ALPE is an important cause of AKI in ADSM who have completed CFT. It may be severe enough to warrant dialysis and has a similar morbidity burden to that of AKI-R. Clinicians caring for AKI pts after exertion should consider ALPE when typical features of rhabdomyolysis are absent. Rapid recognition and cooling of patients with exertional heat illness has mitigated the morbidity of AKI-EHI in this population.

Funding: Other U.S. Government Support

TH-PO050
Acute Kidney Injury due to Vitamin D Intoxication in Kashmiri Population: A Cross-Sectional Study

Background: Vitamin D deficiency is highly prevalent in Kashmir. Most of the elderly get D vitamin as injection; at times dose prescribed is far above the permitted limit, resulting in many cases of Vit D toxicity with hypercalcemia and reversible acute kidney injury (AKI). We report 50 patients with malpractice-related Vit D intoxication with hypercalcemia and AKI.

Methods: 58 cases of Vit D toxicity were seen over 24 months (2011-2012). Detailed investigations and follow up was available in 50 cases. The diagnosis of Vit D intoxication was made on basis of history of multiple vitamin D injection intake (600,000 IU/injection), toxic blood levels of 25 OH Vit D and after ruling out common causes of hypercalcemia (malignancy and hyperparathyroidism). Their presentation was either de novo AKI (Group 1) or acute on top of chronic kidney disease (Group 2).

Results: Demographic and lab data is shown in table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.3±14.4</td>
<td>62.1±13.01</td>
<td>NS</td>
</tr>
<tr>
<td>Admission days</td>
<td>7.05±3.3</td>
<td>7.77±3.86</td>
<td>NS</td>
</tr>
<tr>
<td>No of injections (million units)</td>
<td>2.28±12.6</td>
<td>3.24±4.14</td>
<td>NS</td>
</tr>
<tr>
<td>Creat at presentation (mg/dl)</td>
<td>1.41±2.7</td>
<td>3.32±1.06</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>13.76±1.47</td>
<td>15.68±2.02</td>
<td>NS</td>
</tr>
<tr>
<td>Creat on follow up (mg/dl)</td>
<td>10.76±2.3</td>
<td>11.1±1.08</td>
<td>NS</td>
</tr>
<tr>
<td>Vit D level (nmol/L)</td>
<td>313.33±54.84</td>
<td>303.73±48.41</td>
<td>NS</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>18.13±9.62</td>
<td>42.31±21.69</td>
<td>NS</td>
</tr>
</tbody>
</table>

The average follow up was of 7.2±6 months. The clinical presentation was weakness in 100%, constipation in 80%, abdominal pain in 60%, nausea/vomiting in 60%, anorexia in 50%, oliguria in 20% and altered sensorium in 20%. The treatment received was IV fluids in all, normal saline and steroids (short course) in 38 and bisphosphonates in 5.

Conclusions: This case series elucidates the alarming trend of AKI secondary to Vit D toxicity in Kashmiri population. It is a cause of reversible AKI which responds to conservative measures in most cases.

TH-PO051
Pre-Operative Fibroblast Growth Factor 23 (FGF23) Levels Predict Post-Operative Acute Kidney Injury in Pediatric Cardiac Surgery Patients: A Prospective Study
Mark Handel, Barbara Gales, Isidro B. Salusky, Katherine Wesseling-Perry. Dept of Pediatrics, UCLA, Los Angeles, CA.

Background: In CKD patients, FGF23 levels increase early in the CKD course, predict renal disease progression, and are associated with excess morbidity and mortality. Less is known about FGF23 in AKI; small, retrospective studies have shown higher FGF23 levels in AKI patients.

Methods: To prospectively assess the role of FGF23 in pediatric AKI, plasma FGF23 levels (2nd generation C-terminal, Immunotopics) were measured pre-operatively and at 2, 6, 12, 24, 48, and 96 hours post-reperfusion in 20 patients without underlying CKD undergoing cardiopulmonary bypass (CPB). Serum creatinine was obtained at baseline and daily post-reperfusion. AKI was defined by the AKIN criteria; eGFR was calculated using the Schwartz formula; and cardiac surgery complexity was classified via RACHIS-1 score.

Results: Of the 20 enrolled patients, 13 developed at least Stage 1 AKI post-operatively. The AKI group was younger than the non-AKI group; other baseline characteristics were similar between the two groups. Pre-operative FGF23 levels were inversely related to age (r = -0.67, p<0.001). Pre-operative FGF23 levels were higher in patients who developed AKI than in those who did not; this finding remained significant upon correcting for age. Post-operatively, FGF23 levels increased in all patients.

Conclusions: Pre-operative FGF23 levels predict the development of post-operative CPB-associated AKI. FGF23 levels increase in pediatric non-CKD patients undergoing CPB, even in patients without significant post-operative changes in serum creatinine, suggesting that FGF23 may be a more sensitive marker of AKI than serum creatinine.

Data presented as mean ± SD or median (IQR). SDs denote standard deviation errors.

TH-PO052
Small Molecule-Mediated Enhancement of Post Injury Repair Mechanisms after Acute Kidney Injury
Nataliya Skrypnyk, Tatiana Novitskaya, Takuto Chiba, Lauren Brill, Lee McDermott, Subramanian Sanker, Neil A. Hukriede, Mark P. De Caestecker. 4Div of Nephrology, Vanderbilt Univ, Nashville, TN; 3Dept of Developmental Biology, Univ of Pittsburgh, PA.

Background: Methyl-4-phenylthiobutanoate (m4PTB) is an HDAC inhibitor (HDACi) that promotes renal progenitor expansion in zebrafish embryos and accelerates recovery after ischemia reperfusion acute kidney injury (IR-AKI) in mice. In these studies we generated series of m4PTB analogues and compare efficacy with that of the HDACi SAHA in accelerating recovery and reducing post injury fibrosis after AKI.

Methods: m4PTB analogues substitute the zinc chelating carboxylic acid in m4PTB, with other HDACi warheads: 1) Carboxylic acid UPHD22 and 25 (m4PTB); 2) Hydroxamic acid UPHD29 and 186 and 29). UPHD22, 25, 29 and SAHA reduce creatinine vs. vehicle in IR-AKI and unilateral nephrectomy acute kidney injury (UN-AKI) models. To prospectively assess the role of FGF23 in pediatric AKI, plasma FGF23 levels (2nd generation C-terminal, Immunotopics) were measured pre-operatively and at 2, 6, 12, 24, 48, and 96 hours post-reperfusion in 20 patients without underlying CKD undergoing cardiopulmonary bypass (CPB). Serum creatinine was obtained at baseline and daily post-reperfusion. AKI was defined by the AKIN criteria; eGFR was calculated using the Schwartz formula; and cardiac surgery complexity was classified via RACHIS-1 score.

Results: Of the 20 enrolled patients, 13 developed at least Stage 1 AKI post-operatively. The AKI group was younger than the non-AKI group; other baseline characteristics were similar between the two groups. Pre-operative FGF23 levels were inversely related to age (r = -0.67, p<0.001). Pre-operative FGF23 levels were higher in patients who developed AKI than in those who did not; this finding remained significant upon correcting for age. Post-operatively, FGF23 levels increased in all patients.

Conclusions: Pre-operative FGF23 levels predict the development of post-operative CPB-associated AKI. FGF23 levels increase in pediatric non-CKD patients undergoing CPB, even in patients without significant post-operative changes in serum creatinine, suggesting that FGF23 may be a more sensitive marker of AKI than serum creatinine.

Data presented as mean ± SD or median (IQR). SDs denote standard deviation errors.
also reduces serum creatinine and post injury fibrosis after IR-AKI. In UO, UPH186, 22, 29 and 36 reduce fibrosis and expression of fibrosis markers. SAHA and UPH252 are ineffective in this model.

**Conclusions:** The short acting PTBA analogue, UPH186 with a Class 1 HDAC selective warhead, most effectively ameliorates AKI and reduces post injury fibrosis in IR-AKI and UO models, and UPH186 is still effective when administered 3 days after IR-AKI. UPH186 has a broad range of applications that could be useful for delayed treatment of patients with AKI.

**Funding:** NIDDK Support

**TH-PO053**

**Class I Histone Deacetylase Activity Is Required for Proliferation of Renal Epithelial Cells**  
Shouqiang Zhang, Dept of Medicine, Rhode Island Hospital, Alpert Medical School of Brown Univ, Providence, RI.

**Background:** The process of renal regeneration after acute kidney injury is thought to recapitate renal development, and proliferation of renal proximal tubular cells (RPTC) is a critical step in the regenerative response. Recent studies indicate that class I histone deacetylases (HDACs) are required for embryonic kidney gene expression, growth, and differentiation. The role and underlying mechanisms of class I HDACs activation in RPTC mediating proliferation of renal epithelial cells through activation of the EGFR/STAT3 signaling pathway, however, remains unclear.

**Methods:** In this study, we used cultured RPTC to examine this issue since four class I HDAC isoforms (1, 2, 3, and 8) are abundantly expressed in this cell type.

**Results:** Blocking class I HDAC activity with a highly selective inhibitor, MS-275, induced global histone H3 hyperacetylation, reduced RPTC proliferation, and diminished expression of cyclin D1 and proliferating cell nuclear antigen (PCNA). Silencing HDAC1, 3 or 8 with siRNA resulted in similar biological effects. Activation of epidermal growth factor receptor (EGFR) and signal transducers and activators of transcription 3 (STAT3) was required for RPTC proliferation, and STAT3 functioned downstream of EGFR.

**Conclusions:** Collectively, these data reveal a critical role of class I HDACs in mediating proliferation of renal epithelial cells through activation of the EGFR/STAT3 signaling pathway.

**Funding:** NIDDK Support

**TH-PO054**

**Contribution of Thio Group in PTBA Analogues for Potency and Specificity of HDAC Activity Inhibition**  
Subramanian Sankar,1 Lee McDermott,1 Mark P. De Caestecker,2 Neil A. Hukriede.1

**Background:** Blocking class I HDAC activity with a highly selective inhibitor, MS-275, induced global histone H3 hyperacetylation, reduced RPTC proliferation, and diminished expression of cyclin D1 and proliferating cell nuclear antigen (PCNA). Silencing HDAC1, 3 or 8 with siRNA resulted in similar biological effects. Activation of epidermal growth factor receptor (EGFR) and signal transducers and activators of transcription 3 (STAT3) was required for RPTC proliferation, and STAT3 functioned downstream of EGFR.

**Methods:** We studied RPTC mediated PDGF-B and CTGF production by cultured PT cells. We investigated the localization of LPA signaling molecules in kidneys after IRI. PDGF-B and CTGF production is significantly enhanced after IRI and this requires its acetylation. HMGB1 deacetylation is unclear, although, partially under the control of HDAC. We hypothesized that deacetylation activity of SIRT1 could participate in regulating nuclear retention of HMGB1, modulating the degree of damage signaling induced by HMGB1 secretion during repair.

**Conclusions:** Collectively, our findings 1) establish HMGB1 as a target for SIRT1 deacetylation, 2) increased cytoplasmic translocation and circulating levels of HMGB1 after injury of SIRT1 activity; and 3) attenuation of cytoplasmic translocation and renal injury by pretreatment with an activator of SIRT1.

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

**TH-PO055**

**Lysoosphatidic Acid (LPA) Transactivates Epidermal Growth Factor Receptors (EGFR) via LPAR1/Gαi/o Signaling to Potentiate LPAR2/Gq/αvβ6 Integrin Dependent TGFβ Signaling and Increase the Production of PDGF-B and CTGF by Proximal Tubule (PT) Cells**  
Hui Geng,1 Rongpei Lan,1 Prajai Kanti Singh,1 Pothana Saikumar,1 Joel M. Weinberg,2 Manjeri A. Venkatachalam.1

**Background:** In cultured PT cells, LPA stimulates the production and secretion of fibroinogenic peptides PDGF-B and CTGF via LPAR2-Gq/αvβ6 integrin mediated TGFβ transactivation; in vivo, during fibrosis after ischemia-reperfusion injury (IRI), TGFβ dependent PDGF-B and CTGF production by PT is associated with LPAR2 and αvβ6 integrin overexpression (Am J Pathol. 181:1236, 2012).

**Methods:** We studied LPAR1 mediated PDGF-B and CTGF production by cultured PT cells and investigated the localization of LPA signaling molecules in kidneys after IRI. PDGF-B and CTGF signaling to increase PDGF-B/CTGF production. Conversely, PTX, EGFR inhibitor AG1478 or Erk inhibitor U0126 synergized with TGFαβ1 integrin inhibitor SB431542 to optimally suppress net TGFβ signaling output and PDGF-B/CTGF production, and to promote PT differentiation. *In vivo after IRI, PT expression of LPAR1, phosphorylated EGFR and TGFβ1 expression was increased progressively and persisted in ‘atrophic’ tubules associated with fibrosis. Expression of lysophospholipase D (autotaxin), the enzyme producing LPA from precursor lysophospholipids, also increased progressively in a similar time course, localizing in ‘atrophic’ tubules associated with fibrosis.

**Results:** Blocking class I HDAC activity with a highly selective inhibitor, MS-275, induced global histone H3 hyperacetylation, reduced RPTC proliferation, and diminished expression of cyclin D1 and proliferating cell nuclear antigen (PCNA). Silencing HDAC1, 3 or 8 with siRNA resulted in similar biological effects. Activation of epidermal growth factor receptor (EGFR) and signal transducers and activators of transcription 3 (STAT3) was required for RPTC proliferation, and STAT3 functioned downstream of EGFR.

**Conclusions:** Collectively, these data reveal a critical role of class I HDACs in mediating proliferation of renal epithelial cells through activation of the EGFR/STAT3 signaling pathway.

**Funding:** NIDDK Support

**TH-PO056**

**HMGB1 Is a Novel Target of Sirt1 Deacetylation: Implications for Stress-Induced HMGB1 Translocation**  

**Background:** During AKI, alarmins are released by stressed organs as part of the innate immune response to unleash a signaling cascade responsible for systemic inflammatory causing potential multi-organ failure. During cellular stress, the alarm high mobility group box 1 (HMGB1) undergoes nuclear-to-cytoplasmic translocation and release and this requires its acetylation. HMGB1 deacetylation is unclear, although, partially under the control of HDAC. We hypothesized that deacetylation activity of SIRT1 could participate in regulating nuclear retention of HMGB1, modulating the degree of damage signaling induced by HMGB1 secretion during repair.

**Methods:** We immunoprecipitated acetylated HMGB1 and incubated it with SIRT1, revealing that HMGB1 acetylation was decreased by 49% within 60 minutes. Proteomic analysis showed that SIRT1 deacetylates HMGB1 at four lysine residues positioned within the pro-inflammatory and NLS domain of HMGB1 (lysines 55, 88, 90 & 177). In vivo, reactivation of HMGB1 increased nuclear retention, decreased systemic release and improved renal function. Conversely, genetic ablation and/or pharmacological inhibition of SIRT1 in endothelial cells stressed with LPS increased HMGB1 translocation, an effect significantly enhanced by inhibition of SIRT1 activity, as measured by staining immunocytochemistry and real-time intravital imaging of HMGB1-GFP transfected cells. In contrast, deletion of SIRT1 or its inhibition both led to enhanced translocation and release of HMGB1. Results indicated SIRT1 regulates the acetylation of HMGB1 and its release during basal and pathophysiologic conditions.

**Conclusions:** In summary, our findings 1) establish HMGB1 as a target for SIRT1 deacetylation, 2) increased cytoplasmic translocation and circulating levels of HMGB1 after inhibition of SIRT1 activity; and 3) attenuation of cytoplasmic translocation and renal injury by pretreatment with an activator of SIRT1.

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

**TH-PO057**

**a(E)-catenin Expression Regulates N-Cadherin and N-CAM Expression and Migration in NRK-52E Cells**  
Alan R. Parrish, LaNita A. Nichols, Elizabeth A. Borngmann, Xinxiu Wang. Medical Pharmacology and Physiolog, Univ of Missouri School of Medicine, Columbia, MO.

**Background:** The aging kidney is associated with a decreased ability to repair following acute kidney injury. We have shown a link in expression of a-catenin and N-cadherin in the aging rat kidney and hypothesize that loss of a-catenin expression in tubular epithelial cells may elicit changes that result in the decreased repair capacity. In these studies, we demonstrated that a-catenin and N-cadherin are decreased in the aging kidney, with decreased proliferation potential detectable as early as 18 months in male Fischer 344 rats. Loss of the proteins is also observed in aged non-human primate kidneys, suggesting that this is not a species-specific response.
Methods: In an effort to elucidate alterations due to the loss of a-catenin, we generated NRK-52E cell lines with stable knockdown of a(E)-catenin (C2 cells).

Results: These cells exhibited decreased cell-cell adhesion, and increased monolayer permeability. Interestingly, C2 cells had decreased expression of N-cadherin. Increased proliferation in serum, and serum-free, was seen in C2 cells. Using a wound repair model, C2 cells had a deficit in wound repair, due to alterations in cell migration. Analysis of gene expression in the migrating control cells indicated that expression of N-cadherin and N-CAM, was increased during repair. Similar to N-cadherin, N-CAM expression was reduced in C2 cells, and the aging kidney.

Conclusions: Taken together, these data suggest that the loss of a-catenin, and subsequent down-regulation of N-cadherin and N-CAM expression, is a mechanism underlying the decreased migration of tubular epithelial cells that contributes to the inability of the aging kidney to repair following injury.

Funding: Other NIH Support - NIA

TH-PO058

Renal Denervation Prevents Epithelial Cell Cycle Arrest and Interstitial Fibrogenesis after Ischemia Reperfusion Injury Jinu Kim, Babu J. Padanilam,1,2 1Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE; 2Medicine, Div of Nephrology, Univ of Nebraska Medical Center, Omaha, NE.

Background: Cell cycle arrest and inflammation after renal ischemia reperfusion injury (IRI) contributes to development of tubulointerstitial fibrosis. We previously reported that renal nerves drive tubulointerstitial fibrogenesis in obstructive nephropathy. Here, we hypothesized that renal nerve-derived neuropeptide/neurotransmitter may promote tubular cell cycle arrest and tubulointerstitial fibrosis after IRI in mice kidneys.

Methods: Unilateral ischemia was performed for 30 minutes following reperfusion for up to 14 days.

Results: IRI induced tubulointerstitial fibrosis demonstrated by collagen deposition and profibrotic protein expression from 4 days after the injury. Kidney inflammation demonstrated by leukocyte infiltration and proinflammatory-profibrinotic protein expression was enhanced after IRI. Kidney denervation at the time of injury or up to 1 d post-injury, however, decreased the profibrotic and proinflammatory response. Furthermore, administration of norepinephrine and calcitonine gene-related peptide (CGRP) in denervated IRI kidneys restored inflammation and fibrosis. Norepinephrine or CGRP-administration increased the number of tubular cells at G2/M phase after IRI. Consistent with the in vivo study, treatment with norepinephrine or CGRP induced G2/M arrest in HK-2 human kidney proximal tubule cells, whereas antagonists against their respective receptors inhibited the induction of cell cycle arrest.

Conclusions: These data demonstrate that kidney denervation prevents tubular cell cycle arrest and inflammation to attenuate interstitial fibrogenesis after IRI.

TH-PO059

Cell-Specific Role of ERK in Kidney Repair following Kidney Ischemia/ Reperfusion Injury Hee-Seong Jang, Jei In Kim, Joshua H. Lipschutz, Kwon Moo Park.1 1Anatomy and Cardiovascular Research Institute, Kyungpook National Univ School of Medicine, Daegu, Korea; 2Medicine, Univ of Pennsylvania and Philadelphia Veterans Affairs Medical Center, Philadelphia, PA.

Background: Extracellular signal-regulated kinase (ERK) signals have shown to involve in kidney pathogenesis. However, the role of ERK in the repair process after kidney injury remains to be defined. Here, we investigated the role of ERK in proliferation and differentiation of tubular epithelial cells, and proliferation of interstitial cells following ischemia/reperfusion (I/R) injury in mouse kidney.

Methods: Mice were subjected to 30 minutes of renal ischemia. Some mice were administered with U0126, a specific inhibitor of ERK, daily during the recovery phase, starting at 2 days after I/R until sacrifice.

Results: I/R caused severe tubular cell damage and functional loss in the kidney. Nine day after ischemia, the kidney was restored functionally even though the fibrotic lesion expanded. ERK was activated by I/R immediately and the activated ERK was sustained for 9 days. U0126 treatment inhibited the proliferation of tubular epithelial cells, basolateral relocation of Na,K-ATPase and lengthening of primary cilia in tubular epithelial cells, whereas it enhanced the proliferation of interstitial cells, the accumulation of extracellular matrix, and the expansion of interstitial area. Furthermore, U0126 treatment elevated the expression of cell cycle arrest markers. U0126 treatment mitigated the post-I/R increase of Sec10, which is a crucial component of exocytosis complex and an important factor in cytokinesis and tubulogenesis. U0126 treatment also enhanced expression of fibrosis markers, TGF-β1 and phosphorylated NF-κB after ischemia.

Conclusions: The results demonstrate that activation of ERK is required for both the restoration of damaged tubular epithelial cells, and the inhibition of fibrosis progression following I/R injury.

Funding: Government Support - Non-U.S.

TH-PO060

Late Inhibition of Inhibitor of IκB Kinase Attenuates Acute Kidney Injury Nimesh Patel, Florence Lilian Johnson, Massimo Collino, Mara Rogazzo, Magdi Yaqoob, Christoph Thiemermann.1 1The William Harvey Research Institute, Queen Mary Univ of London, London, United Kingdom; 2Dept of Drug Science & Technology, Univ of Turin, Turin, Italy.

Background: Acute kidney injury (AKI) caused by ischemia-reperfusion injury (IRI) is being increasingly regarded as a risk factor for chronic kidney disease (CKD). Activation of nuclear factor-κB (NF-κB) is known to play a key role in the production of various cytokines and chemokines, and is seen to be a significant contributor to injury following IRI. NF-κB is a diverse family of transcription factors that can be activated by IκB kinase (IKK). We hypothesized that the specific inhibition of IκB with IKK6 will aid in the attenuation of renal, glomerular and tubular dysfunction.

Methods: Forty-three male Wistar rats underwent a right nephrectomy and unilateral renal ischemia by clamping the left renal artery with non-traumatic vascular clips for 30min. The rats were randomised into 5 groups; sham, control, 0.1mg/kg IKK6, 0.3mg/kg IKK6, 1mg/kg IKK6. IKK6 was administered i.v. 24h after the onset of reperfusion. Twenty-four hours prior to termination of the experiment, rats were placed into metabolic cages for the collection of urine at 48h. The experiment was terminated 48h after the commencement of reperfusion for the collection of serum and urine.

Results: When compared to rats subjected to sham-operation, rats subjected to unilateral renal IRI (control) demonstrated a significant increase in serum creatinine, creatinine clearance and fractional excretion of sodium indicating the development of renal, glomerular and tubular dysfunction, respectively. The administration of IKK6 demonstrated a dose dependent attenuation of dysfunction, which was seen to be significant in all 3 parameters when administered at a dose of 1mg/kg 24h into reperfusion.

Conclusions: We have shown here, for the first time that the late administration of an IκB kinase accelerates the rate of recovery of renal, glomerular and tubular dysfunction. The late inhibition of AKI may, therefore, have therapeutic potential in the recovery of AKI and the prevention of CKD. Further investigations are required to determine the exact role of IKK in the development of CKD.

Funding: Private Foundation Support

TH-PO061


Background: The Sigma-1 receptor (SIR) agonist Fluvoxamine (FLU) diminishes heart ischemia/reperfusion (IR) injury through SIR – nitric-oxide synthesize (NOS) system. Here we tested the effect of FLU pretreatment on IR survival, renal damage and expression of Sigma-Aκ-NOS axis.

Methods: Male Wistar rats pretreated with FLU (20mg/bwkg); FLU+S1R antagonist NE-100 (1mg/bwkg; FN); FLU+ non-selective NOS blocker L-NNAME (10mg/bwkg); FLU+eNOS blocker L-NIO (20mg/bwkg) or FLU+nNOS blocker 7-NI (25mg/bwkg) had left renal pedicle clamped for 50 min. followed by 24h of reperfusion (T24) and were compared to vehicle-treated (VEH) rats and shams (n=8/group). We measured renal function, histology and protein level of SIR, pAkt, peNOS and nNOS. Intrarenal capillary hemodynamics was determined by multiphoton microscopy. Additional groups were followed for 7 day survival.

Results: FLU pretreatment improved survival and resulted in less functional and histological kidney damage. IR induced renal vasoconstriction at T24 was ameliorated by FLU vs. VEH and FN respectively. This FLU effect was neutralized both by the SIR inhibitor and all NOS blockers. Protein levels of SIR, pAkt, peNOS and nNOS at T24 were more elevated in FLU vs. VEH and FN.

Moreover at 30 min after pretreatment, FLU produced intrarenal vasoconstriction in shams without IR. Parallel to this, protein levels of S1R, pAkt and all NOS blockers were increased, while nNOS remained unchanged.

Conclusions: The antidepressant FLU improves survival and is protective against postischemic renal damage. This better outcome may be attributed to the SIR-NOS-mediated intrarenal vasoconstrictor effect of FLU in a time and NOS isoform specific manner. Fundings: LP2011-608, OKTA/PAPDI3431-NKi4087/2010; TAMOPA.2.1.1/10.1.

Funding: Government Support - Non-U.S.

TH-PO062

Nephroprotective Effects of TVP1022 in Experimental Model of Diabetic Renal Ischemic Injury Nirav Abu-Salah, Hoda Awad, Moger Khanna, Ravit Cohen, Samuel N. Heyman, Zaher Armaly, Zaid Abassi, TeyTechon, Haifa, Israel; 1Joslin Diabetes Center, Boston; 2Hadassah Hebrew Univ Hospital, Jerusalem, Israel; 3Nazareth Hospital, Israel.

Background: Ischemic acute kidney injury (IAKI) in diabetes mellitus is associated with a rapid kidney dysfunction. Both diabetes and IAKI are characterized by increased oxidative stress. TVP1022, non-MAO inhibitor S-isomer of rasagiline, has been shown...
to possess anti-oxidative and anti-apoptotic properties in experimental models of cardiac and neuronal injuries. The current study examines the effects of TVP1022 and Tempol, on iAKI.

**Methods:** Control and streptozotocin-injected rats were studied, with unilateral iAKI performed by clamping of the left renal artery for 30 min. Animals were also subjected to Tempol and TVP1022 (10 and 7.5 mg/kg/day, P.O. for 7 days, respectively), or to their vehicle (i.e., citrate buffer or saline). Serum creatinine (sCr), blood urea nitrogen (BUN), glomerular filtration rate (GFR), and urine protein were measured 48 h following iAKI. Renal morphology was assessed in H&E stained slides, and 4HNE and nitrotyrosin immunohistochemistry were performed.

**Conclusions:** TVP1022 treatment ameliorates renal dysfunction and histological changes in the iAKI diabetic model, suggesting a role for TVP1022 therapy in diabetic kidney protection under warm ischemic settings.

**TH-PO063**

**Formoterol-Induced Mitochondrial Biogenesis Restores Renal Function**

**Post Ischemic-AKI**

**Sue Robert Jesinkley,** Jason A. Funk, Lauren P. Wills, L. Jay Stallons, Craig Cano Beeson, Rick G. Schnellmann, and L. Jay Stallons.

**1Center for Cell Death, Injury, and Regeneration, Dept of Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC; 2Medicine, Univ of Arkansas for Medical Sciences, Little Rock, AR; 3Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC.

**Background:** At this time there are no drug therapies for acute kidney injury, resulting in high mortality. We hypothesized that stimulation of mitochondrial biogenesis 24 hours (h) after ischemia/reperfusion (I/R)-induced acute kidney injury (AKI) in mice would accelerate recovery of mitochondrial and renal function.

**Methods:** C57BL/6 mice were subjected to either sham or I/R-induced AKI followed by once daily injection (ip) with either vehicle or formoterol, a stimulator of mitochondrial biogenesis (Wills et al., 2012), 24 h after for 5 days. Renal function was measured by serum creatinine, and renal injury was determined histologically and by measuring renal KIM-1. Mitochondrial injury and biogenesis was determined by measuring the abundance of nuclear- and mitochondrial-encoded mitochondrial proteins and by evaluating state 2 and 3 respiration in isolated mitochondria.

**Results:** On day 6, I/R alone resulted in increased serum creatinine and KIM-1 protein expression, and renal necrosis. Mitochondrial proteins NDUFB8 (nuclear-encoded) and COX1 (mitochondrial-encoded), and state 3 respiration were decreased. Formoterol treatment after I/R mice restored serum creatinine to control levels, and decreased renal necrosis and KIM-1 expression. Mitochondrial protein levels and state 3 respiration returned to control levels.

**Conclusions:** These results represent the first proof-of-principle study of a novel drug therapy to treat AKI by restoring mitochondrial function and accelerating the recovery of renal function after AKI has occurred.

**Funding:** Other NIH Support - NIH Training Grant T32HL007260-35, R01GM084147-04, Veterans Affairs Support

**TH-PO064**

**Disruption of Mitochondrial Homeostasis and Suppression of Mitochondrial Biogenesis in Folic Acid-Induced AKI**

Ryan Whitaker, L. Jay Stallons, Rick G. Schnellmann.

**Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.

**Background:** Recent studies demonstrate that mitochondrial dysfunction is a mediator of AKI development and progression. We demonstrated persistent disruption of mitochondrial homeostasis and inhibition of mitochondrial biogenesis (MB) following I/R-induced AKI. These studies examine the mitochondrial dysfunction associated with folic acid (FA)-induced AKI.

**Methods:** Male C57BL/6 mice were injected with a single IP dose of 250 mg/kg FA dissolved in saline. A group of mice was injected with a single IP dose of 25 mg/kg folic acid dehydrogenase inhibitor. Serum and urine samples were collected and mice were euthanized at 0, 2, 6, and 14 days. Serum and urine creatinine, and blood urea nitrogen (BUN) were measured using commercially available kits. Kidneys were removed and prepared for histology, qPCR and biochemical analyses.

**Results:** FA caused a rapid decrease in renal function in mice as serum creatinine and BUN levels increased 3-fold and 8-fold over controls, respectively. Renal cortical NGAL expression was increased in 1-2 d after FA. All of these markers recovered to near control levels 6 d after FA. In contrast, renal morphology as assessed by PAS staining revealed marked renal injury throughout 14 d after FA. Mitochondrial electron transport chain expression and biogenesis remained disrupted 14 d after FA with decreased mRNA expression of PGC-1α, Tfam, NDUF8, COX1 and ATP5F1. Protein expression of the components of the mitochondrial electron transport chain and transcriptional mediators of MB were increased to near control levels by 14 d after FA. Mitophagy and mitochondrial dynamics were also disrupted with changes in PINK1 and mitochondrial fission/fusion proteins.

**Conclusions:** We conclude that mitochondrial dysfunction and disruption of mitochondrial homeostasis are key components of FA-induced AKI. Similar disturbances have been observed in other models of AKI and may represent a conserved mechanism of persistent renal dysfunction. The incomplete recovery of renal morphology after AKI may be linked to a persistent suppression of mitochondrial number and function and restoration of mitochondrial function following AKI may be key to the recovery of kidney function.

**Funding:** NIDDK Support, Veterans Affairs Support

**TH-PO065**

**Modulation of the Early Innate Immune Response by Heme Oxygenase-1 in Acute Kidney Injury**

**Ahmed I. Kannal,** Subhashini Bolisetti, Ravindra Boddu, James George, Anupam Agarwal.

**1Medicine; 2Cardiothoracic Surgery, Birmingham, AL.

**Background:** Ischemia reperfusion injury (IRI) is a major cause of acute kidney injury. Heme oxygenase-1 (HO-1) is cytoprotective and anti-inflammatory by regulation of the innate immune response. We hypothesized that HO-1 regulates renal macrophage recruitment, infiltration and phenotype in renal IRI. We utilized HO-1 knockout (KO) mice and wild-type (WT) littermates to avoid nonspecific effects of pharmacologic modulators of HO activity.

**Methods:** Age and sex-matched HO-1 KO and WT mice were subjected to renal IRI by bilateral renal pedicle clamping for 10 minutes. This time was chosen due to increased sensitivity and mortality in HO-1 KO mice subjected to renal IRI at ischemic times of 15 or more minutes. Both kidneys were harvested at 1 or 7 days post IRI. Renal infiltrating cells were analyzed by flow cytometry and immunofluorescence staining.

**Results:** Even with 10 min IRI, 50% mortality was observed in HO-1 KO mice by 7 days. Renal function measured by serum creatinine at 24 hrs showed significantly increased mortality occurred in the HO-1 KO IRI group compared to all other groups (1.0±3 vs. 1.2±0.0, 0.1±0.0, 1.6±0.05 and 0.17±0.02 mg/dl for HO-1 KO IRI, WT sham, WT IRI and KO sham, respectively, n=4-8, P<0.05). Renal resident monocytes (CD45+CD11b+MHCII+Ly6c+CD62L+) were significantly decreased in the HO-1 KO IRI kidneys compared to HO-1 WT IRI and sham groups (7.4±1.05 vs. 29.4±3.34, 6±2.9 and 31.1±4.8 % of CD45+, P<0.01). There was a significant increase in CD11b+ cells (P<0.01), nonresident (CD45+CD11b+MHCII+Ly6c+CD62L+) macrophages (P<0.01) and neutrophil infiltration in the HO-1 KO IRI group (P<0.05). At 7 days, the HO-1 KO IRI mice exhibited increased serum creatinine (n=3, P<0.05).

**Conclusions:** Lack of HO-1 resulted in increased sensitivity to IRI and intra-renal infiltration by macrophages and neutrophils that suggested the exaggerated inflammatory responses are a consequence of HO-1 deficiency. These results underscore an important role for HO-1 in modulating inflammatory responses in acute kidney injury and may represent a key target for therapeutic intervention.

**Funding:** NIDDK Support

**TH-PO066**

**Interleukin-10 Deficiency Modifies Repair After Ischemic Acute Kidney Injury**

**Yu Chen,** Sanjeev Noel, Samantha Bandapalle, Maria Noel Martina Lingua, Abdel Hamad, Lorraine C. Racusen, Hamid Rabb.

**1Dept of Medicine, Johns Hopkins Univ, Baltimore, MD; 2Dept of Pathology, Johns Hopkins Univ, Baltimore, MD; 3Dept of Medicine, Nanjing Medical Univ, Nanjing, Jiangsu, China.

**Background:** The role of inflammation in repair process following AKI is largely unknown. Previous studies in rats and cultured mouse cortical tubule cells have shown that interleukin-10 (IL-10) treatment protects from ischemic AKI (Deng, Star et al, Kidney Int, 2001). In this current study we hypothesized that IL-10 plays an important role in the repair following AKI.

**Methods:** C57BL/6 wild type (WT) and IL-10 deficient (IL-10-) mice underwent unilateral renal pedicle ischemia for 45 minutes followed by reperfusion. Kidneys were harvested at 3 days or 10 days to examine histological, proliferative and inflammatory changes.

**Results:** Ischemic kidneys from IL-10- mice had significantly (P<0.05) less necrotic tubules than WT in the cortex at day 3 (51±4.7 vs 66.8±13.1) and day 10 (110,0±7.3 vs 73.3±8.8) as compared to WT mice. Outer medulla showed significantly (P<0.05) less necrosis in IL-10- mice at day 10 as compared to WT mice (12.5±5.9 vs 46.7±18.0). The epithelial cell proliferation measured by Ki-67 staining, revealed significantly (P<0.05) less proliferating epithelial cells in IL-10- mice as compared to WT mice at day 3 (314±3.6, 25.4 vs 667.1±32.5) and day 10 (84.5±6.5 vs 128.3±8.0). Higher number of kidney mononuclear cells (KMNCs) was found in IL-10- mice as compared to WT mice (15.8±2.0 vs 6.8±11.9), 10 days after ischemic injury. Percent of CD25 FoxP3 (Treg) cells in CD4 TCRγ+ cells was significantly (P<0.05) lower in IL-10- mice as compared to WT mice (14.3±1.6 vs 25.6±3) at day 10. There were no significant differences in CD4+, CD8+, NK1.1 cells between IL-10- and WT mice either at day 3 or 10.

**Conclusions:** These data demonstrates that IL-10 deficiency leads to abnormalities in kidney structure, epithelial cell proliferation, and leukocyte trafficking in the repair phase of ischemic AKI. While IL-10 has previously been shown to be protective in the initiation phase of AKI, it might have negative consequences during repair.

**Funding:** NIDDK Support

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

**Underline represents presenting author/disclosure.**

117A
**TH-PO067**

Hydrogel Delivery of Co-Embedded EPC-MSC for Treatment of AKI and Modulation of Macrophage Proinflammatory Cytokine Release

**Background:** We have shown that endothelial progenitor cells (EPC) embedded in hydrogels confers improvement in renal function during AKI and promotes angiogenesis. We attempted to improve EPC delivery by co-embedding with mesenchymal stem cells (MSC), while examining their paracrine mechanisms that affect proinflammatory macrophages.

**Methods:** A live/dead cell assay determined if EPC-MSC co-embedding improved viability during LPS exposure. Delivery of co-embedded EPC-MSC to AKI mice demonstrated additive improvement (as compared to EPC delivery alone and no treatment) of kidney function and survival. In vitro studies demonstrated that co-embedded EPC-MSC increased their viability during LPS exposure, an effect augmented by MSC hypoxic preconditioning. Delivery of co-embedded EPC-MSC to AKI mice demonstrated additive improvement (as compared to EPC delivery alone and no treatment) of kidney function and survival. In vitro studies demonstrated that co-embedded EPC-MSC increased their viability during LPS exposure, an effect augmented by MSC hypoxic preconditioning.

**Results:** Hydrogel co-embedding improved stem cell viability during LPS exposure, an effect augmented by MSC hypoxic preconditioning. Delivery of co-embedded EPC-MSC to AKI mice demonstrated additive improvement (as compared to EPC delivery alone and no treatment) of kidney function and survival. In vitro studies demonstrated that co-embedded EPC-MSC increased their viability during LPS exposure, an effect augmented by MSC hypoxic preconditioning.

**Conclusions:** Hydrogel delivery of co-embedded EPC-MSC for treatment of AKI and modulation of macrophage proinflammatory cytokines confers improvement in renal function during AKI and promotes angiogenesis. Since hydrogel delivery of co-embedded EPC-MSC has a nephroprotective effect when delivered in rats with renal ischemia and reperfusion (IR) injury, preventing extensive fibrosis as a late complication. The aim of the present study was to evaluate whether the overexpression of VEGF in the hASCs increases their nephroprotective effect in the IR models.

**Methods:** hASCs were isolated and characterized for immunophenotypic and differentiation properties. A cell line expressing CD24, c-kit and the renal progenitor markers CXCR4 and CXCR7 was transduced with VEGF. For the CXCR4+ naïve group received 1x10^6 VEGF cells. Serum creatinine and proteinuria levels were measured at 24h, 48h and 2 months after IR injury. Histological analysis was performed to quantify tubular necrosis and hyaline cast formation at 48h and interstitial fibrosis at 2 months. Additionally, the expression of Ki-67, ED-1 and α-SMA was assessed using immunohistochemistry at 48h. In kidneys from mice with IR injury, VEGF-hASCs showed less fibrosis than the naïve group and the VEGF group showed more fibrosis than control.

**Conclusions:** VEGF-hASCs are more nephroprotective than naïve hASC when delivered in rats with renal ischemia and reperfusion injury, however it can have a dose dependent toxic effect and aggravate this injury.

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

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

---

**TH-PO068**

**Background:** Differentiation properties of human amniotic fluid derived stem cell (hAFSC) have a nephroprotective effect when delivered in rats with renal ischemia and reperfusion (IR) injury, preventing extensive fibrosis as a late complication. The aim of the present study was to evaluate whether the overexpression of VEGF in the hAFSCs improves their nephroprotective effect in the IR models.

**Methods:** hAFSCs were isolated and characterized for immunophenotypic and differentiation properties. A cell line expressing CD24, c-kit and the renal progenitor markers CXCR4 and CXCR7 was transduced with VEGF. For the CXCR4+ naïve group received 1x10^6 VEGF cells. Serum creatinine and proteinuria levels were measured at 24h, 48h and 2 months after IR injury. Histological analysis was performed to quantify tubular necrosis and hyaline cast formation at 48h and interstitial fibrosis at 2 months. Additionally, the expression of Ki-67, ED-1 and α-SMA was assessed using immunohistochemistry at 48h. In kidneys from mice with IR injury, VEGF-hAFSCs showed less fibrosis than the naïve group and the VEGF group showed more fibrosis than control.

**Conclusions:** VEGF-hAFSCs are more nephroprotective than naïve hAFSC when delivered in rats with renal ischemia and reperfusion injury, however it can have a dose dependent toxic effect and aggravate this injury.

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

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

---

**TH-PO069**

**Deleterious Effects of Fibrate-Treated eEOCs in Acute Ischemic Kidney Injury**

**Background:** Early Endothelial Outgrowth Cells (eEOCs), a major subpopulation of EPCs (Endothelial Progenitor Cells) have reliably been shown to protect mice from acute ischemic renal failure. In addition, different exogenous strategies have been evaluated for improving renoprotective competence of eEOCs in AKI. PPAR-alpha can promote EPC differentiation. Since fibrates act as PPAR-alpha agonists we aimed to analyze consequences of fibrate treatment of EEOCs in murine AKI.

**Methods:** Male, 8-12 weeks old C57Bl/6N mice were subjected to bilateral renal ischemia followed by systemic injection with either untreated or clo-fenofibrate (CF/ FF) treated ECFCs. Proangiogenic markers were evaluated by flow cytometry. Cellular consequences of fibrate treatment were evaluated by different in vitro assays (TGF-beta induced EOC apoptosis/necrosis, eEOC migration, secretion of pro-/antiangiogenic mediators).

**Results:** Administration of CF treated eEOCs dramatically aggravated postischemic kidney function while FF treatment of the cells neither improved nor aggravated renal function after ischemia. Both substances significantly reduced cellular secretion of proangiogenic VEGF, such effect was more pronounced in the presence of CF. Migration analysis showed a complete CF induced disruption of cultured eEOCs. TGF-beta mediated eEOC apoptosis/necrosis was intensified by FF but not by CF.

**Conclusions:** Fibrates do not act as eEOC agonists in murine AKI. Contrasting to the literature on other cell types, fibrate induced PPAR-alpha activation decreases the functional competence of cultured eEOCs in vitro.

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

---

**TH-PO070**

**VEGF Transduced Amniotic Fluid-Derived Stem Cells in the Ischemic Acute Renal Injury in Rats**

**Background:** Endothelial progenitor cells (EPC) are the possible mechanisms underlying this function. Since hydrogel delivery of co-embedded EPC-MSC has a nephroprotective effect when delivered in rats with renal ischemia and reperfusion (IR) injury, preventing extensive fibrosis as a late complication. The aim of the present study was to evaluate whether the overexpression of VEGF in the hASCs increases their nephroprotective effect in the IR models.

**Methods:** hASCs were isolated and characterized for immunophenotypic and differentiation properties. A cell line expressing CD24, c-kit and the renal progenitor markers CXCR4 and CXCR7 was transduced with VEGF. For the CXCR4+ naïve group received 1x10^6 VEGF cells. Serum creatinine and proteinuria levels were measured at 24h, 48h and 2 months after IR injury. Histological analysis was performed to quantify tubular necrosis and hyaline cast formation at 48h and interstitial fibrosis at 2 months. Additionally, the expression of Ki-67, ED-1 and α-SMA was assessed using immunohistochemistry at 48h. In kidneys from mice with IR injury, VEGF-hASCs showed less fibrosis than the naïve group and the VEGF group showed more fibrosis than control.

**Conclusions:** VEGF-hASCs are more nephroprotective than naïve hASC when delivered in rats with renal ischemia and reperfusion injury, however it can have a dose dependent toxic effect and aggravate this injury.

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

---

**TH-PO071**

**Human Cord Blood-Derived Endothelial Colony Forming Cells Are Protective in Ischemic Acute Kidney Injury in Mice**

**Background:** Endothelial colony forming cells (ECFCs) diminish injury in ischemia/ reperfusion (IR) models, through unknown mechanisms. The purpose of this study was to determine the direct effect of human ECFCs in acute kidney injury (AKI) in mice.

**Methods:** ECFCs were isolated from human umbilical cord blood and expanded in culture. Non-obese diabetic severe combined immunodeficient (NOD-SCID) mice underwent bilateral renal I/R and ECFCs (10^6/mouse) were injected via the jugular vein at reperfusion.

**Results:** Renal I/R caused significant increases in plasma creatinine, associated with tubular necrosis and apoptosis, interstitial macrophage infiltration, loss of proximal tubule brush border and renal production of reactive oxygen species (ROS) (P<0.05 for all vs sham, n=6-10). Administration of ECFCs decreased plasma creatinine and all indices of tubular injury, renal function and the in vivo filtration (~5-fold vs I/R, P<0.001). ECFCs reduced from human umbilical cord blood and expanded in culture. Non-obese diabetic severe combined immunodeficient (NOD-SCID) mice underwent bilateral renal I/R and ECFCs (10^6/mouse) were injected via the jugular vein at reperfusion.

**Conclusions:** Renal I/R caused significant increases in plasma creatinine, associated with tubular necrosis and apoptosis, interstitial macrophage infiltration, loss of proximal tubule brush border and renal production of reactive oxygen species (ROS) (P<0.05 for all vs sham, n=6-10). Administration of ECFCs decreased plasma creatinine and all indices of tubular injury, renal function and the in vivo filtration (~5-fold vs I/R, P<0.001). ECFCs reduced from human umbilical cord blood and expanded in culture. Non-obese diabetic severe combined immunodeficient (NOD-SCID) mice underwent bilateral renal I/R and ECFCs (10^6/mouse) were injected via the jugular vein at reperfusion.

**Funding:** Government Support - Non-U.S.
TH-PO072

Human Antigen-Expressing Rat and Human Marrow Stromal Cells or Human Adipose-Derived Stem Cells Induce an Antibody Response That Abolishes Their Robust Renoprotective Activity in Rats with Acute Kidney Injury

Anna Gooch,1 Ping Zhang,1 Zhma Hu,1 Florian Toegel,1 Christo Westenfelder.1,2 Medicine, U of Utah and VA Medical Centers, Salt Lake City, UT; 1Physiology, U of Utah, Salt Lake City, UT; 2Brigham and Women’s Hospital, Boston, MA.

Background: Our pre-clinical (APJ Renal 2005) and Phase 1 Clinical studies (Nat Rev Neph 2010) showed that allogeneic rat and human Marrow Stromal Cells (MSCs) effectively protect renal function post IRI Acute Kidney Injury (AKI) in rats and in on-pump cardiac surgery patients. Allogeneic cells do not elicit an antibody response, confirming MSCs’ immune privileged properties. The present study tested whether the expression of human antigens such as alkaline Phosphatase by Fischer344 rat (hPAP F344) MSCs, by human MSCs (hMSC) or by human Adipocyte-derived Development Cells (hASC) elicits an antibody response, and whether the presence of such antibodies affects the kidney-protective efficacy of cells in rats with AKI.

Methods: Bilateral IRI AKI was induced in F344 rats (n=6/group). Post reflow, rats were infu ed with hPAP-ratMSC, hASCs, hMSC, or vehicle. At endpoint, renal outcomes were examined, and sera were FACS analyzed for anti-hPAP and anti-human MSC- or ASC-specific IgG antibodies. Two groups of F344 rats (n=6 each) received hASC ip, inducing an antibody response by day 14, at which time IRI AKI was induced, followed by a single infu on of hASCs or vehicle.

Results: Vs. controls, all 3 cell types significantly protected renal function and hastened recovery from AKI. Although robust renoprotective actions were observed by d 1-3, within 14 days, each treatment elicited a significant IgG antibody response (57-99%) directed at the infused cell type. Rats inoculated with hASCs and confirmed to have antibodies to hASCs were no longer renoprotected by hASCs when treated with them for AKI.

Conclusions: Xenogeneic hMSCs and hASCs are renoprotective in rats. However, the induction or presence of antibodies to xenogeneic antigens (e.g. Fetal Bovine Serum or bovine antigens) could render them unsafe and ineffective clinically, mandating the use of non-animal based culture media in clinical applications.

Funding: Veterans Affairs Support

TH-PO073

Novel Prostacyclin Analog ONO-1301 (SR-ONO) Ameliorates AKI in a Rat Experimental Contrast-Induced Nephropathy Model

Haruyo Ujike,1 Yohei Maeshima,1 Norikazu Hinamoto,1 Hiroyuki Watatani,1 Kana Masuda,1 Katsuyuki Haruyo Ujike,1 Yohei Maeshima,1 Norikazu Hinamoto,1 Hiroyuki Watatani,1 Kana Masuda,1 Katsuyuki Haruyo Ujike,1 Yohei Maeshima,1 Norikazu Hinamoto,1 Hiroyuki Watatani,1 Kana Masuda,1 Katsuyuki Haruyo Ujike,1 Yohei Maeshima,1 Norikazu Hinamoto,1 Hiroyuki Watatani,1 Kana Masuda,1 Katsuyuki

Background: Contrast-induced nephropathy (CIN) is the third most common cause of acute kidney injury. Multiple factors including renal vasoconstriction, direct renal tubular toxicity, and oxidative stress contribute to tubular damage in CIN. ONO-1301 (SR-ONO) is a novel sustained-release prostacyclin analog, possessing thromboxane A2 (TXA2), synthase and TXA2 synthase inhibitory properties. We previously observed inhibitory effects of SR-ONO on oxidative stress, lipid peroxidation, synthesis of pro-inflammatory factors, MAPKs and nuclear NF-kB.

Methods: Male SD rats were divided into four groups (n=10-14/group): sham, control CIN, and SR-ONO-treated CIN groups. CIN was induced by intravenous injection of SR-ONO (1 or 3 mg/kg) directed at the infused cell type. Rats inoculated with hASCs and confirmed to have antibodies to hASCs were no longer renoprotected by hASCs when treated with them for AKI.

Results: After cisplatin treatment, the protein expression of GPR40 in the kidney was decreased in association with the increase of serum creatinine levels and the ratio of Bax/Bcl-2 expression. In HK-2 cells, cisplatin treatment increased the number of cells with condensed nuclei, which was ameliorated by GW9508 pretreatment. TUNEL stain showed that the pretreatment of GW9508 decreased AKI-induced apoptosis.

Conclusions: Activation of GPR40 attenuates cisplatin-induced apoptosis in cultured human tubular epithelial cells.

TH-PO076

Activation of G-Protein-Coupled Receptor 40 Attenuates Cisplatin-Induced Apoptosis

Seong Kwon Ma,1 Soo Yeon Joo,1 Sang Heon Shuh,1 Chang Seong Kim,1 Joon Seok Choi,1 Eun Hui Bae,1 Jongun Lee,2 Soo Wan Kim.1 Medicine, Chonnam National Univ Medical School, Gwangju, Republic of Korea; 1Physiology, Chonnam National Univ Medical School, Gwangju, Republic of Korea.

Background: G-protein-coupled receptor 40 (GPR40) plays diverse physiological functions including cellular proliferation and inflammation. We investigated the role of GPR40 on the cisplatin-induced kidney injury.

Methods: We determined the protein expression of GPR40 and apoptotic markers in rats with cisplatin-induced kidney injury and cisplatin-treated human renal proximal tubule (HK-2) cells. HK-2 cells were cultured with cisplatin in the absence or presence of GW9508, a selective GPR40 agonist.

Results: After cisplatin treatment, the protein expression of GPR40 in the kidney was decreased in association with the increase of serum creatinine levels and the ratio of Bax/Bcl-2 expression. In HK-2 cells, cisplatin treatment increased the number of cells with condensed nuclei, which was ameliorated by GW9508 pretreatment. TUNEL stain showed that the pretreatment of GW9508 decreased AKI-induced apoptosis.

Conclusions: Activation of GPR40 attenuates cisplatin-induced apoptosis by the inhibition of pro-apoptotic factors, MAPks and nuclear NF-kB.

5-Aminolevulinic Acid (ALA) Protects Against Cisplatin-Induced Acute Kidney Injury via Protection of Mitochondrial Viability and Prevention of Tubular Apoptosis without Compromising Its Anticancer Effectiveness in vivo

Inoue Yosho,1 Takayoshi Masa,1 Tatsuki Marumoto,1 Yoshiko Shimamura,1 Kosuke Inoue,1 Yoshinori Taniguchi,1 Taro Horimoto,1 Keiji Inoue,1 Taro Shuin,1 Koji Ogata.1 Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Nankoku, Kochi, Japan; 2Dept of Urology, Kochi Medical School, Nankoku, Kochi, Japan.

Background: Nephrotoxicity is major limitation in cisplatin(CDDP)-based chemotherapy. 5-Aminolevulinic acid (ALA) is widely distributed, and it is a precursor of tetrapsrolyte compounds such as heme that is important in energy metabolism. The aim of this study is to evaluate protective role of ALA in CDDP-induced acute kidney injury (AKI). We also evaluated the effects of ALA on anticancer efficiency of CDDP in rats.

Methods: We used CDDP-induced AKI rats and cultured renal tubular cells (NRK-52E). We divided four groups of rats control, CDDP only, CDDP+AL24h, AL24h:CDDP =10mg/kg: 5mg/kg. CDDP+AL48h:post/ALA is started 5 days before CDDP.

Results: ALA treatments protect CDDP-induced AKI. CDDP increased Cr up to 6.5mg/dl, BUN up to 230mg/dl, ALA significantly decreased by CDDP, and ALA ameliorates these reduction.

Conclusions: ALA treatments protect CDDP-induced AKI. ALA treatments protect CDDP-induced AKI. CDDP increased Cr up to 6.5mg/dl, BUN up to 230mg/dl, ALA significantly decreased by CDDP, and ALA ameliorates these reduction.
Inhibition of Poly (ADP-RIBOSE) Polymerase-1 (PERP-1) Activity Ameliorates Renal Proximal Tubular Epithelial Cells (PTEC) Injury Induced by Cisplatin

**Background:**
Cisplatin is a chemotherapy drug which is widely used to treat cancers. It is platinum-based and inhibits DNA production of cancer cells. However, it is well known cisplatin damages epithelial cells and induces acute kidney injury (AKI). AKI, particularly the elderly with females>males, is a significant cause of AKI, particularly among the elderly and because renal Mg handling is impaired by cisplatin, we examined the potential to prevent CDDP nephrotoxicity without compromising its efficacy.

**Methods:**
Human cultured PTEC of 4th passage were used. Cultured PTEC were incubated with cisplatin or cisplatin plus olaparib, which is PARP-1 inhibitor. The amount of LDH in the cell supernatants to total LDH was measured. The cytotoxicity was expressed as ratio of the LDH amount in the cell supernatants to total LDH. PPAR-1 expression was evaluated by immunoassay study using anti-PARP-1 antibody.

**Results:**
Cisplatin (5.0-100 μM) injured PTEC for 24 hours incubation. Olaparib (0.5 μM) protected against cisplatin-induced cell injury by cisplatin (control: 37.6±10.8%, 5.0 μM cisplatin: 52.2 ±8.0%, p<0.001 vs control, 5.0 μM cisplatin plus 5.0 μM olaparib: 32.0±2.1%, p<0.001 vs 5.0 μM cisplatin, 5.0 μM olaparib: 29.1±10.8%). PARP-1 expression was enhanced by 5.0 μM cisplatin and the enhanced PARP-1 expression was inhibited by 5.0 μM olaparib.

**Conclusions:**
We demonstrated that PARP-1 inhibitor ameliorated PTEC injury induced by cisplatin and enhanced PARP-1 expression was blocked by PARP-1 inhibitor. These data suggested that PARP-1 inhibitor might be useful for the prevention of AKI induced by cisplatin.

**Funding:**
Private Foundation Support

---

**Cisplatin-Mediated Renal Cell Apoptosis and Acute Kidney Injury**

**Background:**
Cisplatin is an effective chemotherapeutic agent for treating ovarian, bladder and breast tumors. However, >25% of patients experience acute kidney injury (AKI), particularly the elderly with females>males. Magnesium (Mg) deficiency is common among the elderly and because renal Mg handling is impaired by cisplatin, we examined the effects of Mg deficiency and supplementation on cisplatin-AKI.

**Methods:**
In vitro: the effect of Mg status on cisplatin-cell death was examined using LLC-PK(1), renal epithelial cells. In vivo: Older female C57BL/6 mice (10/group, 10mo old) were fed either normal (100%Mg) or 10%Mg-deficient diets for 24h and then injected with saline or cisplatin (12mg/kg, iv.). In addition, one group of Mg-deficient mice was supplemented with MgCl2, in water and MgSO4, s.c. prior to cisplatin. Kidney injury was assessed 48hrs post-cisplatin by blood urea nitrogen (BUN) levels, renal tubular damage (H&E staining), oxidative stress, apoptosis (TUNEL assay) and renal p53 expression (Western Blotting).

**Results:**
Cisplatin-induced LLC-PK(1) cell death was significantly enhanced by Mg deficiency (P<0.001) and decreased by Mg replacement (P<0.001). In mice, Mg deficiency decreased BUN levels (P<0.05), renal NaCl and NaHCO3 expression (P<0.05) and renal cell apoptosis following cisplatin compared to 100%Mg controls (P<0.05). Mg deficient mice following cisplatin showed increased oxidative stress, renal damage (P<0.01) and enhanced renal p53 expression/phosphorylation compared to controls (P=0.01). Mg replacement significantly reversed the damaging effects of cisplatin (P<0.01).

**Conclusions:**
Mg deficiency significantly exacerbates cisplatin-AKI and promotes renal oxidative stress and apoptosis in older female mice; Mg replacement reverses this effect. Mechanistic studies support the renoprotective role of Mg in regulating p53 expression and activation, a critical pathway involved in cisplatin-induced apoptosis. These findings warrant future studies examining Mg status and aggressive Mg replacement therapy in cisplatin-treated cancer patients.

**Funding:**
NIDDK Support

---

**Remote Ischemic Pre-Conditioning Mobilizes Mesenchymal Stem Cells and Endothelial Progenitor Cells and Has Therapeutic Potential for Acute Kidney Injury**

**Background:**
Remote Ischemic Pre-Conditioning (RIPC) is a safe and effective therapy for AKI. This study examined the hypothesis that RIPC increases the numbers of MSCs mobilized with a simple non-invasive procedure. Our laboratory has previously shown that has shown potential both in animal models and in clinical trials is the use of Remote Ischemic Pre-Conditioning (RIPC). RIPC therapy consists of several brief episodes of ischemia/reperfusion at a remote location such as a limb, where short periods of ischemia are generated with a simple non-invasive procedure. Our laboratory has previously shown in animal model and in a Phase I Clinical Trial that Mesenchymal Stem Cells (MSCs) are a safe and effective therapy for AKI. This study examined the hypothesis that RIPC mobilizes therapeutically beneficial progenitor cells into the circulation.

**Methods:**
To evaluate whether or not RIPC increases the numbers of MSCs mobilized in vivo, we used femoral arterial non-occlusive clamping. RIPC-mobilized MSCs were isolated from RIPC-treated rats and confirmed by flow cytometry. MSCs were then injected intravenously into either RIPC or sham procedure groups (n=8 per group). RIPC was performed on both hind limbs with 3 cycles of 4 min ischemia/4 min reperfusion. One day following RIPC,

**Results:**
The number of MSCs increased significantly in the RIPC group compared to the sham group. These data suggested that RIPC increased the mobilization of MSCs and may have potential therapeutic benefits for AKI.

**Conclusions:**
These data suggest that RIPC is a safe and effective therapy for AKI. This study examined the hypothesis that RIPC increases the numbers of MSCs mobilized with a simple non-invasive procedure. Our laboratory has previously shown that has shown potential both in animal models and in clinical trials is the use of Remote Ischemic Pre-Conditioning (RIPC). RIPC therapy consists of several brief episodes of ischemia/reperfusion at a remote location such as a limb, where short periods of ischemia are generated with a simple non-invasive procedure. Our laboratory has previously shown in animal model and in a Phase I Clinical Trial that Mesenchymal Stem Cells (MSCs) are a safe and effective therapy for AKI. This study examined the hypothesis that RIPC mobilizes therapeutically beneficial progenitor cells into the circulation.

**Funding:**
NIDDK Support
whole blood was sampled and evaluated by flow cytometry for the relative abundance of MSCs, endothelial progenitor cells (EPCs), and hematopoietic stem cells (HSCs). MSCs were defined as CD45−CD271+ EPCs as CD45−CD34+ and HSCs as CD45+/CD34−.

Results: At 24 hours following the RIPC procedure, the numbers of circulating MSCs were increased 3.7 fold (from 195±57 to 732±112 MSCs per mL of whole blood, p<0.001) and the numbers of EPCs in circulation were increased 3.8 fold (from 29.5±1.1 to 114.6±14 EPCs per mL of whole blood, p<0.001). RIPC did not significantly change the numbers of circulating HSCs.

Conclusions: RIPC significantly increases the numbers of circulating MSCs and EPCs. Since both are known to afford renoprotection post AKI, our data identify an important mediator mechanism that explains, at least in part, whereby RIPC promotes renal repair following AKI.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO082

The Water Soluble Triptolide Derivative PG490-88 Protects against Cisplatin-Induced Acute Kidney Injury

Hyun-Jung Kim,1 Kameswaran Ravichandran,1 Zhibin He,1 Danica Ljubanovic,2 Charles L. Edelstein, 1 'UC Denver; 2Univ Hospital Croatia.

Background: Triptolide, a traditional Chinese medicine, has anti-inflammatory, anti-proliferative and pro-apoptotic activities in pre clinical studies. As interstitial inflammation and tubular apoptosis are features of cisplatin-induced AKI and Triptolide has anti-inflammatory and pro-apoptotic actions, we determined the effect of the water soluble Triptolide derivative PG490-88 (PG) in a mouse model of cisplatin-induced AKI.

Methods: Mice injected with Cisplatin (C), (20mg/kg) develop apoptosis on day 1, ATN on day 2 and renal failure on day 3. Mice were injected with PG (0.5mg/kg) prior to C. sc.

Results: PG protected against renal failure and ATN despite having no effect on tubular apoptosis. SCR (mg/dl) was 0.25 in vehicle (V), 0.23 in PG, 1.53 in C (p<0.001 vs. V), 0.77 in PG/C (p<0.01 vs. C). BUN (mg/dl) was 30 in V, 26 in PG, 206 in C (p<0.001 vs. V), 136 in PG/C (p<0.05 vs. C). ATN score was 0 in V and PG, 4.3 in C (p<0.001 vs. V), 2.4 in PG/C (p<0.01 vs. C). Apoptotic tubular cells (/10 HPF) was 0 in V and PG, 10.3 in C (p<0.001 vs. V), 15.3 in PG/C (p<0.01 vs. V, NS vs. C). Triptolide is known to inhibit pro-inflammatory cytokines and chemokines. IL-1β, IL-6, IL-8, IL-33 and TNFα were significantly increased in C, but unaffected by PG. MAPK pathways are activated in cisplatin-induced AKI and known to be inhibited by PG. On immunoblot and densitometry analysis p-p38 was not increased by NS nor inhibited by PG (p=NS vs. V), p-JNK was 1.6 fold increased by C (p=NS vs. V) and 1.2 fold inhibited by PG (p=NS vs. V) and p-ERK was 3.6 fold increased by C (p<0.0001 vs. V) and 2.0 fold inhibited by PG (p=0.05 vs. V). On densitometry analysis, the p-NFκB/p-NFκB ratio was 10.5 fold increased in the nuclear extracts in AKI (p=0.001 vs. V) and the increase in nuclear extracts was completely inhibited by PG.

Conclusions: The protection of PG against cisplatin-induced AKI was associated with a decrease in ERK and NFκB pathways. Inhibition of NFκB in cisplatin induced AKI merits further study.

Funding: Other NIH Support - SR01DK074835-04

TH-PO083

Endothelial Progenitor Cells Exist in the Adventitia of the Renal Artery and Migrate to Repair Kidney Microvascular Acute Injury

Paul Pang, Padsawan Khamluce, Vanesa Bijol, Andrew M. Siedlecki. Medicine, Brigham and Women's Hospital, Boston, MA.

Background: Endothelial progenitor cells resident in arterial vessels are defined by the expression of CD34 in the adventitial layer; distinct from mature endothelial cells present in the intima. Presence and function of endothelial progenitor cells in adventitial layer of renal arteries has not been described.

Methods: Renal artery tissue was digested and sorted for CD34+ cells. Animals underwent ischemia/reperfusion injury followed by isolation of CD34+ cells from renal arteries 5 days after injury.

Results: The adventitia of renal arteries from adult mice and humans contained CD34+ cells.
Conclusions: IKKα-Dependence NF-κB p52/RelB alternative pathway could be activated after IR injury, low-expression of IKKα may block inflammation resolution via down-regulated NF-κB alternative pathway family members of both p52 and RelB.

Methods: In a murine model of cisplatin-induced AKI, delayed treatment with a single low dose of lithium accelerated recovery of kidney function, promoted repopulation of renal tubular epithelia and improved kidney repair. This was associated with reduced GSK3β activities and elevated expressions in renal tubular epithelia of pro-potentiating molecules, including Cyclin D1, c-Myc and HIF-1α. In cultured renal tubular cells, GSK3β activity was transiently repressed by cisplatin followed by a prolonged upregulation. Rescue treatment with lithium reduced GSK3β activity, enhanced nuclear expression of Cyclin D1, c-Myc and HIF-1α, and accelerated cellular proliferation. Moreover, ectopic expression of a kinase dead mutant of GSK3β enhanced the expression of Cyclin D1, c-Myc and HIF-1α and amplified cellular proliferation following cisplatin injury, reminiscent of the effect of lithium; whereas forced expression of a constitutively active mutant of GSK3β abrogated the lithium’s effect, suggesting that GSK3β inhibition is sufficient and indispensable for lithium’s pro-reparative effect. Mechanistically, GSK3β colocalized and physically interacted with Cyclin D1, c-Myc and HIF-1α in renal tubular cells. In silico analysis revealed that Cyclin D1, c-Myc and HIF-1α all harbor putative GSK3β consensus phosphorylation motifs, inferring a GSK3β directed phosphorylation and subsequent degradation of these molecules.

Conclusions: Pharmacological targeting of GSK3β by lithium might represent a novel therapeutic strategy to improve renal salvage after AKI.

Funding: NIDDK Support

TH-PO085

A Mouse Model of Nephrectomy-Induced Renal Repair: An Elegant Tool to Study Renal Regeneration


Background: Enhanced renal repair is defined as the remarkable repair of an acutely injured kidney upon removal of the healthy contralateral kidney. If the latter kidney is left in place, repair is only marginal and the injured kidney turns fibrotic. The molecular mechanism of this phenomenon is unknown. As most original observations were done in species less accessible to genetic manipulation for mechanistic studies, i.e. dogs and rats, we aimed at optimizing an “enhanced renal repair” model in C57BL/6j mice.

Methods: Acute kidney injury was induced by left ischemia/reperfusion (I/R) after which either right nephrectomy (Nx) or mock-Nx was performed 3 days later. Two critical ischemic parameters (i.e. duration of and body temperature during ischemia) were varied. Wild type mice (25g, n=4-6 per group) underwent either 30 min of ischemia at 35, 36 or 37°C or, alternatively, 21, 23, 25 or 30 min of ischemia at 36°C. Control mice underwent mock-I/R and mock-Nx surgery. Mice were euthanized 6 weeks after I/R. Kidneys were weighed and qPCR analysis of the pro-fibrotic genes Col1, Col4, TGFbeta and CCN2 was performed.

Results: In the groups undergoing I/R in combination with mock-Nx, no mortality was noted. Of the groups undergoing I/R in combination with Nx, only the mice undergoing 21 min. of ischemia at 36°C survived. Others perished within 48 hours after Nx. In the I/R (21min) without Nx group the median left kidney-to-body weight ratio (mg/g) was 2.8 (range 2.1-3.1), whereas that of its right healthy kidney was 6.7 (range 6.4-7.0). In the Nx group, left kidney-to-body ratio was 6.9 (range 6.0-7.3) and that of its right kidney at the time of Nx 6.5 (range 5.9-7.5). When no Nx was performed, Col1, Col4, TGFbeta and CCN2 were upregulated 18-, 5-, 7- and 3-fold compared to controls, respectively. In case of Nx, this decreased to 5-, 2-, 2- and 0-fold upregulation, respectively.

Conclusions: We clearly demonstrated in C57BL/6j mice that Nx performed 3 days after I/R (21 min, 36°C) is able to strongly attenuate development of renal atrophy and repair is only marginal and the injured kidney turns fibrotic. Of the groups undergoing I/R in combination with Nx, this decreased to 5-, 2-, 2-, and 0-fold upregulation, respectively. In case of the time of Nx 6.5 (range 5.9-7.5). When no Nx was performed, Col1, Col4, TGFbeta and CCN2 were upregulated 18-, 5-, 7- and 3-fold compared to controls, respectively. In case of Nx, this decreased to 5-, 2-, 2- and 0-fold upregulation, respectively.

Funding: Government Support - Non-U.S.

TH-PO086

Delayed Administration of a Single Dose of Lithium Promotes Recovery from Cisplatin-Induced Acute Kidney Injury

Hui Bao, Yan Ge, Lance D. Dworkin, Ai Peng, Rujun Gong. Nephrology, Brown Univ, Providence, RI; Nephrology, Shanghai Tenth People’s Hospital, Shanghai, China.

Background: Evidence suggests that glycogen synthase kinase (GSK3)β is a key regulator of tissue injury, repair and regeneration. Lithium, a selective inhibitor of GSK3β and FDA approved first-line mood stabilizer, has been well known for its pro-reparative activities in multiple organ systems. However, its effect on renal repair following acute kidney injury (AKI) remains uncertain.

Methods: The role of GSK3β in post-AKI kidney repair was examined in a murine model of cisplatin-induced nephrotoxicity and in cultured renal proximal tubular cells in vitro.

Results: In a murine model of cisplatin-induced AKI, delayed treatment with a single low dose of lithium accelerated recovery of kidney function, promoted repopulation of renal tubular epithelia and improved kidney repair. This was associated with reduced GSK3β activities and elevated expressions in renal tubular epithelia of pro-potentiating molecules, including Cyclin D1, c-Myc and HIF-1α. In cultured renal tubular cells, GSK3β activity was transiently repressed by cisplatin followed by a prolonged upregulation. Rescue treatment with lithium reduced GSK3β activity, enhanced nuclear expression of Cyclin D1, c-Myc and HIF-1α, and accelerated cellular proliferation. Moreover, ectopic expression of a kinase dead mutant of GSK3β enhanced the expression of Cyclin D1, c-Myc and HIF-1α and amplified cellular proliferation following cisplatin injury, reminiscent of the effect of lithium; whereas forced expression of a constitutively active mutant of GSK3β abrogated the lithium’s effect, suggesting that GSK3β inhibition is sufficient and indispensable for lithium’s pro-reparative effect. Mechanistically, GSK3β colocalized and physically interacted with Cyclin D1, c-Myc and HIF-1α in renal tubular cells. In silico analysis revealed that Cyclin D1, c-Myc and HIF-1α all harbor putative GSK3β consensus phosphorylation motifs, inferring a GSK3β directed phosphorylation and subsequent degradation of these molecules.

Conclusions: Pharmacological targeting of GSK3β by lithium might represent a novel therapeutic strategy to improve renal salvage after AKI.

Funding: NIDDK Support
Conclusions: Our results demonstrated that besides miR-21, the miR-17/106 family is additionally activated during the maintenance and recovery phases of renal I/R. A correlation between these miRNAs warrant further investigations. Cyclooxygenase-1 staining revealed recovery of renal tubular epithelium. Thus, our results suggest that these miRNAs may be involved in the regeneration processes and could represent possible therapeutic tools in the treatment of I/R. Support: OTKA/K81972.

TH-PO089

Activation of Tim-3/Gal-9 Pathway Promotes the Proliferation of Foxp3+ Treg in Mice with Renal Ischemia Reperfusion Injury

Yamei Wang, Yuhong Tao. Dept. of Pediatrics, West China Second Univ Hospital, Sichuan Univ, Chengdu, Sichuan Province, China.

Background: Foxp3 regulatory T cells (Treg) participate in the repair of renal ischemia reperfusion injury(IRI). Other studies have shown that galectin-9 (Gal-9), a beta galactoside binding mammalian lectin, binds to the regulatory molecule T cell immunoglobulin mucin-3 (Tim-3) on T cells and regulates immune responses by increasing Foxp3+ Treg. This study is to investigate whether Tim-3/Gal-9 pathway promotes the proliferation of Foxp3+ Treg in mice with renal IRI for the first time.

Methods: The left renal pedicle was clamped in C57BL6 male mice for 45 min, followed by reperfusion. Expression of Gal-9 was detected by qRT-PCR, immunohistochemistry staining and Western blot. TIM-3 in kidney mononuclear cells (KMNCs) was determined using qRT-PCR and flow cytometry. The expression of Foxp3 mRNA in CD4+ T cells and expression of Foxp3 mRNA were measured with flow cytometry and qRT-PCR, respectively. To explore the influence of Tim-3/Gal-9 pathway on the proliferation of Foxp3 Treg and the protection from renal IRI, recombinant adenovirus-associated virus (RAAV) carrying Gal-9 was injected into mice two days before kidney IRI surgery in order to overexpress Gal-9 and activate Tim-3/Gal-9 pathway. Then, the percentage of Foxp3+ Treg cells, the expression of Foxp3 mRNA and cytokines were evaluated at day 3, 10 and 21.

Results: The expression of Gal-9 and Tim-3 in the injured kidney at day3,10 and 21 increased significantly compared with that in injured kidney at day 1 or baseline. The percentage of Foxp3+ Treg in CD4+ T cells and expression of Foxp3 mRNA were upregulated with time. Mice treated with RAAV carrying Gal-9 were significantly protected from renal IRI. Overexpression of Gal-9 decreased the levels of inflammatory cytokines (TNF-alpha and IFN-gamma) and increased the levels of cytokines (IL-10 and TGF-beta) in injured kidney. Furthermore, the proportion of Foxp3+ Treg cells and the level of Foxp3 mRNA in injured kidney were significantly higher than those in uninjured kidney or adenovirus group.

Conclusions: Tim-3/Gal-9 pathway involves the proliferation of Foxp3+ Treg in mice with renal IRI. Gal-9 becomes a novel potential immunotherapeutic target in renal IRI.

Funding: Government Support - Non-U.S.

TH-PO090

Thrombospondin-1 Mediates ECFC Recruitment after Renal Ischemia-Reperfusion Injury

Tim-Jung Jeon, Noov Simon Paul Perumpaneni, Jan Studnicka, Vladimir T. Todorov, Benz Hohenstein, Christian Hug. 1Dept of Internal Medicine III, Div of Nephrology, Dresden, Germany; 2Dept of Internal Medicine III, Div of Nephrology, Dresden, Germany; 3Dept of Internal Medicine III, Div of Nephrology, Dresden, Germany; 4Dept of Internal Medicine III, Div of Nephrology, Dresden, Germany; 5Dept of Internal Medicine III, Div of Nephrology, Dresden, Germany.

Background: Thrombospondin-1 (TSP-1) is an important mediator of renal I/R injury. Induced early on TSP-1 as an anti-angiogenic molecule might not only relate to tubular injury, but could also mediate indirect-progenitor cell driven-effects. Various studies suggest a role of mainly circulating EPC following I/R injury. The present study investigated the role of TSP-1 in the recruitment of ECFCs after I/R in the mouse kidney.

Methods: Unilateral I/R (25min) was induced in left kidneys (after right kidney nephrectomy) of 25 C57Bl6 and 12 TSP-1 deficient mice. Five mice served as healthy controls. Tissues were harvested 4, 24 and 72 hours after I/R and processed for histology. CD34+/Flk-1+/CD133+/CD45-ECFC and CFU were measured using FACS analysis.

Results: 1/R injury led to profound changes in renal morphology after 24h in TSP-1 deficient and WT mice. PAS staining showed less tubular damage in TSP-1 deficient mice (by scoring, p<0.01). Compared to WT kidneys, ECFCs were significantly decreased in TSP-1 deficient mice after 24 and 72h (24h=p<0.01;72h=p<0.001), matching histological differences. Surprisingly, differences in renal ECFC numbers could be detected after 4 hours of I/R, which is before the occurrence of major histological changes (TSP-1−/− vs WT p<0.05).

Conclusions: TSP-1 deficiency protects from I/R injury. Less this ECFC were recruited, either as consequence or cause of histological differences in TSP-1−/− vs WT mice. The early (4h) difference supports a direct link between TSP-1−/− and progenitor cell activation. Further studies should reveal the concise biochemical interactions.

Funding: Private Foundation Support

TH-PO091

The Hemodynamic Correlates of “Renal Counterbalance” Phenomenon in Conscious Rats

Aaron J. Polichnowski, Hector Liceas-Vargas, Rongpei Lan, Maria M. Picken, Jianrui Long, Geoffrey A. Williamson, Karen A. Griffin, Manjari A. Venkatachalam, Anil K. Bidani. 1Medical, Edward Hines Jr VA Hospital and Loyola Univ Chicago, Hines, IL; 2Medicine/Pathology, Loyola Univ Chicago, Maywood, IL; 3Pathology, Univ of Texas Health Sci Ctr, San Antonio, TX; 4Electrical and Computer Engineering, Illinois Institute of Technology, Chicago, IL.

Background: In contrast to bilateral ischemia reperfusion (IR) injury, unilateral IR (UIR) results in progressive kidney fibrosis and atrophy. However, contralateral nephrectomy (NX) even 2wks after UIR results in striking structural and functional recovery (Circ Res, 1980; 46:440) through poorly understood mechanisms.

Methods: Chronically instrumented male Sprague-Dawley rats (BP radiotransmitters, transeceral renal flow probes) underwent left RBF and 24 hr GFR measurements (FITC inulin, osmotic minipumps) at 2 weeks after 40 min of left UIR or Sham UIR. Both UIR and control rats underwent NX or sham NX at 15 days after UIR. After multiple RBF and GFR measurements, rats were sacrificed at 4wks after UIR (2 wks after NX).

Results: Mean/SE UIR was associated with a persistent reduction (P<0.05) in RBF (Fig 1a). NX increased RBF within 1-2 days in a pattern qualitatively similar to that in sham IR rats (Fig 1b). Although differences in total GFR were not seen in the absence of NX (Fig 1c), the pattern of recovery after NX was similar to RBF (Fig 1d).

Striking beneficial effects (P<0.05) of NX were also seen on left kidney weights after UIR (10.4±0.9 vs 4.7±0.3 g/kg without NX). Compensatory hypertrophy was also seen in sham UIR rats (5.7±0.2 vs 4.2±0.2 g/kg), but of lesser magnitude.

Conclusions: These data indicate that NX associated hemodynamic improvements occur early and likely play a role in subsequent structural recovery after UIR (Am J Physiol Renal, 2012, 302:1210).

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

TH-PO092

Tissue Engineering of Microvessels to Perfuse Isolated Glomeruli In Vivo

William Gee Chang, 1 Alessia Fornoni, 2 Jordan S. Pober, 3 Medicine, Yale Univ, New Haven, CT; 4Medicine, Univ of Miami, Miami, FL; 5Immunobiology, Yale Univ, New Haven, CT.

Background: More than 400,000 patients receive treatment for end stage renal disease in the United States. Kidney transplantation is the most effective therapy, but there are not enough donor organs to meet the rising demand. Tissue engineering of a kidney is a potential solution to this organ shortage. However, kidneys are more anatomically complicated than other tissues that have been produced by biotechnologists because they contain structures such as glomeruli and tubules that are composed of distinct cell types with distinctive relationships within the vascular system.

Methods: Our laboratory has previously reported that human umbilical vein endothelial cells transduced with the anti-angiogenic protein Bcl-2 (designated Bcl-2-EC) can spontaneously organize into perfused microvessels within type I collagen/fibronectin gels when implanted in immunodeficient mice. As a first step in tissue engineering of renal microvasculature, we combined Bcl-2-ECs with microdissected intact whole rat glomeruli in type I collagen gels and implanted them within immunodeficient mice.

Results: We observed that rat glomeruli remained viable for up to two weeks, and maintained podocyte specific nephrin staining. Using GFP-expressing rat glomeruli and intravital rhodamine dextran injection, we saw that ~30% of glomeruli were perfused by microvessels derived from Bcl-2-ECs. However, in the absence of Bowman’s capsule and tubular outflow, several glomeruli lost their glomerular capillary tuft morphology and became perfused capillary plexi. Transmission electron microscopy revealed endothelial swelling, loss of endothelial fenestrae, and podocyte foot process effacement after two weeks.

Conclusions: Anastomosis of capillaries derived from Bcl-2-ECs with isolated glomeruli provides proof of concept that self-assembled microvessels can perfuse specialized organ structures. We hypothesize that addition of tubular outflow would
ameliorate some of the morphological changes observed, and that the tissue engineered constructs described here could be further modified to engineer functional kidney tissue in the future.

**Funding:** Other NIH Support - Clinical and Translational Science Award KL2-RR024138 from the National Center for Advancing Translational Science; National Institutes of Health (NIH) Grants R01-HL085416

**TH-PO093**

**Development of the Kidney Peritubular Microvascular Niche *Ex Vivo***

Giovanni Ligresti,1 Takahide Abaratani,1 Sijie Sun,2 Kimberly A. Muczynski,1 Susan K. Anderson,3 Jonathan Himmelfarb,4 Jeremy Stuart Duffield,4 Ying Zheng,1 1Dept of Medicine, Univ of Washington, Seattle; 2Dept of Bioengineering, Univ of Washington, Seattle.

**Background:** Dysfunction or loss of peritubular capillaries (PTCs) features chronic kidney disease and fibrosis where pericytes (PCs) associate with the endothelium and become scar-forming myofibroblasts, which promote the formation of scar tissue. Much remains unknown about the interactions between endothelial cells (ECs) and pericytes in normal and injured kidney, partially because kidney vasculature has complex architecture, flow dynamics and pleiotropic functional properties. Studies are also limited due to the lack of *ex vivo* models that recapitulate such a biological complexity, particularly in human kidney. In this study we overcome these challenges by engineering a microphysiological system (MPS) for the kidney peritubular microvascular niche *ex vivo* to study the interactions between ECs and PCs under varying flow conditions.

**Methods:** We isolated kidney microvascular endothelial cells (KMECs) and pericytes from both mouse and human kidneys by flow cytometry, and seeded them in the engineered MPS.

**Results:** KMECs self-organize into a vascular network resembling kidney blood microvessels. Confocal microscopy shows a continuous endothelial monolayer with CD31 and VE-cadherin staining at cell contacts. Scanning EM reveals that KMECs have a homogenous endothelium. The system should allow identification of key molecular mechanisms that can be exploited for therapeutic purposes in kidney fibrosis.

**TH-PO094**

**A Bioinformatics Approach Identifies an Intricate Transcriptional Network Regulating the Uromodulin Gene**

Rainahees Srivastava,1 Radmila Micanovic,1 Sarath Chandra Janga,1 Tarek M. El-Achkar2 1School of Informatics, IUPUI, Indianapolis; 2School of Medicine, Indiana Univ and Indianapolis VA, Indianapolis.

**Background:** Uromodulin is a glycoprotein uniquely produced by the kidney. Although its expression is thought to modulate renal homeostasis, the set of sequence specific transcription factors (TFs) which regulate the Uromodulin gene (UMOD) and their upstream binding locations are not well characterized. Our study aims to build a high resolution map of the transcriptional regulation of UMOD.

**Methods:** Phylogenetic foot-printing on the upstream regulatory regions of a diverse set of human UMOD orthologs was performed using MEME-SUITE. This allowed the identification of 10 high confidence conserved binding motifs (BMo) and the corresponding position specific weight matrices. We further analyzed the predicted BMs by TOMTOM, which identified TFs likely to bind these discovered motifs. Predicted TFs were then integrated with existing protein-protein interaction databases like Biogrid and tissue-specific protein expression resources to delineate the important regulators controlling the expression of UMOD.

**Results:** Based on the reliable set of BMo in the upstream regulatory regions of UMOD (Fig. 1a), we build a high confidence list of transcription factors that could potentially bind to these discovered motifs such as GATA3, HNF1, SP1, SMAD3, RUNX2 and KLF4. Construction of a manually curated protein interaction network between the predicted TFs controlling UMOD regulatory region in human revealed several highly connected TFs such as GATA3, HNF1, SP1, SMAD3, RUNX2 and KLF4.

**Conclusions:** Our findings will form a roadmap for understanding the regulation of Uromodulin expression in health and disease.

**TH-PO095**

**The Shape of the Curve of Protein Concentration as a Function of Distance across the Glomerular Basement Membrane: Analysis and Implications for Fundamental Mechanisms**

Douglas L. Somers,1,2 Univ of Iowa, Iowa City, IA; 1Iowa City VA, Iowa City, IA.

**Background:** Fujigake et al (K1 1993) measured protein distribution across the Glomerular Basement Membrane (GBM) using immuno-gold labeling of in-situ fixed glomeruli. Transferrin concentration declines steeply from endothelial to epithelial interfaces, whereas albumin concentration increases to a peak (albumin peak anomaly) partway through the GBM, then declines steeply to low concentrations at the epithelial interface. These results also demonstrate the podocyte paradox -podocytes are important to prevent proteinuria, but proteins never get to the podocyte. No model of GBM protein transport has yet explained the variation between different proteins, the steepness of protein concentration decline, the podocyte paradox, nor the albumin peak anomaly.

**Methods:** Protein concentrations are calculated from probability distribution functions. Assumptions include: i. Endothelial glyocalyx (EG) is the initial barrier to protein translocation, providing an energy trap for some proteins (i.e. albumin), but not others (i.e. transferrin), ii. Proteins escape from EG to GBM with a thermal energy distribution, but those proteins with binding to EG are emitted with less energy, and iii, proteins emitted from the EG travel a certain distance (depending on emission energy) into GBM under constant endothelial-towards-endothelial acceleration, so turning around and returning to the EG.

**Results:** This model reproduces the variation between different proteins, the albumin peak anomaly, and the sharp decline in concentration toward the epithelial interface. Protein deceleration in the GBM represents a decrease in protein momentum. There are few realistic physical mechanisms available to change protein momentum; momentum transfer from a different molecular species emitted from the podocyte provides a force and resolves the podocye paradox.

**Conclusions:** The results of Fujigake et al suggest: i. Endothelial glyocalyx is the initial protein barrier in the glomerular capillary wall for some, though not all, proteins, ii. The glomerulus appears to be a diffusion pump.
recirculated (40mL), while dialysate (140mEq NaCl) was recirculated in a counter-current fashion (40mL). Dialysis was performed with zero transmembrane pressure at Qd=Qf=30mL/min. Solute clearance (K) was calculated by fitting concentrations measured hourly for 4h (n=3) to an exponential decay function: C(t)=C_{0}e^{-t/\tau}; C(t): concentration at time t; C_{0}: initial concentration; t: time; V: volume. Platelet adhesion and activation on SMF were evaluated by immunohistochemistry (IHC) after flowing heparinized porcine blood (~1hr post-collection) for 4 hours at 5ml/min.

**Results:** The mini-dialyzer was tested without complications for a total of ~24 hours and exhibited ~4 mmHg pressure drop. Creatinine and urea clearances were calculated to be 49.4±1.9, 73.0±2.2 mL/min/1.73m² (artificial serum) and 38.6±0.7, 67.2±1.5 mL/min/1.73m² (blood), respectively. There was no significant change in albumin. Diffusion of solutes into dialysate was confirmed. Single-pass changes were below the level of detection. IHC showed a qualitative reduction in platelet activation on PEG-coated SMF and no thrombi were visualized after 4 hours.

**Conclusions:** These preliminary results confirm that SMF exhibit clearance consistent with mathematical models, while PEG coatings offer a hemocompatible interface for blood flow.

**Funding:** NIDDK Support, Other NIH Support - NIH T32 Training Grant; NIH Quantum Grant

**TH-PO097**

**Multi-Detector Computed Tomography to Identify Device Defects and Failure Modes in an Implantable Silicon Hemofilter**

Steven Kim,1,2 Olufolade G. Olorunosola,1 Charvi Shetty,1 James A. Heller,2 Zohora Iqbal,1 Rishi Kant,1 Steven Hettis,1 Youngho Seo,3 Mark Wilson,1 Shuvo Roy,1 Nephrology, UCSF; 2Bioengineering, UCSF; 3Radiology, UCSF; 4Nephrology, Vanderbilt.

**Background:** New innovations in membrane technology using microelectromechanical systems techniques have led to the development of a silicon nanopore membrane (SNM) based hemofilter for use in an implantable bioartificial kidney. Such a device will require non-invasive imaging methods to monitor device functionality, identify potential problems, and detect failure modes. This study aims to address these challenges by developing imaging techniques to non-invasively visualize a hemofilter prototype.

**Methods:** The hemofilter was constructed with a parallel plate design (3.8 x 1.8 x 8 cm). A titanium plate measuring 3.8 x 0.3 x 6.5 cm with a blood path height of 2.4mm was mounted with SNM. A bottom plate without SNM served as an internal control. The non-blood-contacting plates were constructed from aluminum. A peristaltic pump infused iodinated contrast through the blood paths (1-20mL/min) and deionized water through the filtrate path (0.2mL/min). Serial imaging was performed using multi-detector computed tomography (MDCT) before and after contrast infusion. Images (140kVP & 250mAs) were acquired in a plane parallel to the direction of flow and reformatted in orthogonal planes.

**Results:** Several potential device-related malfunctions were correctly identified using MDCT. Qualitative assessment of contrast in the blood path showed areas of inhomogeneous flow. Trapped loculated gas was easily visible and allowed for localization and tracking without disassembly. Microscopic leaks were detectable, manifesting as active extravasation of contrast from the device. Finally, membrane fracture leading to device failure was also confirmed using MDCT.

**Conclusions:** Despite the challenges of imaging a predominately metallic object, we were able to non-invasively image flow and identify device defects within a hemofilter prototype. The imaging method allows for internal evaluation of the device without requiring disassembly, which will be invaluable in future studies for the development of the bioartificial kidney.

**Funding:** Other NIH Support - T32 Training Grant; NIH R01 Biocompatibility of Implantable Renal Replacement Devices

**TH-PO098**

**Therapeutic Plasma Exchange Using High Cut-Off Membrane Plasma Separator**

Atsushi Ohkubo,1 Naoki Kurashima,1 Ayako Nakamura,1 Satoko Miyamoto,1 Hiroshi Seshima,1 Soichiro Iimori,2 Naofumi Yui,2 Tatemitsu Rai.2 1Dept of Clinical Engineering, Tokyo Medical and Dental Univ; Japan; 2Dept of Nephrology, Tokyo Medical and Dental Univ, Japan.

**Background:** Therapeutic plasma exchange (PE) using albumin solution as replacement fluid is considered a life-saving treatment in acute exacerbation of inflammatory demyelinating disorders of the central nervous system (CNS-IDDs). Though it is important to remove IgG for the treatment of inflammatory demyelinating disorders of the CNS, the standard method is albumin plasma exchange. However, albumin plasma exchange has limitations in terms of cost and availability.

**Methods:** We performed a prospective observational study of patients treated with high cut-off plasma membrane separator (high cut-off group) or the conventional type of membrane separator (control group). We recruited 18 patients, 11 patients in the high cut-off group and 7 patients in the control group. We measured the rate of removal of IgG and complement C3 during PE, and the rate of improvement of MRI T2-weighted lesions.

**Results:** The removal rates of IgG and complement C3 were significantly higher in the high cut-off group compared with the control group (1.21±0.01 vs 0.87±0.09 plasma volume, respectively). The rate of improvement of MRI T2-weighted lesions was also significantly higher in the high cut-off group compared with the control group (2.1%±1.6% vs 0.18%±0.22%, respectively).

**Conclusions:** The high cut-off membrane plasma separator with smaller pore size is an effective method for removing IgG in patients with inflammatory demyelinating disorders of the CNS, and the rate of removal of IgG and complement C3 were significantly higher in the high cut-off group compared with the control group.
TH-PO101
Monitoring Intravascular (Vb), Interstitital (Vi), and Intracellular (Vc) Volume Changes during Hemodialysis (HD) in Patients (pts) with End-Stage Renal Disease (ESRD) in Chronic Out-Patient (CU) and Acute In-Patient (AU) Unit Settings

**Background:** A multi-frequency electrical impedance spectroscopic (EIS) technique was developed that enables non-invasive measurement of compartmental volume (CV) changes during HD. The aims: (1) to evaluate the feasibility & precision of EIS to quantify acute changes in Vb, Vi, & Vc during HD, & (2) to assess differences in CV changes in relation to the total amount of fluid removed (Vt) in CU & AU.

**Methods:** Using EIS, we evaluated changes in Vb, Vi, & Vc in ESRD pts in CU & AU. Each HD was completed according to the nephrologist’s prescription. Volume changes were obtained by analysis of electrical impedance spectra taken on the left calf of each pt at approximate 1-min intervals throughout each HD by a quadrangular EIS device as previously described. (Montgomery, et al., Med. Biol. Eng. Comput 3 April 2013).

**Results:** Table 1 shows the mean volumes of fluid removed during HD from Vb, Vi, Vc, and Vt in CU & AU. Table 2 shows the mean pre & post HD CVs & the associated % distributions in CU & AU. A negative value indicates a gain in volume.

<table>
<thead>
<tr>
<th>AU (n=22)</th>
<th>CU (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vb (%)</td>
<td>Vc (%)</td>
</tr>
<tr>
<td>21 +/-12</td>
<td>13 +/-13</td>
</tr>
<tr>
<td>12 +/-8</td>
<td>11 +/-12</td>
</tr>
<tr>
<td>3/+ -8</td>
<td>38 +/-12</td>
</tr>
<tr>
<td>9 +/-4</td>
<td>17 +/-13</td>
</tr>
</tbody>
</table>

**Conclusions:** Changing patterns of CV changes differed between CU & AU. 2-AU pts retained a larger % of total fluid in the Vi & Vc compartments. 3-Vc increased during HD in pts at both centers. The EIS technique was able to track acute fluid volume changes in the 3 principal fluid compartments of ESRD pts’ calves during HD. Results indicate that Vc in the monitored calves tended to increase during HD at both centers as overall cv fluid volumes were being reduced.

**Funding:** Other NIH Support - SBIR

TH-PO102
Use of the Hemodialysis Procedure to Measure Individual Pharmacokinetics

**Background:** Hemodialysis is an underappreciated opportunity to assess individual pharmacokinetics. As dialysis is started and stopped, drug clearance suddenly changes, differing drug equilibration between pharmacokinetic compartments. Individual response to this perturbation reveals individual pharmacokinetics. Here, we utilize linear systems theory to create individualized pharmacokinetic models from intradialytic data.

**Methods:** A simple two compartment pharmacokinetic model was simulated, incorporating a patient receiving regular drug doses and one dialysis session. Equally timed samples of the plasma concentration and dialysate during the transient response of the dialysis perturbation were extracted from the dataset. The samples were used to estimate a linear systems model of the patient. The model was then excited with a signal representing the original dosing schedule of the patient. The resulting output signal was compared with the original dataset to assess prediction accuracy. In addition, the effect of decreasing the sample size and adding varying levels of white Gaussian noise were studied to evaluate the robustness of our approach.

**Results:** In ideal cases of large sample sizes with little noise, the produced linear systems model was shown to reproduce the simulated data almost exactly. In simulations of more real-world scenarios, robust estimates in the presence of noise were still achievable with as few as 10 samples.

**Conclusions:** Our simulations suggest that the dialysis procedure can be used to create individualized pharmacokinetic models of the patient. By reformulating the effect of dialysis in the language of linear systems, one could easily characterize a particular patient’s pharmacokinetics and make reasonable predictions of the patient’s drug levels over time.

**Funding:** Pharmaceutical Company Support - Nipro
from normovolemia (CRI=1) to decompensation (CRI=0). We hypothesized that changes in CRI would anticipate future IME in chronic end-stage renal disease (ESRD) patients undergoing HD.

Methods: Demographic, clinical information and continuous measurements of CRI, blood pressure (BP) and heart rate (HR) were collected from chronic ESRD patients during HD. IME were defined as a decrease in systolic BP or symptom (e.g. cramps, dizziness) triggering intervention. Univariate and multivariate logistic regression generalized estimating equation models were designed to evaluate correlation with future IME.

Results: 85 ESRD patients had CRI and HR recorded during HD; 56 also had continuous BP recorded. There were 44 IME among 53/85 (38%) patients. There were no differences in age, gender, race, weight gain, duration of treatment, volume of ultrafiltrate removed, heart disease or diabetes status among patients who sustained an IME versus those who were event-free (p<0.05). In multivariate analysis, a 0.15 decrease in CRI over a 15-minute interval was independently associated with an IME in the upcoming 15 minutes (4.076, 95% CI 1.748-9.508, p=0.003), whereas 10-point changes in HR and BP were not (p<0.05). Patients with this type of change in CRI were 4 times more likely to experience an IME.

Conclusions: Decreasing CRI is associated with future IME. Demographic, clinical and traditional vital sign parameters did not correlate with IME. CRI is a novel, noninvasive parameter that is able to anticipate and may help to prevent intradialytic morbidity events in chronic ESRD patients who undergo HD.

TH-PO105

Simulation and Validation of Flow in a Hemofilter Device
Amanda Buck,1 Daniel Colvin,1 Mark S. Goodin,2 Joseph J. Groszek,1 Shuvo Roy,1 William Fissell.1

Background: When designing biomedical devices for use in vasculature, it is vital that flow through the device not initiate or exacerbate blood clotting, which may lead to device failure. Computational fluid dynamics (CFD) simulations can predict pathophysiologically relevant variables; however, they require assumptions related toflow conditions. In vitro studies require fewer assumptions and can be used to validate CFD results. The purpose of this study was to compare MR-measured and CFD-simulated flow fields in a hemofilter device.

Methods: Steady flow in the device was measured using phase contrast MR (PCMR). The PCMR data were acquired using a 9.4 T Varian scanner. Citrated bovine blood was used. The pipeline is a robust tool and provides a means to evaluate the impact of WSS on AVF maturation. Correlational analyses of WSS and other hemodynamic profiles with lumen area changes, in a large number of patients from our multi-center study, should provide novel insight into factors that contribute to AVF failure and success.

Funding: Other NIH Support - NIDDK

TH-PO107

A Novel Method for High-Resolution Characterization of Vein Deformation under Arterial Blood Pressure
Yan-Ting E. Shiu,1 Arnold David Gomez,1 Huan Li1, Ilya S. Zhuplatov,1 Alfred K. Cheung,1 Edward Hsu.1

Background: Hemodialysis arteriovenous grafts often fail due to neointimal hyperplasia (NIH) at the venous anastomosis (VA). An understanding of the hemodynamic factors that lead to abnormal wall deformation and NIH in artery is needed. Abnormal wall deformation at the VA induced by increased hydrostatic blood pressure may play a role in the focal nature of NIH formation, but a clear correlation has not yet been demonstrated. We have developed a new method to characterize venous wall deformation, laying the foundation to investigate this correlation.

Methods: Techniques for characterizing arterial wall deformation are seldom useful to measure changes in the thickness of thin venous wall, which are often ≤ 100 μm - below the resolution of conventional MRI or ultrasound. Our method uses micro-computed tomography (μCT) and deformable image registration to measure strain. A μCT-compatible device was built to image a freshly explanted porcine vein under hydrostatic pressure (0-160 mmHg). An iodine-based staining protocol was optimized to provide soft-tissue contrast for visualization while preserving the tissue’s morphological structure. μCT images (17 μm resolution) were segmented to reconstruct the vein (Fig. 1, top), which was used to calculate the strain.

Results: Best contrast and negligible tissue shrinkage of the vein was obtained using 10% Lugol solution and a 3-hour soaking. The strain map (Fig. 1, bottom) shows highly heterogeneous strain values in the vein, in addition to complex anatomical features such as non-uniform wall thickness and a valve.

Conclusions: We have developed a robust method to assess the strain of thin vein under hydrostatic pressure. Serial analyses using this method should illuminate the relationship between early wall deformation and subsequent focal NIH formation and have implications in the design of anti-NH strategies for vascular accesses.

Funding: Other NIH Support - NIDDK Support

TH-PO108

Correlation between Wall Shear Stress and Subsequent Lumen Area Change at Venous Anastomosis Is Different from That at Arterial Anastomosis
Yan-Ting E. Shiu,1 Daniel B. Pike,1 Christi M. Terry,1 Yong He,2 Huan Li1, Ilya S. Zhuplatov,1 Alfred K. Cheung,1 Edward Hsu.1

Background: Neointimal hyperplasia (NIH) occurs much more commonly at the venous anastomosis (VA) than at the arterial anastomosis (AA) of arteriovenous grafts (AVG). Aberrant wall shear stress (WSS) may play a role in increased susceptibility of the vein to NIH formation. We examined this hypothesis by comparing the WSS and subsequent lumen area between the venous and arterial anastomoses in a swine model of AVG stenosis.

Methods: AVG were implanted between the common carotid artery and external jugular vein in swine. At 1, 2, 3, or 6 wk (n=5 at each wk) after graft implantation, contrast-free optical coherence tomography (OCT) images were acquired and used to calculate the WSS and NIH formation. Correlational analyses of NIH and other hemodynamic profiles with lumen area changes, in a large number of patients from our multi-center study, should provide novel insight into factors that contribute to AVF failure and success.

Funding: Other NIH Support - NIDDK Support
to assess the lumen geometry and blood inflow and outflow rates. These parameters were then used for computational fluid dynamics simulations. WSS magnitudes and lumen area changes were calculated for 4 cm lengths of arterial and venous segments, upstream and downstream from their respective anastomoses.

**Results:** Although WSS at wk 3 was higher in the artery than in the vein (116 ± 57 vs. 36 ± 21 dyne/cm²; p<0.05), subsequent lumen area changes from wk 3 to wk 6 were largest in the vein (44 ± 35 vs. 12 ± 4 mm²; p<0.05). No significant correlation was found in the artery between WSS at wk 3 and lumen area changes from wk 3 to wk 6 (r=0.12, p=0.50). In contrast, a biphasic correlation was found in the vein: when WSS was low (<20 dyne/cm²) at wk 3, lumen area increased from wk 3 to wk 6 (r=0.98; p<0.05); when WSS was high (>40 dyne/cm²) at wk 3, lumen area decreased from wk 3 to wk 6 (r=-0.93; p<0.05); no correlation was found where WSS was in the 20-40 dyne/cm² range (r=0.47; p=0.69).

**Conclusions:** The observation of differential WSS-lumen area correlations between the vein and the artery is novel. The finding of a biphasic relationship between early WSS and later lumen area change in AVGs is also novel. These differential hemodynamics relationships enhance our understanding of the pathogenesis of NH in AVG and have implications in the design of anti-NH strategies.

**Funding:** Other NIH Support - NIDDK

**TH-PO109**

**Antimicrobial Peptide Coating Prevents Bacteria Survival and Protein Fouling on Catheter Materials**


**Background:** Catheter related bacteremia associated with dialysis access is a major cause of mortality and morbidity. Technologies to prevent infection that will not select for resistant bacteria are needed. A catheter coating containing a cationic antimicrobial peptide (CAP) was tested for its effect on bacteria attachment and survival, fibrinogen (FB) deposition, and CAP release profile.

**Methods:** Polyurethane (PU) discs coated with a CAP/polymer formulation were tested for bacterial attachment and survival. Samples were challenged with 5x10⁷ cfu/mL when WSS was high (>40 dyne/cm²) at wk 3, lumen area decreased from wk 3 to wk 6 larger in the vein than in the artery (44 ± 35 vs. 12 ± 4 mm²; p<0.05). No linear correlation and ascending loops of Henle and distal tubules) and collecting ducts by laser

**Results:** Within 2 hrs, the CAP/polymer coating resulted in a 3 log reduction in bacteria attachment relative to uncoated PU followed by near complete sterilization of samples by 96 hrs in HIS (Figure 1). Placebo coated (polymer only) samples showed nearly 2 log reduction in bacteria attachment at early incubation times in HIS (Figure 1), and a 70% reduction in FB adsorption by 1 week. Sustained release of CAP at therapeutically effective levels was confirmed by RP-HPLC over a period exceeding 1 week.

**Conclusions:** The formulated polymer coating displayed improved non-fouling properties and reduced FB deposition. Incorporating CAP and tailoring its release profile further led to a significant reduction in bacteria attachment and survival. Antimicrobial coatings often facilitate protein deposition, making it difficult to achieve a nonfouling surface. This CAP/polymer formulation provides a promising approach to reduce both infection and occlusion of catheters without contributing to development of drug resistant bacteria.

**Funding:** NIDDK Support

**TH-PO110**

**Proteomic Analysis of Nephron Segments of Formalin-Fixed Paraffin-Embedded Human Kidney Tissues**

Tadashi Yamamoto,1 Shigeru Miyazaki,2 Hirokiyo Fujinaka,1 1Dept of Structural Pathology, Institute of Nephrology, Niigata Univ, Niigata, Japan; 2ShinraKaSen Hospital, Japan.

**Background:** Nephrons are the functional units of the kidneys and consist of several parts (glomerulus, proximal tubule, descending and ascending loop of Henle and distal tubule) connected to collecting ducts. Knowing of proteome profile of each nephron segment will contribute to complete understanding of kidney functions.

**Methods:** We separated nephron segments (glomeruli, proximal tubule, descending and ascending loops of Henle and distal tubules) and collecting ducts by laser microdissection of FFPE-human kidney sections after immune-labeling of each part with antibodies against unique proteins in each part. Tissue sections of total area of ~1 mm² each were digested with trypsin after autoclave treatment (On-site direct digestion, OSDD method). Peptides were collected from the sections and purified by C18 Stage-Tips and analyzed by LC-MS/MS (Thermo Orbitrap LTQ) and proteins were identified by Mascot with FDR less than 5%.

**Results:** More than 1000 proteins were identified by a single MS analysis of each sample and proteins uniquely expressed in each nephron segment were selected: glomerulus; 153, proximal tubule; 306, distal tubule; 58, and collecting duct; 40. Gene Ontology annotation analysis showed that the most enriched cellular components were cytoskeleton proteins in the glomerulus, cytoplasm proteins in the proximal tubule, mitochondrion proteins in the descending and ascending loop of Henle, and cytoplasmatic part proteins in the collecting duct. The protein quantity was compared by label-free normalized spectral index. Among the uniquely expressed proteins the highest were proteins translated from S100A6 gene in the glomerulus, MPDZ in the proximal tubule, HIST1H2B in the distal tubule, and MAST4 in the collecting duct. The protein quantity of each protein segment demonstrated their significant features and provided useful knowledge of their functions.

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

**TH-PO111**

**MRI Characterization of UUO Kidney Injury Using CEST and MTR Techniques**

Feng Wang,12 Keiko Takahashi,12 Zhongliang Zu,1 Raymond C. Harris,1 Christopher Chad Quarles,12 Takamune Takahashi.1 Vanderbilt Univ Institute of Imaging Science; 2Vanderbilt O'Brien Kidney Disease Center, Nashville, TN.

**Background:** Chemical exchange saturation transfer (CEST) and magnetization transfer (MT) MR imaging enables the assessments of metabolites with exchangeable protons and macromolecules in tissues, respectively. Since these techniques are poorly applied to kidney disease, we evaluated its ability in sensing kidney injury/progression using mice with unilateral ureteral obstruction (UUO).

**Methods:** MRI protocols were optimized on Agilent 7T MRI. MT ratio (MTR) was measured based on a 2D RF-spoiled gradient echo sequence. Off-resonant RF irradiation was accomplished using Gaussian RF pulses (6000 Hz, 12ms), and a control scan was performed without MT pulses. CEST was performed using a continuous wave CEST sequence (a 8.0 s irradiation pulse followed by a multishot SE-EPI readout). A control scan was performed by setting the RF offset to 20000 Hz. MTR_max was acquired using asymmetric analysis. The CEST and MTR maps were generated for UUO and sham-operated mice at day 1, 3, and 6 after surgery.

**Results:** 1. MTR was significantly reduced in inner medulla (IM) and papilla (P) in UUO day 3 kidneys, while the changes in cortex (C) and outer medulla (OM) were minimum. At day 6, the IM and P of UUO kidneys showed remarkably reduced MTR, perhaps due to severe cell injury or death. At this stage, MTR was also slightly decreased in C and OM in UUO kidneys. 2. CEST: The T2 spectrum of IM and P in day 3 and 6 UUO kidneys was highly asymmetric and the CEST contrasts were broadly and largely increased from ~1.2 to 3.50 ppm in MTR_max curve. The CEST contrasts at 2 and 3.5 ppm offsets in the IM of UUO kidneys and at 1.2 ppm in contralateral kidneys increased from day 3 to day 6. The MTR and MTR_max maps in UUO kidneys showed focal variations on the disease progression.

**Conclusions:** The CEST and MTR techniques can be used for the assessment of UUO injury and progression. The MTR may be used for assessing severe renal cell injury that decreases tissue macromolecular components, while CEST may provide the changes in metabolites including glucose, amine and amide.

**Funding:** NIDDK Support

**TH-PO112**

**Image-Based Screening for Erythrocyte Characteristics of Patients Receiving Dialysis Service**

Chia-Hung Dylan Tsai,1 Shuhei Yoshikawa,1 Shinya Sakuma,1 Fumihito Arai,1 Makoto Kaneko,1 Osaka Univ, Suita, Osaka; 2Nagoya Univ.

**Background:** Dialysis process includes massive blood exchange between a patient and dialysis device. It is known that erythrocytes of a patient receiving dialysis tend to have shorter life cycles. This work is aimed to understand how the dialysis process changes cell characteristics in terms of cell size and cell deformability.

**Methods:** An image-based screening for erythrocyte condition is introduced. The system is constructed of three parts: a high-speed camera, a PDMS microchannel and an image-processing algorithm. The frame rate of the camera can be up to 10,000 fps, which provides the capability of high-throughput screening. The microchannel with width of 4.5μm forces erythrocytes through the channel one after another. Image-based algorithm is implemented for processing images captured from the camera, and erythrocyte condition, such as size and deformability, are evaluated.

**Results:** Erythrocytes from 4 patients receiving dialysis service and 4 healthy subjects were tested. The cell length inside a microchannel is found highly correlated with cell diameter, which shows that the cell length is a valid index for cell size. The results indicate that the patients have greater variation in the size of their erythrocytes and, furthermore, distribution of cell size is wider among the patients than the healthy ones.

**Conclusions:** The greatest advantage of the proposed system is that erythrocyte can be evaluated one-by-one, and we can visually check the cell from the captured frames, if necessary. We confirmed that the patients receiving dialysis services tend to have bigger erythrocytes and wider distribution. This could be a reason causing shorter life cycle of patients' erythrocytes. For the future work, cell motion inside the channel will be analyzed for evaluating cell deformability.

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

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

Underline represents presenting author/disclosure.

128A
TH-PO113

Regional Renal Perfusion Assessment with Contrast Enhanced Ultrasound in Ischemia-Reperfusion Injury. Kristina Fischer,1 Can Meral,1 Ference A. Jolesz,1 Takaharu Ichimura,2 Joseph V. Bonventre.2 Women’s Hospital; 2Renal Div, Brigham and Women’s Hospital, Boston, MA.

Background: Alterations in renal microperfusion play an important role in the development of acute kidney injury. Currently, however, there is no reliable technique that provides assessment of the renal perfusion at the bedside. Contrast enhanced ultrasound (CEUS) is an ultrasound imaging technique which uses gas microbubbles administered into the bloodstream.

Methods: We developed a renal perfusion estimation method, using Vevo 2100 ultrasound equipment and MicroMarker contrast agent (VisualSonics) with our own analysis software. CEUS with destruction-refilling sequences was performed in a 28-min bilateral ischemia-reperfusion (IR) model in mice (n=6) at pre-IR, 15, 30, 45, 60 min and 24 hr post-IR. Plateau image intensity was used to estimate renal perfusion. High resolution, pixel-by-pixel, analysis was performed on each imaging clip, resulting in parametric maps of the kidney, representing relative blood volume in each pixel.

Results: Region analysis showed that the perfusion decreased the most in the outer medulla (OM) by 63% (p=0.004) 60 min post-IR and remained 38% (p=0.002) less than pre-IR at 24 hr post-IR.

Parametric perfusion maps confirmed that the outer medullary perfusion decreased disproportionately to the reduction in the cortical © and inner medullary (IM) perfusion.

Conclusions: CEUS can detect and monitor renal microvascular perfusion changes in space and time in IR injury in mice and represents a technique that can be translated to use in man.

Funding: NIDDK Support

TH-PO114

Immunomodulation with a Selective Cytopheretic Device (SCD) Reduces Myocardial Infarct Size in a Canine Model of Ischemia-Reperfusion Injury (IRI). H D. Humes,1,2,3 D. Buffington,1 A. Westover,1 P. Smith,1 Hani N. Sabbah.1,4 Innovative BioTherapies,1 ’Univ of MI,1 ’CytoPhers,4 Henry Ford HS.

Background: IRI, characterized by a vigorous inflammatory response immediately post reperfusion via molecular signals generated by injured endothelium and cardiomyocytes, results in increased injury from leukocyte (LE) infiltration into the peri-infarct zone. This response becomes important in healing necessary to reestablish cardiac performance, but is excessive and maladaptive. The SCD, a novel biomimetic device, has shown efficacy in preclinical models of acute/chronic diseases for which inflammation is an exacerbating factor. When placed in an extracorporeal blood circuit (EBC) with regional citrate anticoagulation (RCA), the low ionized calcium environment provides a synchronized effect to both sequester and alter the activity of the transiently bound LE. The safety/efficacy of the SCD was demonstrated in clinical studies of ICU ARF/MOF patients and is currently being evaluated in a US multicenter, randomized pivotal IDE trial. Pilot studies were initiated to determine SCD effects on the acute inflammatory cascade indicative to IRI.

Methods: SCD was evaluated in a canine model of IRI, based on left circumflex coronary artery occlusion. Myocardial Infarct (MI) was induced for 3h and SCD therapy established using an EBC with RCA, 30min prior to reperfusion and continued for up to an additional 3h post. Systemic inflammation was monitored by CD11b expression of LE populations using flow cytometry and LE infiltration was evaluated by histology. Systemic cytokines and cardiac injury marker troponin-I (cTn-I) levels were assessed. Left ventricular (LV) function, MI size and edema were evaluated in treated (n=3) and compared to control (n=4) animals.

Results: SCD therapy resulted in 50% reduction of MI size (19.2±2.7 vs. 10.2±4.5% of LV volume respectively, p<0.05), less edema (LV wall thickening) and 10x lower cTn-I levels. LE infiltration was prominent in the peri-infarct zone of controls but negligible in the SCD group.

Conclusions: Pilot studies demonstrate that immunomodulation with the SCD represents a novel therapy with the potential to improve outcomes associated with myocardial IRI.

Funding: Other U.S. Government Support

TH-PO115

Application of Fourier Transform Infrared Spectroscopy to Plasma Biomarker Detection in Experimental Glomerulonephritis. Mei-Ching Yu,1 Frederick W.K. Tam,1 Robert J. Unwin,2 Peter R. Rich,1 Liberty Foreman.1 Kidney & Transplant Institute, Imperial College London; 2UCL Centre for Nephrology, Univ College London Medical School, Royal Free Hospital, Structural and Molecular Biology, UCL, United Kingdom.

Background: FTIR has been used in medicines for studying molecular composition and structures in cells and tissues. However, the application to biofluids, particularly blood is limited. Our previous work showed specific characteristic bands of urine spectra in the experimental glomerulonephritis (GN), and the changes were accordance with the progression of renal injury (ASN 2012). Although plasma creatinine ($P_c$) is a common clinical test to assess renal impairment, it is insensitive at the early stage of renal disease. The aim of this work is to employ FTIR to analyze plasma from nephrotic nephritis (NTN) for exploring potentially biomarkers of early renal injury.

Methods: Plasma from NTN Wistar Kyoto rats on day 8 (9), day 14 (6), day 21 (8) and day 28 (6) were compared to normal (15). 5pl plasma was required and dried for FTIR. Sample spectrum intensity normalized by the intensity of the 1640 cm⁻¹ peak of urea was compared to by the 1542 cm⁻¹ peak of Amide II. The subsequent analytic procedures were the same as our previous work (ASN 2012).

Results: The change in the band at 1460 cm⁻¹ showed the same pattern after normalization either with urea or Amide II peaks, or the progression of the experimental GN. Additionally, significant differences were validated.

In this model, $P_c$ remains normal until at least day 14. To detect this novel marker is more sensitive than measuring $P_c$.

Conclusions: Several renal biomarkers relevant to progression of experimental GN have been identified from IR spectra of plasma and urine samples. Conclusively, FTIR is becoming an emerging non-invasive diagnostics of rapidly screening patients at risk of progressive kidney disease.

Funding: Private Foundation Support

TH-PO116

Sensitive and Specific Measurement of Urine Neutrophil Gelatinase-Associated Lipocalin by Localized Surface Plasmon Resonance Using Artificial Antibodies on Gold Nanocages. Jeremiah J. Morrissey,1 Limei Tian,1 Keng-Ku Lin,1a,2 Naveen Gandra,1 Evan D. Kharaesh,1,2 Seikanth Sangamani,1,2 Anesthesiology, Washington Univ in St. Louis; 2Mechanical Engineering and Materials Science, Washington Univ in St. Louis; 3Siteman Cancer Center, Washington Univ in St. Louis; 4Biochemistry and Molecular Biophysics, Washington Univ in St. Louis, St. Louis, MO.

Background: Biosensing platforms based on localized surface plasmon resonance (LSPR) provide highly sensitive, cost-effective, and point-of-care diagnostic tools. Similar to ELISAs, current plasmic biosensors use expensive and labile natural antibodies. Macromolecular imprinting aims to overcome storage, stability and variability problems of natural antibodies by synthesizing specific artificial antibodies with high stability, reusability and cost-efficiency.

Methods: We used organo-siloxane monomers to provide amine, hydroxyl and methyl functional groups mimicking a natural antibody and when polymerized around absorbed recombinant human neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of acute and chronic kidney injury, molded reversible recognition cavities specific for NGAL detected as a shift in LSPR wavelength.

Results: The artificial antibodies, cast on cuboidal gold nanocages (about 60nm/side) reliably detected 25 ng/ml of NGAL and each sensor pad, after stripping, may be recycled for at least 5 times. The LSPR signal from NGAL was stable over a pH range from 5.0 to 8.5 and specific gravity from 1.005 to 1.030. Other human urinary proteins with lipocalin-like domains such as FABP, FABP3 or orosomucoid; and myoglobin or hemopexin (1-10 ug/ml); and hemoglobin or serum albumin (up to 500 ug/ml) interfered less than 20% with the LSPR signal of NGAL.

Funding: Other U.S. Government Support

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

Underline represents presenting author/disclosure.

129A
**TH-PO117**

**Development of a Microphysiological Organ-on-a-Chip Incorporating Primary Human Renal Epithelial Cell Cultures**

_Edward J. Kelly, 1 Zhican Wang, 1 Jenna L. Voellinger, 2 Jeremy Stuart Duffield, 2 Thomas Neumann, 1 Anna Tourouvskaia, 1 Gregory Kramer, 1 Jonathan HimmelDahr, 2 Pharmaceutics, Univ WA, Seattle, WA; 2 Medicine, Univ WA, Seattle, WA; 3 Nortis Inc., Seattle, WA.

**Background:** Kidney disease is a public health problem that affects more than 20 million in the USA, yet little is understood about the impact of kidney disease on drug disposition. Consequently there is a critical need to model the human kidney to improve our understanding of drug efficacy, safety, and toxicity, especially during drug development. The proximal tubule (PT) plays a central role in the elimination of endogenous toxins and xenobiotics, but cultured PT cells bear little resemblance to their in vivo counterparts. It is possible to recapitulate a functioning PT ex vivo in a MPS for up to several weeks. This system more accurately reproduces PT cell viability for >21 days ex vivo. These tubules are currently being evaluated functionally, and the ability to culture PT cells for extended periods is opening up a novel class of plasmonic nanostructures with sensitive and specific bioactivity.

**Methods:** We have developed and optimized methods for purifying, expanding, storing, and human kidney PT cells. We developed single lumen 3D microphysiological devices with the ability to culture PT cells under conditions of continuous flow. In optimized culture conditions in 2D human PT cells uniformly express E-cadherin, aquaporin-2, KIM-1 and form tight junctions as demonstrated by ZO-1 localization. PT cells proliferate with a doubling time of ~30hrs and remain viable following detachment. PT cells proliferate under conditions of continuous flow. PT cells cultured under these conditions retain cell viability for >21 days ex vivo. These tubules are currently being evaluated functionally, the results of which will be presented.

**Conclusions:** It is possible to recapitulate a functioning PT ex vivo in a MPS for several weeks. This system more accurately reflects human physiology, being able to predict renal handling of xenobiotics and potentially assess mechanisms and biological response relating to kidney injury.

**Funding:** Other NIH Support - U01TR00504

---

**TH-PO118**

**RNA-Seq of Microdissected Renal Tubules Identifies Segment-Specific Transcription Factors**

_Jae Wook Lee, Chung-Lin Chou, Fahad Saeed, Mark A. Knueper. NIH.

**Background:** We carried out RNA-seq in microdissected rat renal tubule segments to identify the transcription factors of the 12 major renal tubule segments and to identify transcription factors that could be involved in cell type-specific gene expression. Several housekeeping family transcription factors were found to be segment-specific, such as Phox2 in proximal tubule segments; Irf1 and Irf2 in the cortical thick ascending limb; Hmns2 and Phox3 in the cortical collecting duct; and Host85 and Phox1 in the inner medullary collecting duct. Interestingly, Host87 (thought to be collecting duct-specific) was found not only in collecting ducts but also thick ascending limbs. Transcription factor mediators of TGF and Wnt signaling such as Smad2, Tcf3, and Tcf2 were found only in collecting duct segments. Other examples of region-specific transcription factors include: Hnf6a (proximal segments); Rarg (thick ascending limbs); Mafb (cortical collecting duct); and Pparg and Elf3 (inner medullary collecting duct).

**Conclusions:** These data provide baseline information needed to model cell type-specific gene expression along the nephron and collecting duct.

**Funding:** Other NIH Support - N01HL14685

---

**TH-PO119**

**PPARs Promotes Na+/H+ Exchanger NHE1 Expression to Inhibit Renal Tubule Cells Apoptosis through Recruiting Ezrin/Radixin/Moesin Proteins and Phosphoinositide 3-Kinase Yung-Ho Hsu, 1 Tso Hsiao Chen, 2 Cheng-Hsien Chen. 1,2 1 Div of Nephrology, Dept of Internal Medicine, Shuang Ho Hospital, Taipei Medical Univ, Taipei, Taiwan; 2 Div of Nephrology, Dept of Internal Medicine, Wan Fang Hospital, Taipei Medical Univ, Taipei, Taiwan.

**Background:** Peroxisome proliferator-activated receptor-alpha (PPARα) is a transcription factor and has been reported to inhibit gentamicin-mediated proximal tubule cell apoptosis. However, the antipapoptotic mechanism of PPAR-α is still unknown.

**Methods:** In this study, we investigated the mechanism of antipapoptotic effect of PPARα by overexpressing PPARα in NRK-52E cells.

**Results:** We found that PPARα overexpression increased the expression of Na+/H+ exchanger NHE1 in NRK-52E cells. Three potential PPARα response elements in NHE1 promoter region were identified by chromatin immunoprecipitation. The Na+/H+ exchanger activity was also increased in PPARα-transfected cells. Flow cytometry showed that PPARα overexpression augmented the resistance to apoptosis-induced shrinkage in NRK-52E cells. A Na+/H+ exchange inhibitor EIPA inhibited the antipapoptotic effect of PPARα on gentamicin-treated cells. NHE1 sirna transfection also inhibited PPARα-induced Na+/H+ exchange activity and the antipapoptotic effect. In immunoprecipitation, NHE1 physically associated with phosphorylated ezrin/ radixin/moesin (ERM) in PPARα-transfected cells. We also found that PPARα induced activation of the pro-survival kinase, Akt. PPARα-induced Akt activity was inhibited by EIPA and NHE1 siRNA transfection. Wortmannin, a phosphoinositide 3-kinase (PI3K) inhibitor, inhibited PPARα-induced Akt activity and the antipapoptotic effect of PPARα. But wortmannin did not influence the association between NHE1 and phospho-ERM.

**Conclusions:** We conclude that PPARα promotes NHE1 expression, and then recruits ERM proteins and PI3K to mediate Akt-dependent cell survival.

**Funding:** Other NIH Support - R01DK102528

---

**TH-PO120**

**Elucidating the Mechanism of Tenofovir-Induced Kidney Injury**

_Laura Chappell-Campbell, Jeremy S. Leventhal, Pengfei Gong, Michael J. Ross. Icahn Sch of Med at Mt Sinai.

**Background:** Tenofovir (TFV) is the most commonly-used antiretroviral drug for treatment of HIV-1 infection. 2% of patients treated with TFV develop AKI and 30% have subclinical signs of proximal tubular epithelial cell (PTEC) dysfunction. Though studies suggest mitochondrial injury is an important component of TFV nephrotoxicity, little is known about the mechanism by which TFV injures mitochondria.

**Methods:** We created an novel in vitro model of TFV toxicity using human PTEC. To investigate susceptibility to TFV toxicity, studies were performed using PTEC stably transfected with OAT1, which mediates basolateral TFV uptake. Protein expression was analyzed for markers of mitochondrial fission and fusion, autophagy-associated protein LC3, and the cellular energy sensor AMPK. Subcellular localization of mitochondria and LC3 was visualized via confocal microscopy. Electron microscopy (EM) was used to analyze mitochondrial morphology and to identify autophagosomes.

**Results:** OAT1 transfection markedly increased the toxicity of TFV. TFV treatment increased expression and activation of AMPK in OAT1-overexpressing PTEC. Since AMPK activation can reflect cellular energy deprivation, we studied whether TFV also increased autophagy in PTEC. TFV incubation markedly increased LC3-I levels, with more modest effects on LC3-II. Confocal imaging of TFV-treated PTEC demonstrated colocalization of mitochondria with LC3, suggesting autophagosomal localization of mitochondria (mitophagy). EM studies corroborated these findings, showing increased autophagosome accumulation and mitophagy in TFV-treated cells. No significant effect of TFV on mitochondrial fission and fusion was observed.

**Conclusions:** These data demonstrate that TFV induces activation of AMPK, an important mediator of autophagy. TFV, 5'-tri-phosphorylated by TFV and our finding that TFV increased LC3-I levels without changes in LC3-II suggests either a defect in autophagosome formation or increased autophagosome turnover. In conclusion, TFV induces activation of cellular energy deprivation response pathways. Future studies are needed to determine whether this response is due to aberrant mitophagy leading to loss of mitochondria or to direct mitochondrial injury.

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

---

**TH-PO121**

**HIV-Induced Downregulation of Deptor Contributes to the Activation of mTOR Pathway in HIV-Associated Nephropathy**

_Pattab Rabi, 1 Kavithalakshmi SaranataraJaran, 2 Viki Kumar, 1 Rivka Lederman, 1 Ashwani Malhotra, 1 Balakuntalam S. Kasinath, 2 Pravin C. Singhal, 1 Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; 2 Medicine, Univ of Texas Health Science Center, San Antonio, NY.

**Background:** mTOR pathway has been shown to play a pathogenic role in the development of HIV-associated nephropathy (HIVAN). However, the role of deptor, a negative regulator of mTOR has not been studied to date. We hypothesized that HIV may be activating mTOR pathway in HIVAN via down regulation of kidney cell dector expression.

**Methods:** Kidneys were harvested from age and sex matched control and Tg26 mice (n=6). Renal cortical sections were immunolabeled for dector, phospho-mTOR, and total mTOR. Protein blots from renal tissues of control and Tg26 mice were probed for dector,
phospho-mTOR, phospho-p70S6K, phospho-Akt, total mTOR, and actin. To determine the effect of HIV on tubular cell expression and mTOR activation, mouse proximal tubular cells (MCT) were infected with either empty vector (EV/MCT) or NL-43 (HIV/MCT). Protein blots of EV/MCTs and HIV/MCTs were probed for phospho-p70S6K and total phospho-p70S6K, an effector molecule of mTOR activation. We demonstrated that autophagy is induced in proximal tubules by acid in vitro and in vivo as assessed by the GFP-positive dot formation in the kidney of acid-loaded GFP-LC3 transgenic mice by treating with NH4Cl in drinking water for 4 weeks. We also used autophagy-deficient proximal tubular cells and examined the role of autophagy in adaptations for MA with conditioned medium.

Results: We demonstrated that autophagy is induced in proximal tubules by acid in vitro and in vivo as assessed by the GFP-positive dot formation in the kidney of acid-loaded GFP-LC3 transgenic mice and degradation of p62 using kidney proximal tubular cells when cultured in an acidic medium. Next, acid-loaded autophagy-deficient mice demonstrated severe MA with significantly reduced ammonium production in kidney compared with those of wild type mice, which was confirmed by in vitro analysis. To prove our hypothesis, we analyzed the mitochondrial function of autophagy deficient condition under MA. COX and SDH stains of kidney indicated the reduced activity of mitochondrial respiratory chain compared to HIV/MCT.

Conclusions: Our results indicate that MA evokes mitochondrial dysfunction and quality control of mitochondria by autophagy has an essential role for the adaptation to MA.

TH-P0123
Klotho Protects against Mouse Renal Fibrosis by Regulation of Autophagy
Hye Eun Youn, Sung Jun Kim, Su Jin Choi, Sungjin Chung, Seok Joon Shin, Internal Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: Autophagy is a cellular process of degradation of damaged components in the cytoplasm and regulates cell death. Klotho is known to have a renoprotective effect. In this study, we investigated whether Klotho protein protects against renal fibrosis by regulating autophagy in an obstructive kidney model.

Methods: We received unilateral ureteral obstruction (UOO) surgery with or without intraperitoneal administration of secreted Klotho protein. We evaluated renal fibrosis and apoptosis and expression of superoxide dismutase (SOD), heat-shock protein 70 (Hsp70), beclin-1, LC3-I/II,LC3-I, Akt, FoxO3a, Bax, Bel-2, Bim, cleaved PARP, and alpha-smooth muscle actin in obstructed kidneys of wild type and Klotho transgenic mice.

Results: Secreted Klotho protein significantly decreased collagen deposition and fibrotic areas in obstructed kidneys compared with those of controls. Secreted Klotho protein significantly increased the expressions of antioxidant enzymes, SOD (SOD1 and SOD2) and Hsp70, phosphorylated beclin-1, an autophagy gene, and increased the LC3-I/II-LC3-I ratio in obstructed kidneys compared with controls. The numbers of apoptotic cells and the expression of Bax/Bcl-2, Bim and cleaved PARP were significantly decreased in obstructed kidneys of Klotho-treated mice compared with controls. Secreted Klotho protein significantly reduced expression of α-SMA, a marker of epithelial mesenchymal transition, in obstructed kidneys compared with controls. In Klotho protein-treated mice, the expression of phosphorylated Akt did not show significant changes in obstructed kidneys, but the expression of phosphorylated FoxO3a was significantly decreased compared with controls.

Conclusions: We speculate that Klotho protects against renal fibrosis in an obstructed kidney model via direct modulation of FoxO3a signaling, without regulation of Akt, and subsequent attenuation of oxidative stress and induction of autophagy. Funding: Government Support - Non-U.S.
Methods: Using MS/MS, we identified the localization of Cdk2 phosphorylation sites on Bcl-xL and generated phosphomimetic Bcl-xL and phosphodefective Bcl-xL. We performed apoptosis assays to investigate the downstream effects of these Bcl-xL modifications. Bcl-xL was shown to elicit its pro-survival function by interacting with pro-death proteins, such as Bax. When Bcl-xL is prevented from interacting with Bax, Bax oligomerizes, and permeabilizes mitochondria to induce apoptosis. A GFP fragment reassembly system was utilized in kidney cell lines to determine Bcl-xL-Bax interaction and localization. GFP was divided into N-terminal and C-terminal fragments, and Bcl-xL and Bax were fused with different fragments of GFP individually. If Bcl-xL and Bax interact, the two GFP fragments are brought close enough together to allow reassembly and emit fluorescence. Here we report the interaction and the localization of wild type and modified Bcl-xL’s with Bax in kidney cells.

Results: We found that in normal kidney cells, Bcl-xL and Bax interact at the mitochondrial membrane, which supports the “embedded together” and “retrotranslocation” model of Bcl-xL and Bax interaction. These models propose that Bcl-xL and Bax interact at the mitochondrial membrane and that Bcl-xL retrotranslocates Bax into the cytoplasm, preventing its conformational activation.

Conclusions: We hypothesize that Cdk2 serves as a catalyst to disrupt Bax and Bcl-xL interaction and/or localization, resulting in cell death and p53 expression.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO128
Aldosteron Promotes Autophagy in Podocytes
Juming Fan,1,2 Nan Mao,1 Ji Wen,1 Zi Li1
1Dept of Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China; 2Div of Nephrology, Dept of Internal Chinese Medicine, Luzhou Medical College, Luzhou, Sichuan, China.

Background: The concentration of aldosterone was inappropriately higher in many kidney diseases, such as hypertension and chronic kidney disease. Previous reports have showed that aldosterone could induce podocyte injury due to reactive oxygen species (ROS). When podocytes were induced with cytokines, some oxidized proteins and damaged organelles may occur. The relationship between autophagy and aldosterone may be unclear. Our study is to determine the effect of aldosterone on the autophagy and the ROSsignaling pathway in podocyte.

Methods: Podocytes were incubated with aldosterone (10⁻⁶ M), Nacetylcysteine (NAC, 50 mM), 3-Methyladenine (3-MA, 4 mM) and rapamycin (1ng/ml), respectively. Morphological changes were observed by transmission electron microscopy and fluorescence microscopy. Examination of autophagic vacuoles with monodansylcadaverine or acridine orange was under confocal microscope. Flow cytometry was performed to detect the generation of intracellular ROS and cell apoptosis. The expression of the LC3B, Beclin-1, Nrf2, SOD, or TGF-β1 siRNA was detected by western blot.

Results: Aldosterone promotes autophagy in podocytes. It was observed that the number of autophagosomes was increased in aldosterone and rapamycin treatment groups, whereas rapamycin further enhanced aldosterone-induced autophagosome formation by transmission electron microscopy and fluorescence microscopy. Examination of autophagic vacuoles with monodansylcadaverine or acridine orange was under confocal microscope. Flow cytometry was performed to detect the generation of intracellular ROS and cell apoptosis. The expression of the LC3B, Beclin-1, Nrf2, SOD, or TGF-β1 siRNA was detected by western blot.

Conclusions: Aldosterone promotes the podocyte autophagy which was inhibited by antioxidants. These results suggested that aldosterone promoted podocyte autophagy through the ROS pathway.

Funding: Government Support - Non-U.S.

TH-PO129
Angiogenin Is Secreted by the Stressed Renal Epithelium and Induces the Production of tRNA
Nicolas Bouvier, Alexandre Karras, Eric Thervet, Nicolas Pallet, Iadh Mami
INSERM U775, Paris, France.

Background: Angiogenin (ANG) is a stress-activated ribonuclease that cleaves tRNA, producing stress-induced tRNA fragments (sRNA) that can directly inhibit protein synthesis by a novel mechanism of RNA interference. The objective of our study is to test whether ER stress induces ANG production, and to delineate the mechanism and biological functions of ANG synthesis and secretion by kidney epithelial cells during ER stress.

Results: ER stress induces the production and secretion of ANG by human renal epithelial cell cultures. Using sRNA, we have demonstrated that the UPR transducers IRE1α, PERK, and ATF-6, but not PERK, regulate ANG production at the transcript and protein levels. ANG expression is also increased in rat kidneys challenged with tunicamycin, cyclosporine, and ischemic stress. Recombinant human ANG reduces UPR-induced apoptotic cell death, UPR-induced autophagy, and the intensity of ER stress. During ER stress, ANG is translocated from the nucleus to the cytoplasm, where it colocalizes with stress granules. ANG promotes the formation of tRNA during ER stress which interfere with the initiation of translation. Therefore, ANG-mediated translation inhibition may involve tRNA production, to decrease protein load, thereby promoting ER stress relief. Our results also indicate that inhibition of ANG expression by RNA interference reduces the intensity of UPR-induced N-KB signaling, as well as proinflammatory cytokine secretion, suggesting that ANG promotes tubule inflammation. Finally, we measured the concentration of ANG in urine of 100 patients with kidney disease by ELISA. Urinary ANG/creatinine ratio were positively correlated with estimated glomerular filtration rate. By immunohistochemistry analysis of human kidney biopsies we show that ANG is expressed in ischemic kidney and during cyclosporine nephrotoxicity, but not in normal kidneys.

Conclusions: ANG is directly and specifically secreted by the stressed kidney epithelial cells to the extracellular space, promoting RNA interference and protecting against UPR-induced apoptosis. ANG is a potential novel diagnostic biomarker of tissue injury.

TH-PO131
Tubular DNA Damage Response and Cell Cycle Arrest Mediate Progression of Diabetic Nephropathy
Jae-Hyoung Chang, Takaharu Ichimura, Joseph V. Bonventre.
Renal Div, Brigham and Women’s Hospital, Boston, MA.

Background: Diabetic nephropathy (DN) has been traditionally considered as a primary glomerular disease. Increasing evidence, however, suggests that the kidney tubule plays a central role, and that tubulointerstitial injury may contribute to glomerular changes in diabetes. Recently, our laboratory has shown that in ischemic, toxic and obstructive mouse models, injured proximal tubular epithelial cells (PTEC) undergo cell cycle arrest in G2/M and assume a phenotypic-simic-fibrotic phenotype as a consequence of maladaptive repair. This process involves activation of DNA damage response (DDR) proteins and results in interstitial fibrosis and glomerulosclerosis.
Methods: Using a mouse model of type 1 diabetes and porcine tubular cell lines, we determined if the diabetic environment facilitates DNA damage in PTEC, activates DDR signaling, and promotes cell cycle arrest, ultimately leading to tubulointerstitial fibrosis and glomerulosclerosis. Results: Hyperglycemic treatment of KIM-1-PKI cells, a porcine tubular cell line which stably expresses human kidney injury molecule-1 (KIM-1), results in enhanced expression of markers of nuclear DNA damage and DDR activation (pATM and pAX), as well as induction of p16, a marker of senescent cell cycle arrest. Also, expression of TGF-β was up-regulated in these cells. In streptozotocin (STZ)-induced diabetic mice, 15 weeks after induction of diabetes, kidneys had interstitial fibrosis, tubular atrophy and glomerulosclerosis, together with significantly enhanced expression of nuclear pAX and apical KIM-1 in PTEC when compared to control non-diabetic animals. At this timepoint, there were significantly fewer Ki67-positive proliferating PTEC in diabetic kidneys compared to the control kidney. Also, cortical tubular expression of p16 and the number of phosphohistone H3 positive tubular cells were increased in diabetic mice, indicating an increase in the proportion of PTEC in cell cycle arrest in diabetes. Conclusions: These data suggest that tubular DDR signaling and premature senescence cell cycle arrest may lead to accelerated fibrosis and may represent novel pharmacological targets for the treatment of DN.

Funding: NIDDK Support

TH-PO132

URAT 1 Inhibition Protects Humans Proximal Tubule Cells from Apoptotic Damage Induced by Uric Acid

Uniwersytet Warmińsko-Mazurski w Olsztynie, Olsztyn, Poland; Medical University of Warsaw, Warsaw, Poland; University ofTrento, Trento, Italy; Centro di Riferimento Oncologico, Aviano, Italy; Medical University of Innsbruck, Innsbruck, Austria; University of Torino, Torino, Italy; Medical University of Vienna, Vienna, Austria; Saarland University, Homburg, Saarland, Germany.

Background: Serum uric acid (UA) has been shown to predict the development of chronic kidney disease (CKD) and has been associated with signs of renal damage such as albuminuria, intrarenal vascular stiffness and tubular atrophy in several conditions. The mechanisms underlying the effects of UA on renal proximal tubular epithelial cells (PTEC) have not been elucidated.

Methods: Apoptotic damage was induced by serum deprivation and adding UA at different concentrations (7.5 -12 mg/dl) for 48 hours. Cell viability was evaluated by MTT test and apoptosis by positivity for cleaved caspase-3 (p17 fragment). Pro- and anti-apoptotic proteins were studied by Western Blot. The pathways involved in UA apoptosis were studied by Caspase inhibitors, NADPH Oxidase inhibitor (DPI), urate transporters antagonists (Isoratin and probenecid).

Results: Highest UA concentration decreased tubule cell viability (-30%, p<0.015) and increased significantly apoptotic cells (14%±5.35 vs 2%±0.87 arrested cells p<0.0001). UA up-regulated Bax (+60% p<0.05) and down regulated X-linked inhibitor of apoptosis protein (XIAP) (-30% p<0.05). Caspase-9 inhibitor blunted apoptosis, while caspase-8 inhibitor had no effects. UA induced changes in the mitochondrial membrane as shown by mitocap trigger apoptosis assay. Dpi had inhibitory effects on apoptosis (-70%, p<0.001). Incubation with probenecid 20 μM and Isoratin 10 μM inhibited apoptosis induced by 12 mg/dl UA exposure (p<0.001 and <0.0001, respectively).

Conclusions: These results indicate that mildly elevated UA levels promote apoptosis in PTECs by triggering intrinsic caspase activation, thus contributing to mechanisms of cell loss which have been already shown to be activated in CKD. This mitochondrial pathway seems to be attenuated by Isoratin and probenecid, probably through their binding to URAT-1.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author/disclosure.
Transfection of sirt-1 Gene Decreases the Apoptosis of Podocyte under the Diabetic Condition

Eun Kyung Lee,1 Kyung Sun Park,2 Jai Won Chang,3 Hyn woo Kim.4
1 Internal Medicine, Dankook Univ Hospital, Cheonan, Republic of Korea; 2Internal Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea; 3Internal Medicine, Asan Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea; 4Internal Medicine, Jeju National Univ Hospital, Jeju, Republic of Korea.

Background: Podocyte injury plays a role in the pathogenesis of diabetic nephropathy, leading to end-stage renal disease. The human sirt-1 gene, the mammalian ortholog of yeast Sir2, is associated with prolonged life span.

Methods: We performed this study as the first step to investigate whether the prevention of apoptosis of podocyte under the diabetic condition can ameliorate decline of renal function. The human nephrin promoter was inserted into the plasmid including human sirt-1 gene. We used lipofectamin for the transfection of final plasmid into the mouse podocytes. We compared the degrees of apoptosis between transfected and non-transfected podocytes under the mixture of 30 mM of glucose, 200 μM of saline and 1 μM of angiotensin II.

Results: Human sirt-1 gene transfected podocytes decreased the degree of apoptosis of them in dose-dependent manner, confirmed by reduction of caspase-3/3 via western blot (p < 0.05). The plasmid containing only nephrin promoter did not show the anti-apoptotic effect on podocytes under the same condition (p = NS). These results were determined by time PCR was performed using a Qiagen autophagy-dedicated microarray. Fold change in expression of several key autophagy genes in the hearts of uremic rats. Whilst this needs to be corroborated with translational evidence of impaired autophagy, previous studies have demonstrated corresponding changes in mRNA levels of autophagy genes associated with changes in autophagy activity, thus these results suggest that basal autophagy is impaired. Given that impaired autophagy is associated with aging, it may have a role in pathological aging in ESRD, and may be a target for pharmacological interventions to correct this.

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

Underline represents presenting author/disclosure.

134A
Background: Progressive interstitial fibrosis produces structural changes in the kidney, where abnormal extracellular matrix (ECM) may lead to functional changes. The collecting tubule AQP2 modifies the tubular water reabsorption through transcriptional and posttranslational regulations of its content as well as its quick cytoplasm-to-apical membrane trafficking. ECM messenger ILK (integrin linked kinase) modulates different transcription factors as well as cytoskeleton function. 

Methods: We studied the ILK implication in the AQP2-dependent tubular absorption by using an in vitro model of cultured inner medulla collecting duct cells line (mMCD3) over collagen 1 (COL 1) or inactive gelatine as control. We depleted ILK expression in mMCD3 by transfection with specific siRNAs. The expression of ILK was decreased by BMP-7. 

Results: We previously shown (ASN kidney week 2012) that in vivo model of conditional ILK-deletion in adult mice, basal poliuria and decreased urine osmolality was due to cortical and medullar AQP2 expression and cytoplasm-to-apical trafficking. ECM messenger ILK (integrin linked kinase) modulates different transcription factors as well as cytoskeleton function. 

Conclusions: AQP2 expression and trafficking in mMCD3, reducing the water reabsorption capability, due to impaired ILK-dependent AQP2 expression and traffic. 

Funding: Government Support - Non-U.S.

TH-PO141
Collagen I Downregulates the Inner Medulla Tubular Cells AQP2 Expression and Traffic through Integrin Linked Kinase (ILK) 

Jose Luis Cano-Penalver,1 Mercedes Grieria,1 Alicia Luengoa,1 Andrea Garcia-Jereza,1 Nuria Troyaona,1 Diego Rodriguez-Puyol,1 Sergio De Frutos Garcia,1 Manuel Rodriguez-Puyol.a 1Biología de Sistemas, Unidad Fisiología, Universidad de Alcalá, Alcalá de Henares, Madrid, Spain; 2Fundacion de Investigacion Biomedica, Hospital Universitario Principe de Asturias, Alcalá de Henares, Madrid, Spain.

Background: The collecting tubule AQP2 modifies the tubular water reabsorption through transcriptional and posttranslational regulations of its content as well as its quick cytoplasm-to-apical membrane trafficking. ECM messenger ILK (integrin linked kinase) modulates different transcription factors as well as cytoskeleton function.

Methods: We studied the ILK implication in the AQP2-dependent tubular absorption by using an in vitro model of cultured inner medulla collecting duct cells line (mMCD3) over collagen 1 (COL 1) or inactive gelatine as control. We depleted ILK expression in mMCD3 by transfection with specific siRNAs.

Results: We previously shown (ASN kidney week 2012) that in vivo model of conditional ILK-deletion in adult mice, basal poliuria and decreased urine osmolality was due to cortical and medullar AQP2 expression and cytoplasm-to-apical trafficking. ECM messenger ILK (integrin linked kinase) modulates different transcription factors as well as cytoskeleton function. 

Conclusions: ILK levels decreased in mMCD3 cells. We depleted ILK expression in mMCD3 by transfection with specific siRNAs. ILK depletion reduced ILK expression in mMCD3 cells. The expression of ILK was decreased by BMP-7. 

Funding: Government Support - Non-U.S.

TH-PO142
Cellular Inhibitor of Apoptosis Protein 1 (cIAP1) Represses Albumin-Induced Chemokines and Adhesion Molecules Synthesis by Kidney Tubular Epithelial Cells

Josef C. K. Leung,1 Ai Ing Lim, Loretta Y.Y. Chan,1 Wai Han Yii,1 Kar Neng Lai,2 Sydney C.W. Tang.1 1Dept of Medicine, The Univ of Hong Kong, Hong Kong; 2Dept of Health Assessment, Hong Kong Sanatorium and Hospital, Hong Kong.

Background: Protein overload activates proximal tubule epithelial cells (PTEC) to release chemokines and stimulates inflammatory response in the interstitium. Bone morphogenetic protein-7 (BMP-7) has been shown to reduce infiltrating cells and kidney damage in acute and chronic renal failure. The present study examines the inhibitory effects and the relevant molecular mechanism of BMP-7 on chemokines and adhesion molecules synthesis by PTEC activated with human serum albumin (HSA).

Methods: PCR array was used to screen the expression profiles of chemokines and adhesion molecules in cultured human PTEC. The molecules that were upregulated by HSA and can be significantly reduced by BMP-7 were identified. The kinetic of their expression in PTEC was determined by ELISA. The activation of NF-κB and the relevant molecules of the signaling pathways were examined by RT-PCR, western blotting, immunofluorescence microscopy and transcriptional factors ELISA.

Results: Expression of CXCL1, CXCL2 and VCAM-1 by PTEC was upregulated by HSA, and the expression was significantly reduced by BMP-7. Further experiments confirm that BMP-7 reduced the HSA up-regulated gene and protein expression of CXCL1, CXCL2 and VCAM-1 dose and time dependently. HSA activated both the canonical and noncanonical NF-κB pathways in PTEC, as shown by the reduced expression of IkBα, the nuclear translocation of p50 and p52, and data from the transcriptional factor ELISA. The NF-κB activation was repressed by BMP-7. Interestingly, the HSA-upregulated expression of cIAP1 and TRAF3 by PTEC, was further increased by BMP-7. To the contrary, the expression of NIK in PTEC was increased by HSA but down-regulated by BMP-7.

Conclusions: Our data suggest that HSA regulates CXCL1, CXCL2 and VCAM-1 via both the canonical and noncanonical NF-κB pathways in PTEC. BMP-7 suppresses these events through increased production of cIAP1 and TRAF3, which inhibits the accumulation of NIK and the subsequent activation of NF-κB pathways.

Funding: Other NIH Support - Supported by Hong Kong General Research Fund

TH-PO143
The Protective Effect of Adrenomedullin on Liver Injury Induced by Bilateral Nephrectomy or Renal Ischemia-Reperfusion in Mice

Tatsuki Tabada,1 Saki Takahashi,2 Hiroko Sonoda,1 Yu Miyahara,1 Mari Isomi,2 Joji Kato,3 Kazuo Kitamura,2 Masahiro Ikeda.1 1Veterinary Pharmacology, Univ of Miyazaki, Miyazaki, Japan; 2Frontier Science Research Center, Univ of Miyazaki, Miyazaki, Japan; 3Internal Medicine, Univ of Miyazaki, Miyazaki, Japan.

Background: Experimental studies have shown that acute kidney injury (AKI) induces disturbance in systemic inflammatory response. The kinin system, which is involved in the regulation of renal blood flow and plasma volume, is activated in AKI. However the mechanism of AKI-induced hepatic dysfunction remains unclear. Recent studies have suggested that uncontrolled toxins cause tissue injury, which is mediated by a mechanism related to hypoxia.

Methods: In this study, therefore we examined whether hypoxia-related mechanisms are involved in AKI-induced hepatic injury using two mice models of bilateral nephrectomy (BNx) and renal ischemia-reperfusion (IR).

Results: Plasma urea nitrogen, creatinine, aspartate transaminase, and alanine transaminase were significantly increased 6 and 24 h after induction of either BNx or IR, compared with those of sham-operated animals. PCR array analyses showed that BNx and IR up-regulated 20 genes associated with hypoxia, including adrenomedullin (AM), and down-regulated 6 genes. As AM has been reported to have protective effect against tissue injury, we then analyzed the expression level of AM-related genes, including AM binding protein-1 and AM receptor components such as calcitonin receptor-like receptor (CRLR) and receptor activity-modifying protein (RAMP) 2 and 3. Real-time PCR analyses showed that BNx and IR up-regulated RAMP2 and RAMP3 within 32 h after either operation. Finally, we examined the expression of AM on BNx- or IR-induced liver injury in vivo. AM (10 mg/kg) was intraperitoneally administered to mice 30 min before and just after each operation. AM significantly lessened the severity of liver injury 24 h after each AKI-operation, without improving renal function, in comparison with controls.

Conclusions: These results suggest that the hypoxia-related mechanism is involved in AKI-induced hepatic injury and that AM may have the potential to protect against AKI-induced liver injury.

TH-PO144
Study of NOV/CCN3 Expression and Effects in Different In Vivo Models of Chronic Kidney Disease

Pierre-Olivier Marchal,1 Chantal Kazazian,1 C. Chatziantoniou,2 Christos E. Chadjichristis,2 Cécile Martinec,1 1INSERM UMR 938/UPMC, Paris, France; 2INSERM UMR 702/UPMC, Paris, France.

Background: Independently of its origin chronic kidney disease (CKD) results in high inflammation and fibrosis. Current treatments are partially effective and consequently new therapeutic targets are required. NOV/CCN3 was reported to be antibioflic for pro-angiogenic and anti-mesangioproliferative effects in anti-Thyl 1 model and to inhibit vascular growth. NOV/CCN3 was reported to be anti-fibrotic with the collecting duct AQP2, AT1R, CTGF/CCN2 in mesangial cells. NOV is a secreted multifunctional protein belonging to the CCN family involved in different physiological and pathological processes (angiogenesis, inflammation, cancers). To further explore NOV involvement in CKD we analyzed its expression in other in vivo models and tested its ability to modulate expression of profibrotic and inflammatory molecules.

Methods: NOV expression was analyzed at various times in the following models: renin transgenic mice (RenTg) at early stages (9-12-21w) and late stages (53w), Angiotensin II (AngII) perfused mice (1-2-4w) and unilateral ureteral obstruction (UUO, 3-7-15s). In UUO models NOV/CCN3 was expressed in cortex by RT-qPCR and Western blot. NOV in vitro effects were studied on rat aortic vascular smooth muscle cells (VSMC). 

Results: In RenTg mice we observed two phases: one early in which NOV expression was increased by AngII (3.5 folds, 12w), especially in VSMC, then returned at basal level (21w) and one late in which NOV was correlated with the increase of TNFα (53w). In VSMC NOV downregulated profibrotic AT1R (90%) and CTGF (40%) whereas it stimulated MCP-1 (23 folds) and was increased by TNFα (3.5 folds). In AngII-perfused mice and UUO we also observed a correlation between NOV, TNFα and MCP-1. Moreover, NOV injection stimulated MCP-1 in kidney of healthy mice.

Conclusions: Our results suggests that NOV could have a dual role: protective at early stage but participates to inflammation at late stage of CKD. Ongoing experiments on NOV KO should bring us more evidences to this hypothesis.

TH-PO145
P2Y12 Receptor Protein Is Co-Localized with AQP2 in the Collecting Duct Principal Cells of Rat and Mouse

S. Bellamkonda K. Kishore,1 Janos Petri-Peteris,2 Karice G. Villanueva,2 David L. Strausburg,1 Noel G. Carlson,2 Donald E. Kohen,1 Yue Zhang.1 1VA Medical Center & Univ of Utah, Salt Lake City, UT; 2Univ of Southern California, Los Angeles, CA.

Background: P2Y12 receptor (R) is an ADP-activated G protein-coupled receptor that inhibits adenyl cyclase activity, thus potentially reducing cellular cAMP levels. We observed that administration of clopidogrel (Plavix®), which irreversibly blocks P2Y12-R, significantly increased urinary concentration and protein abundance of AQP2 in the medulla, and ameliorated lithium-induced polyuria in rats. Immunoblots using a commercial antibody confirmed the expression of P2Y12-R protein in the kidney, however, the precise cellular localization of it in the kidney has not yet been established.
Autophagy Is Impaired in Unilateral Ureteral Obstruction (UUO) Model of Renal Fibrosis. Yang Ou,1 Djianuali Muhoza,1 Christian Herzog,1 Randy S. Haan,2,3 Gur P. Kaushal.2 Internal Medicine, Univ of Arkansas for Medical Sciences; 2Pharmaceutical Sciences, Univ of Arkansas for Medical Sciences; 3Central Arkansas Veterans Healthcare System, Little Rock, AR.

Background: Autophagy is a highly conserved protein degradation system in eukaryotes. Very little is known about the role of autophagy during progressive renal fibrosis. We examined whether renal fibrosis results from defective autophagy using UOO as a model of renal fibrosis.

Methods: Renal fibrosis was induced in mice using the UOO model. Autophagy was inhibited by autophagy flux inhibitor chloroquine and upregulated by autophagy enhancing drug Torin-1. We used Beclin-1 transgenic (Beclin-1 Tg) mice under the control of the androgen-inducible KAP2 (kidney androgen-regulated promoter) promoter and obtained overexpression of Beclin-1 in the proximal tubules.

Results: The autophagy-related proteins Beclin-1, Atg5, Atg7, and Atg12, and the conversion of LC3-I to LC3-II were increased at 1d, 3d, 5d, and 9d after UOO. Production of matrix proteins including α-SMA, fibronectin, and collagen-I was elevated following UOO. Accumulation of autophagy-specific substrate p62, Keap1, ubiquitinated proteins and LC3/LC3-II conversion were observed in obstructed kidneys. The level of p62 and LC3-I/LC3-II conversion were not further increased in UOO mice administrated with chloroquine, indicating that autophagy is impaired during the progression of renal fibrosis. Conversely, accumulation of p62, Keap1, ubiquitinated proteins supports the notion that autophagy is defective in the UOO model since Keap1 is degraded in a p62-dependent manner and p62 plays a central role for targeting ubiquitinated proteins to autophagosomes. Accumulation of p62 and collagen-I was slightly reduced in Beclin-1 Tg mice and in mice receiving Torin-1, suggesting that impaired autophagy status following UOO injury could not be efficiently recovered by upregulation of autophagy.

Conclusions: Accumulation of renal fibrosis is accompanied by defects in autophagy in the UOO model. Overexpression of Beclin-1 in transgenic mice and administration of Torin-1 were unable to completely reverse the autophagy deficiency.

Funding: Veterans Affairs Support

TH-PO149

Autophagy Is Impaired in Unilateral Ureteral Obstruction (UUO) Model of Renal Fibrosis - I

Poster/Thursday

Funding: Government Support - Non-U.S.

TH-PO146

Elevated Soluble Tumor Necrosis Factor Alpha Receptor 1 and 2 Concentrations in Hemodialysis Patients Are Not Reflected by Alterations in Membrane Expression

Background: Elevated serum concentration of soluble TNF receptor 1 (sTNFR1) and 2 (sTNFR2) and TNFα in hemodialysis (HD) patients are at least partly attributed to decreased renal clearance. It is not known whether the membrane expression of these receptors is altered in HD and as consequence also contributes to the differences in serum concentrations of TNFα.

Methods: Whole blood samples of healthy controls (C) and predialysis samples of HD patients were labelled with fluorescent antibodies (mTNFR1, mTNFR2 and anti-mTNFR2 and analyzed by flow cytometry. The mean fluorescence intensity (MFI) was measured when all leukocytes were gated together (mTNFR1, mTNFR2 and anti-mTNFR2 and analyzed by flow cytometry. The mean fluorescence intensity (MFI) was measured when all leukocytes were gated together (MFI: as well as the MFI of the monocytes, granulocytes and lymphocytes when gated separately. Soluble concentrations were measured by ELISA.

Results: The soluble concentrations were markedly higher in HD for sTNFR1 (C: 993 vs HD: 9558 pg/ml, p < 0.001), sTNFR2 (C:2245 vs HD: 16344 pg/ml, p < 0.001) and TNFα and HD patients were labelled with fluorescence anti-membrane (mTNFR1, mTNFR2 and anti-mTNFR2 in parallel in order to unravel the link between both.

Conclusions: The data indicates that the elevated concentrations sTNFR1 and sTNFR2 in hemodialysis patients compared to healthy controls were rather due to a decreased renal clearance than an altered cellular expression.

Funding: Government Support - Non-U.S.

TH-PO147

Blockage of IL-8 Receptor Signaling Inhibits Cyst Development in ADPKD

Background: In this study, we focused on whether IL-8 signaling is associated with renal cyst formation, and tested the possibility of IL-8 as a new therapeutic target for PKD. First, IL-8 secretion and expression of its receptor increased remarkably in human PKD cells. Furthermore, receptors specific for IL-8 was easily detected particularly at the cyst-lining epithelium of the kidney in human patients with PKD. IL-8 secretion decreased under treatment with an IL-8 receptor antagonist, and activation of the signaling molecules diminished as well. A three-dimensional culture was performed to understand how IL-8 affected cyst formation, and resulted in alleviation of cystogenesis after blocking the IL-8 receptor signals.

Conclusions: These results suggest that IL-8 and its mediating signals might be a factor stimulating cystogenesis in ADPKD and have potential as a new biomarker and therapeutic target for the disease.

Funding: Veterans Affairs Support

TH-PO148

Prostaglandin E2 Inhibits Growth and Stimulates Sodium Transporters through EP4, but Increases Fibronectin and ROS Production through EP1

Background: Proximal tubule (PT) growth promotes hypertrophy in chronic kidney disease, which in turn contributes to hyperfiltration. Prostaglandin (PG) E2, is a key regulator of renal growth and tubular transport, but its role in the PT is unknown.

Methods: Transforming growth factor β (TGFβ) is a main regulator of PT in kidney disease, thus we compared the effects of PGE2 to TGFβ. Mouse PT cells (MCT) were stimulated for 24-hours with PGE2, in the presence or absence of TGFβ.

Results: By Realtime PCR we showed that PGE2, EP receptors are increased 2-3 fold by PGE2, and TGFβ, but EP, is unchanged. EP, was inhibited with the EP, receptor antagonist ONO-8711. Both TGFβ and PGE2; attenuated DNA and protein synthesis, with 50-80 % reductions in proliferation and the formation of |PAC| in human medulla, co-localizing with AQP2. P2Y2, receptor labeling in CD was present exclusively in AQP2, P2Y2-positive cells suggesting expression in principal, but not intercalated cells.

Conclusions: The observed expression pattern of P2Y2, P2Y2, and AQP2 in vasopressin-responsive principle cells is consistent with the in vivo effects of pharmacological blockade of P2Y2 in normal and human tumor-bearing animals. The functional significance of the expression of P2Y2 on the brush border of PT cells and in the cortical arterioles needs to be elucidated.

Funding: Veterans Affairs Support, Private Foundation Support
TH-PO150

Background: Aging is associated with progressive organ fibrosis. Microvascular rarefaction is a prominent companion of fibrotic process occurring with a relative synchrony in all organs, kidney included, partly due to impaired angiogenesis in the elderly. Therefore, we hypothesize that a common denominator – an anti-angiogenic substance - might exist to explain it.

Methods: Endostatin, a key anti-angiogenic factor, is a 20-22 kDa c-terminal fragment of collagen XVIII, a ubiquitous component of sub-endothelial membranes especially in vessels with fenestrated endothelium, like those in renal glomeruli and peritubular capillaries. Therefore, we sought to investigate the level of endostatin in kidney and plasma of aging mice by immunoblotting and ELISA as well as cellular and tubular effect of endostatin.

Results: In aged mice (22 mo-old) kidney, the expression of p16 gene and the ratio of short/long (S/L) endoglin, markers of senescence, were increased as examined by RT-PCR. Examination of aged kidney showed decreased microvascular density. The protein level of endostatin in the plasma and kidney samples from aged mice was 2.3 and 3 fold increased.

To understand cellular effects of Endostatin, we isolated primary endothelial cells (ECs) from kidney of control mice by enzymatic digestion followed by double selection on CD31-coated magnetic beads. The isolated ECs (CD31+, VE-cadherin+ and Endoglin+ ) were treated with mouse Endostatin at concentrations 25 µg/ml for 5.5 days. Cells showed signs of impaired angiogenesis, as evidenced by decreased formation of cord-like structures. Endostatin treatment also decreased VE-cadherin expression with a concomitant increase in the expression of α-smooth muscle actin in primary EC, indicative of a phenotypic switch toward myofibroblast-like normal transition.

Conclusions: These data document that 1) Endostatin levels are increased in the aged kidney and plasma and 2) Endostatin causes primary EC transdifferentiation into mesangial-like cells. The mechanism of endostatin action may account for microvascular rarefaction of kidney aging.

Funding: NIDDK Support

TH-PO151
RNA-Seq Mapping of G Protein-Coupled Receptor Expression along the Neprhon and Collecting Duct Jae Wook Lee, Fahad Saeed, Chung-Lin Chou, Mark A. Knepper. NIH.

Background: G protein-coupled receptors (GPCRs) are important regulators of physiological function in renal tubule epithelia. Here we describe the expression profile of all known GPCRs along the renal tubule using RNA-seq.

Methods: We manually microdissected each renal tubule segment from collagenase-treated kidneys, using a high resolution microscopy system capable of discriminating cell types. After reverse transcription and amplification, cDNA libraries were sequenced using an Illumina HiSeq 2000 sequencer. Sequences were mapped to the rat reference genome of all known GPCRs along the renal tubule using RNA-seq.

Of 853 annotated rat GPCRs, 60 GPCRs had RPKM > 1.0 in at least one renal tubule segment. Expression patterns of vasopressin receptors (Avpr1a and Avpr2), calcium-sensing receptor (Casr), and other receptors (Pthr, Gpr3, Gpr4, and Gpr56) were consistent with the literature. Based on rule-based clustering algorithm, we identified segment-specific expression patterns for additional GPCRs. These include: growth hormone-releasing hormone receptor (Ghrhr) in the thin descending and ascending limbs (median RPKM 0.7 and 17.5); taste receptor type 1, member 1 (Tas1r1) in the medullary and cortical thick ascending limbs (6.1 and 3.1); frizzled proteins in the connecting tubule, cortical collecting duct, and outer medulary collecting duct (Fzd1, 8.9, 31.8, 11.5 and Fzd4, 44.1, 27.4, 14.7); soluble frizzled-related protein 2 (Sfrp2) in the cortical collecting duct and distal convoluted tubule (50.5 and 60.8); and purinergic receptors in the collecting duct (P2yr2) in the cortical collecting duct, 6.6; P2ryr14 in the outer medullary collecting duct, 166.7). Eleven orphan GPCRs were found. Gpr35 and Gpr5c5 showed widespread expression along the renal tubule.

Conclusions: Further studies are needed to assign physiological functions to the GPCRs not previously known to be expressed in the kidney. Additional analysis of these RNA-seq data (in addition to GPCR genes) will provide further information on segment-specific signaling pathways.

Funding: Other NIH Support - NHLBI

TH-PO152
APOL1 Risk Variants Cause a Greater Increase in Autophagy, Apoptosis and Necrosis in Podocytes, Accompanied by Decreased Podocyte Viability Compared to Wild-Type APOL1 Xianlan Jiang, Kang Cheng, Partab Rai, Tejinder Singh, Nirupama Chandel, Rivka Lederman, Ashwani Malhotra, Pravin C. Singhal. Medicine, Hofstra North Shore LIJ Medical Center; Great Neck, NY.

Background: Compared with European Americans, African Americans develop much higher rates of nephropathy including hypertension-associated end-stage renal disease (ESRD), focal segmental glomerulosclerosis (FSGS), and HIV-associated nephropathy (HIVAN). Recently, emerging reports show that this major health disparity is strongly associated with two coding sequence variants in the APOL1 gene encoding Apolipoprotein L1 (Apol1). However, the cellular function of Apol1 and the role of these variants in the risk for nephropathy are still unknown.

Methods: Lentiviruses for over expression of Apol1 wild type and variant proteins were constructed, using constructs kindly provided by the laboratory of Karl Skorecki at the Technion in Haifa. Human podocytes were infected with these lentiviruses. Western blots, MTT assay, and staining assays with acridine orange, Annexin V, or 7-AAD were performed to compare the effects of wild type and variant APOL1 on human podocytes.

Results: Western blots results showed that Apol1 wild type and variant proteins were successfully over expressed in human podocytes. Staining assays revealed that expression of wild type Apol1 increased autophagy, apoptosis, and necrosis, while all of these effects were further increased by overexpression of the Apol1 risk variants. MTT assay indicated that cell viability was dramatically decreased by Apol1 risk variants.

Conclusions: Apol1 risk variants displayed cytotoxicity to podocytes through enhancing autophagy, apoptosis, and necrosis. Since loss of podocytes is an initiating step in the development of FSGS, the present study supports a pathogenic role for podocyte expression of APOL1 risk variants in the development of kidney lesions in susceptible subjects.

Funding: NIDDK Support

TH-PO153
Effect of Uremic Toxins on Leukocytes: The Enigma of Organic Solute Transport Finally Unraveled Eva Scheper,1 Henrikus A. M. Mutua,2 Annemieke Dhondt,1 Nathalie Neirynck,1 Rosalinde Masereeuw,1 Raymond C. Vanholder,1 Griet Lrl Glorieux.1 1Internal Medicine, Nephrology Division, Ghent Univ Hospital, Ghent, Belgium; 2Pharmacology and Toxicology, Radboud Univ Nijmegen Medical Centre, Nijmegen, Netherlands.

Background: Several uremic toxins (UT), both protein bound and not, have been shown to cause leukocyte dysfunction. As a consequence of the increased levels of UT in the circulation in chronic kidney disease, induction of cytotoxicity must be linked to increased hematopoietic levels. However, until now, the expression of organic solute transporters, as abundantly expressed on e.g. proximal tubular cells, has never been demonstrated on leukocytes.

Methods: Monocytes were isolated by a positive selection using MACS after Ficoll density gradient centration from healthy controls (C) and hemodialysis patients (HD). Gene expression of the uptake transporters organic anion transporter 1 (OAT1), OAT3, organic cation transporter 2 (OCT2), OATpolypeptide4C1 (OATP4C1) was evaluated using RT-PCR. In addition, expression at protein level of OATP4C1 [mean fluorescence intensity (MFI)] was evaluated by flow cytometry.

Results: Only the uptake transporter, OATP4C1, was expressed in monocytes. No difference in OATP4C1 mRNA levels could be observed in monocytes from HD (n=9) versus C (n=10) (ACT: 7.9±0.4 vs. 8.1±0.6, NS). Protein expression of OATP4C1 on monocytes was confirmed by flow cytometry also revealing expression on lymphocytes and granulocytes. However, no significant difference in the protein expression level in HD (n=8) versus C (n=4) was observed (470±139 vs. 479±155; 282±102 vs. 272±120; 532±146 vs. 692±181, respectively; NS), OATP4C1 was significantly more expressed on monocytes and granulocytes compared to lymphocytes (P<0.05).

Conclusions: These data show for the first time the expression of an organic uptake transporter protein, OATP4C1, on leukocytes. This transporter has been suggested to play a role in the uptake of the known UT. Thus, different UT could enter leukocytes via OATP4C1 contributing to many of the known cytotoxic effects. The functionality of the transporter in HD remains to be evaluated but this protein could be a target for preventing cytotoxicity in CKD.

TH-PO154
Nanoscale Protein Architecture of the Mouse and Human Kidney Glomerular Basement Membrane Hani Suleiman,1 Lei Zhang,1 Jeffrey H. Miner,2 Andrey S. Shaw,1 Adish Dani.1 1Pathology & Immunology, Washington Univ, Saint Louis, MO; 2Renal Div, Washington Univ, Saint Louis, MO.

Background: In multicellular organisms, proteins of the extracellular matrix play structural and functional roles in a variety of organs, so understanding ECM protein organization is an important goal. The kidney glomerular basement membrane (GBM) is a unique, thick BM that is an integral part of the glomerular filtration barrier and participates in filtering large volumes of plasma to form the ultrafiltrate. The GBM is thought to result from fusion of two distinct basement membranes secreted by two different cells, podocytes and endothelial cells.

Methods: We used well characterized epitope-specific antibodies to carry out sub-diffraction resolution stochastic optical reconstruction microscopy (STORM) and deep-etch electron microscopy correlation to resolve the in situ molecular organization of proteins within the mouse and human GBM.

Results: We constructed a molecular reference frame that revealed a laminar organization of ECM proteins within the GBM, Agrin, a large heparan sulfate proteoglycan, was localized to two parallel leaflets with a peak distance between each of 138 nm. Within this reference, we mapped the position of a panel of antibodies in the GBM, including the integrin β1 ectodomain. The laminin α5 C-terminus co-localized with podocyte and endothelial cell integrin β1, whereas the more N-terminal LM-521 epitopes were found near the center of the GBM, revealing a definitive orientation. The human GBM possesses an outer layer of collagen α3β4α5(IV) covering more than 50% of the GBM’s thickness, but it is excluded from the GBM’s edges where integrin β1 penetrated.

Funding: Other NIH Support - NHLBI

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

Underline represents presenting author/disclosure.
Conclusions: Separate analyses of domains near the N- and C-termini of agrin, laminin, and collagen IV in mouse and human revealed a highly organized arrangement within the GBE visualized in situ. The results are consistent with separate basement membrane layers contributed by podocytes and endothelium. Integrin β1’s major ligands are likely the laminin α5-C-terminus and agrin.

Funding: NIDDK Support

TH-PO155
Indoxyl Sulfate Signals for Rapid mRNA Stabilization of Cbp/p300-Interacting Transactivator with Glu/Asp-Rich Carboxy-Terminal Domain 2 (CITED2) and Suppresses the Expression of Hypoxia-Inducible Genes in Experimental CKD and Uremia
Tetsuhiro Tanaka, Junna Yamaguchi, Yoshiki Higashijima, Masasumi Nangaku. Div of Nephrology and Endocrinology, Univ of Tokyo School of Medicine, Tokyo, Japan.

Background: Tubulointerstitial hypoxia serves as a final common pathway in progressive renal disease. Circumstantial evidence suggests that the function of hypoxia-inducible factor (HIF)-1α may be suppressed in a CKD milieu. In this study, we investigated the effect of indoxyl sulfate (IS) on the expression of hypoxia-inducible genes in vitro and in vivo.

Methods: In vitro, the expression of HIF-1α, cITED2 and HIF-1 target genes was quantified by immunoblotting and real-time PCR. Binding of HIF-1α to the target gene promoters was evaluated by chromatin immunoprecipitation (ChIP). mRNA stability of cITED2 was measured by actinomycin D treatment. The role of MAP kinase pathways was evaluated by using specific inhibitors. In vivo, the effect of IS on HIF-1α target genes was investigated in the rat remnant kidney, with or without the oral adsortent, AST-120. Additionally, angiogenic, HIF-1 target genes was quantified in the ischemotolented induced heart failure (HF) model in rats treated with or without Indoxyl.

Results: In vitro, IS reduced the hypoxic induction of HIF-1α-target genes, which was not associated with quantitative changes in HIF-1α, but with the functional impairment of the HIF-1α C-terminal transactivator domain (CTAD). Among candidate suppressors of the HIF-1αCTAD, CITED2 was significantly upregulated by IS. The induction of CITED2 was mediated by post-transcriptional mRNA stabilization through the ERK1/2 signaling. In a CKD model in vivo, tubular expression of several HIF-1α-target genes, such as vascular endothelial growth factor (VEGF) and heme oxygenase-1 (HO-1) was markedly restored by treatment with AST-120. Furthermore, Indoxyl significantly suppressed the induction of hypoxia inducible, angiogenic genes in rats with heart failure.

Conclusions: Results of these studies reveal a novel role of IS in modulating the transcriptional response of HIF-1α and provide insight into the molecular mechanisms underlying progressive nephropathies as well as cardiorenal anemia syndrome.

Funding: Government Support - Non-U.S.

TH-PO156
Pharmacological Blockade of ADP-Activated P2Y1 Receptor in Rat IMCD Potentiates dDAVP-Induced AQP2, AQP3 and V2 Receptor Expression
Yue Zhang,1 Younis Baqi,2 Noel G. Carlson,1 Donald E. Kohan,1 Christa E. Cobitz, John J. Lepore. 1Division of Nephrology and Endocrinology, University of Rochester, Rochester, NY; 2Univ of Bonn, Bonn, Germany.

Background: P2Y1 receptor (R) is an ADP-activated G protein-coupled receptor that inhibits adenyl cyclase activity. We found that P2Y1−R protein is expressed in rat renal medullary collecting ducts (IMCD), and its irreversible blockade by the administration of ISYS-39179 is associated with the suppression of transcription of VEGF and heme oxygenase-1 (HO-1) genes in rats with heart failure. ISYS-39179 also markedly restored renal cortical expression of multiple HIF-1α-target genes, such as VEGF and HO-1 in rats treated with or without Indoxyl.

Methods: In vitro, ISYS-39179 reduced the hypoxic induction of HIF-1α-target genes, which was not associated with quantitative changes in HIF-1α, but with the functional impairment of the HIF-1α C-terminal transactivator domain (CTAD). Among candidate suppressors of the HIF-1αCTAD, CITED2 was significantly upregulated by IS. The induction of CITED2 was mediated by post-transcriptional mRNA stabilization through the ERK1/2 signaling. In a CKD model in vivo, tubular expression of several HIF-1α-target genes, such as vascular endothelial growth factor (VEGF) and heme oxygenase-1 (HO-1) was markedly restored by treatment with AST-120. Furthermore, Indoxyl significantly suppressed the induction of hypoxia inducible, angiogenic genes in rats with heart failure.

Conclusions: Results of these studies reveal a novel role of IS in modulating the transcriptional response of HIF-1α and provide insight into the molecular mechanisms underlying progressive nephropathies as well as cardiorenal anemia syndrome.

Funding: Government Support - Non-U.S.

TH-PO157
Targeting PHD2 with Antisense ASOs Can Increase Erythropoietin Production for the Treatment of Anemia Associated with Chronic Kidney Disease

Background: Anemia is a prevalent and premature comorbidity in chronic kidney disease (CKD). It is associated with multiple adverse clinical consequences including increased mortality. Today Erythropoietin-stimulating agents (ESAs), together with iron supplements, are the cornerstone of therapy for correcting anemia in CKD patients. Prolyl hydroxylase domain protein 2 (PHD2) is an oxygen/redox-sensitive enzyme that induces cellular adaptations to stress conditions. Inactivation of PHD2 enhances a hypoxia-inducible transcription factor (HIF)-mediated detoxification program in healthy organs, with the dramatic oxidative damage, organ failure, and tissue demise. In the present study, we examined the effects of reducing PHD2 mRNA expression in liver and kidney in half-c mice, using an optimized antisense oligonucleotide (ASO) designed specifically for PHD2.

Methods: ASO was administered subcutaneously at a dose of 25 mg/kg, twice a week for 3 weeks.

Results: ASO treatment caused ~80% and 65% reduction in PHD2 mRNA expression in liver and kidney respectively. A 7-fold increase in spleen weight was observed as compared to saline treated group, similar to what was observed in PHD2 conditional knockout mice (BLOOD, 15 March 2008, Vol 11 (6) 3229-3235). In addition, PHD2 ASO treated kidney EPO mRNA levels were increased 600 fold compared to the saline treated group. Further analysis of the kidney in situ EPO RNA staining confirmed the increase and showed it to be localized to the cells in the interstitial space. As a result, serum EPO levels were also elevated after PHD2 ASO treatment, ~500 ± 128 (pg/ml) in PHD2 treatment group compared to saline control group, which is ~60 ± 13 (pg/ml).

Conclusions: In conclusion, specific reduction of PHD2 with ASO treatment in mice increased EPO production and this approach may have therapeutic implications for treatment of anemia associated CKD.

Funding: Pharmaceutical Company Support - ISIS Pharmaceuticals

TH-PO158
Four-Week Safety, Efficacy and Pharmacodynamic Study of Prolyl Hydroxylase Inhibitor GSK1278863 in Anemic Non-Dialysis Subjects Not Receiving Recombinant Human Erythropoietin

Background: Prolyl hydroxylase inhibitors (PHIs), such as GSK1278863, are an emerging therapeutic class of oral agents for the treatment of anemia. PHIs inhibit hypoxia inducible factor (HIF)-prolyl hydroxylases, resulting in accumulation of stable HIFs. Translating these findings, thus stimulating pathways activated during hypoxia, including erythropoiesis and iron mobilization. PHIs raise hemoglobin (Hgb) concentrations with lower circulating erythropoietin (EPO) levels than recombinant human erythropoietins (rhEPOs; Provenzano, 2011), therefore potentially reducing the increased cardiovascular risk that has been associated with rhEPO therapy (Pfeffer, 2009).

Methods: This randomized, placebo-controlled, double-blind study explored the relationship between GSK1278863 dose and Hgb response in subjects with anemia secondary to chronic kidney disease (CKD; stage 3-5) who were naïve to rhEPO and not on iron supplementation (NDS). The study also explored the effects of GSK1278863 on circulating EPO, hepcidin and vascular endothelial growth factor (VEGF) levels. Subjects with a stable baseline Hgb of 8.5-11.0g/dL were randomized to receive 0.5, 2 or 5mg GSK1278863 or placebo for 4 weeks.

Results: GSK1278863 produced a dose-dependent change in mean Hgb from baseline at Week 4 (placebo: -0.26g/dL; 0.5mg: 0.12g/dL; 2mg: 0.32g/dL; 5mg: 0.95g/dL). Hepcidin levels also decreased in a dose-dependent manner. The increases in Hgb occurred with small, dose-dependent increases in EPO within or close to the normal physiologic range and no changes in VEGF. GSK1278863 was generally safe and well tolerated.

Conclusions: These data inform the dose-response relationship of GSK1278863 for Hgb elevation in anemic NDD CKD subjects not receiving rhEPO, and they suggest that GSK1278863 can raise Hgb within a clinically relevant range with small elevations in EPO and without increasing VEGF.

Funding: Pharmaceutical Company Support - GlaxoSmithKline

TH-PO159
Hepcidin in Chronic Kidney Disease after Iron Infusion and Its Relationship to Haemoglobin Increment Sourabh Chaud,1 Douglas G. Ward,2 Zhi-Yan Valerie Ng,1 Mark Trehan Drayson,3 Richard Borrows.1 Queen Elizabeth Hospital Birmingham, United Kingdom; 1Univ of Birmingham.

Background: There is a drive to use less EPO and more iron infusions for CKD anaemia management but this still comes at a financial and potentially toxic cost. Hepcidin is an iron regulator which promotes iron retention in the reticulo-endothelial system. We investigated hepcidin and traditional clinical iron markers to their predictive utility to haemoglobin (Hb) increment post iron infusion in CKD patients and what inferences hepcidin levels in CKD.

Methods: Over a 6 month period, 129 consecutive non-dialysis CKD patients attended our bolus Ferinject® service as part of their anaemia management. Hepcidin levels as determined by mass spectrometry, transferrin saturation (TSAT), ferritin, eGFR, liver function tests, Hb and high sensitive CRP levels (hsCRP) were measured pre iron infusion and 6 weeks later.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Results: Ferinject® mean dose was 12.6mg/Kg. Ferritin and TSAT were highly correlated. In a multivariate model (adjusted for ferritin, hsCRP, eGFR, age, iron dose/ weight, gender, functioning renal transplant, access, use of ESA, anti-proliferative, ACE I/ARB, low B12 and a low folate) only ferritin was significantly associated with hepcidin levels (CI 0.594 (0.473-0.715) p<0.001). eGFR was the only predictor of pre-infusion HB level. In the multivariate model adjusted for pre-infusion HB level, hepcidin was an independent predictor of Hb increase post Ferinject® infusion (CI -0.84 (-1.38 to -0.31) p<0.002). Ferritin and hepcidin had similar predictive utility for a 1g/dL HB increase post Ferinject® infusion (c-statistics: 0.68, 0.70, 0.69). Alkaline phosphatase was significantly increased post Ferinject® infusion (p<0.001).

Conclusions: Hepcidin is an iron storage marker which is moderately predictive for HB increase following iv Ferinject® infusion. Although displaying similar predictive performance to ferritin and TSAT, hepcidin may also play a mechanistic role. This data suggests hepcidin antagonists may be of use for patients with higher hepcidin levels to increase iron utilisation following intravenous infusion.

TH-PO160
Atherosclerotic Plaque Characterization and Heme Oxygenase-1 Expression in Chronic Kidney Disease: The ‘Vulnerable Plaque Phenotype’
Kristien El Daenen,1 Inge Fourneau,2 Eric Verbeken,1 Bert Bammens,1
1Laboratory of Nephrology, KU Leuven, Belgium; 2Vascular Surgery, KU Leuven, Belgium; 1Dept of Imaging and Pathology, KU Leuven, Belgium.

Background: CKD is characterized by accelerated atherosclerosis as compared to the general population. Heme Oxygenase-1 (HO-1), an inducible heme degrading enzyme, is protective against atherosclerosis and has a major role in plaque stabilization a.o. through inhibition of monocyte adhesion and differentiation.

Methods: Patients planned for peripheral artery or abdominal aorta aneurysm surgery were included to retrieve an arterial biopsy during surgery (n=82). For the purpose of this study, the biopsies of 23 patients with CKD stages 3-5D were compared with those of 36 patients without CKD. Atherosclerotic plaques were scored blindly for lesion type [intimal thickening or xanthoma (IT or IX)], (thin) fibrous cap atheroma (Tf/FCA) or fibrocalcific plaque (FCP), according to an adapted scoring system based on the AHA classification by Virmani et al, presence of inflammation and/or plaque complications (erosion, rupture, hemorrhage, necrosis specified). HO-1 expression was judged semi-quantitatively by immunostaining of the paraffin sections.

Results: CKD and non-CKD patients were well-matched for Framingham risk factors, cardiovascular event history and lipidlowering therapy. There was an equal distribution of lesion types in the two groups. Plaques of CKD patients showed higher inflammatory activity by higher number of foam cells, independent of statin use (p=0.035). There were more complicated plaques in the CKD group (p=0.03). There was clear HO-1 expression in (Tf/FCA and FCP, but the semi-quantitative scoring system didn’t reveal any significant differences between the CKD and non-CKD patients.

Conclusions: Atherosclerotic plaques of CKD patients have higher inflammatory activity and higher rates of complications as compared to non-CKD patients. These findings are supportive for a ‘vulnerable plaque phenotype’ of atherosclerosis in CKD. Expression of HO-1, although known to play a role in plaque stabilisation, is not different between the two groups. Whether this finding represents a relative lack of HO-1 effectiveness in CKD needs further investigation.

TH-PO161
LDL Receptor Deficient Mice Are a Suitable Model of Aggravated Atherosclerosis in Renal Impairment and the Impact of Bone Marrow Derived Cytokines
Shivyle Von Vienthinhoff, Shuwang Ge, Barbara Hertel, Inga Soerensen, Hermann G. Haller. Internal Medicine, Hannover Medical School, Germany.

Background: Chronic kidney disease significantly elevates the risk of atherosclerosis. Inflammatory leukocyte infiltration of the vascular wall is mediated by specific cytokines in normal kidney function. To date, the experimental study of atherosclerosis in renal failure has used the Apolipoprotein E deficient mouse that is limited by (a) excessive hyperlipidemia and (b) the fact that ApoE is expressed in diverse cell types including bone marrow cells.

Methods: LDLr−/− mice underwent unilateral nephrectomy or sham surgery and were maintained on high-fat diet for six weeks. Glomerular filtration rate was assessed by FITC-inulin clearance. Bone marrow transplantation was conducted after lethal irradiation two weeks before renal surgery. Efficiency of bone marrow transplantation was assessed by PCR and flow cytometry. Aortic lesion size was quantified histologically and leukocyte infiltration determined by confocal microscopy and flow cytometry.

Results: Unilateral nephrectomy did not significantly alter serum creatinine but reduced measured glomerular filtration rate by 30% six weeks after surgery. This significantly increased aortic root lesion size. Similar effects were observed in male and female mice. Circulating leukocytes, erythrocyte and thrombocyte counts, total cholesterol and triglycerides were not significantly altered, however, in renal impairment there was a trend towards lower assessed LDL and VLDL, assessed by lipid chromatography. Renal impairment enhanced aortic leukocyte accumulation and proliferation. Bone marrow transplantation depleted specific T cell cytokine expression and decreased the effect of renal impairment on atherosclerotic lesion size.

Conclusions: Unilateral nephrectomy significantly decreases GFR and increases atherosclerotic lesion size in LDLr−/− mice. Reconstitution with specific cytokine deficient bone marrow in a new approach for the study of the impact of kidney function on inflammation in atherosclerosis.

Funding: Government Support - Non-U.S.

TH-PO162
Possible Involvement of microRNAs in Vascular Damage in Experimental CKD
Fatih Taib,1 Valérie Metzinger-Le Muth,2 Eleonore Ourouda Mbaya,1 Laurent Metzinger,2 Ziad Massy,2
1Univ Picardie Jules Verne, Amiens, France; 2Univ Paris 13 Nord, Paris, France; 1Chief, Div of Nephrology, Paris-Ile-de-France-Ouest Univ (UVSQ), Paris, France.

Background: Chronic kidney disease (CKD) is associated with vascular calcifications and atherosclerosis. There is a need to discover novel biomarkers in order to achieve earlier detection of these disorders, predict illness progression and response to adjuvant therapy. We focused on microRNAs since they are implicated in a variety of cellular functions in cardiovascularphysiopathology.

Methods: We examined changes over time in microRNAs in aortas of CKD and non-CKD wild type mice and of CKD and non-CKD apolipoprotein E knock-out mice. We evaluated the expression of miRNAs known to be implicated in vascular biology (miR-126, -143, -145, -212, -222 and -223), in order to assess their prognostic significance.

Results: The vascular smooth muscle-specific miR-143 and miR-145 were lowered in the pathological states and the level of protein target Myocardin was accordingly increased. The inflammatory miR-223 was increased at the later stages of CKD, and specific protein targets NFI-A and GLUT-4 were dramatically decreased. Expression of miR-126 was severely increased and expression of protein targets VCA-M1 and SDF-1 was altered during the course of CKD. Finally, we detected marginal changes in miR-221 and miR-222 expression. The phosphate binding drug sevelamer alleviates miRNA deregulations suggesting a direct link between the miRNA alterations we found and vascular disorders.

Conclusions: In conclusion, miR-126, -143, -145 and -223 are deregulated during the course of CKD and miRNAs are involved in our CKD and atherosclerotic models, and are thus potential biomarkers of these diseases.

Funding: Government Support - Non-U.S.

TH-PO163
Apolipoprotein B/A1 Ratio, as a Risk Predictor of Cardiovascular Disease in Patients with Chronic Kidney Disease
Soo Bong Lee, Il Young Kim, Dong Won Lee, Min Ji Shin, Byeong Yun Yang, Harin Rhee, Eun Young Seong, Ihm Soo Kwak. Dept of Internal Medicine, Pusan National Univ Sch of Medicine, Republic of Korea.

Background: The apolipoprotein B/A1 ratio (apoB/A1) was known to be risk predictor of cardiovascular disease (CVD). CVD is the leading cause of death in chronic kidney disease (CKD) patients. Measuring carotid artery intimal-medial thickness (CIMT) is non-invasive modality used to evaluate subclinical atherosclerosis and to predict future CVD. In this study, we hypothesized that apo B/A1 could be associated with CVD in CKD patients and investigated the association between apo B/A1 and CIMT.

Methods: We retrospectively reviewed the 293 patients who had visited the health screening and promotion center in our university hospital in Korea. The patients were divided into 2 groups which are CKD group (n=99, estimated glomerular filtration rate (eGFR) 15-59 mL/min) and non-CKD group (n=194, eGFR ≥ 60 mL/min). Information on demographics and clinical data were obtained in each patient at the time of measuring CIMT. CIMT was measured by high-resolution B-mode ultrasonography. To investigate which factors are associated with CIMT in each 2 groups, simple and multiple linear regression analysis between variables in baseline characteristics and CIMT were performed.

Results: In simple linear regression analysis, non-CKD group showed age, presence of diabetes and presence of hypertension correlated with CIMT. However, in CKD group, not only age, presence of diabetes and presence of hypertension but also apo B/A1(r=0.521, P=0.001) correlated with CIMT. In multiple linear regression analysis, non-CKD group presence of diabetes, and presence of hypertension were independently associated with CIMT. In CKD group, apo B/A1 in addition to age , presence of diabetes, and presence of hypertension was independently associated with CIMT.

Conclusions: This study showed serum apo B/A1 was independently associated with CIMT in non-CKD group. Because CIMT is a strong predictor of cardiovascular risk stratification in CKD patients.

TH-PO164
Increased Inducibility of Ventricular Arrhythmia in a Rat Model of Chronic Kidney Disease
Chin-Hsiang Hsueh,1 Neal X. Chen,2 Peng-Sheng Chen,1 Shien F. Lin,1 Sharon M. Moe.2 1Div of Cardiology, Indiana Univ, Indpls, IN; 2Div of Cardiology, Indiana Univ, Indpls, IN.

Background: Patients with chronic kidney disease (CKD) suffer from higher incidence of cardiovascular mortality than those without CKD and over 25% of patients on dialysis die of sudden cardiac death (SCD). The mechanisms remain unclear. We used a rat model to study mechanisms of sudden cardiac death in CKD.

Methods: We studied 7 normal rats (NL) and 9 C/−/− Hsd:SPRD rat with CKD (CKD) at 35-45 weeks old, which we have observed to have unexpected sudden death with progressive CKD. Hearts were removed for Langendorff perfusion and optical mapping.

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

139A
We determined ventricular fibre inducibility (VF inducibility), action potential duration (APD), cardiac transient duration (CaT), dominant frequency during VF and used real time PCR to quantify gene expression.

**Results:** CKD rats had higher blood urea nitrogen (BUN) than control (52.4±6.9 vs. 23.8±1.5 mg/dL, p<0.01). Echocardiography and histology documented hypertrophic myocardium in CKD rats, but the LV ejection fraction of CKD rats was comparable to that of normal rat (72±4%). CKD rats had longer RR interval (237±11 ms) than normal (206±9 ms, p<0.05). APD at the 80% of repolarization (APD80) in CKD rats (78±5) was longer than normal (61±4 ms, p<0.05), but CaT80 was unchanged (98±4 vs. 91±4 ms). VF was induced in 7 of 9 CKD rats compared to 1 of 7 normal rats (p<0.005). Dominant frequency during VF was higher in CKD rats than in NL rats (26.1 ±2 Hz) than in NL rats (19 ±8.2 Hz). p<0.05. There was up-regulation of calcium transporters (TRP6P and NCX1), angiotensin I receptor, and TGFβ1 mRNA (p<0.05) suggesting altered micro-environment in CKD rats that are known to predispose to arrhythmias.

**Conclusions:** CKD rats with advanced CKD, compared to age matched normal rats, had bradycardia, hypertrophic myocardium and longer APD than control. The hearts exhibited increased VF inducibility with slower activation rate (lower dominant frequency). These data demonstrate that structural and/or cellular level changes in CKD predispose to ventricular arrhythmias and are likely to be involved in the increased risk of ventricular arrhythmias and sudden cardiac death in CKD.

**TH-PO165**

**Glyoxalase I Prevents Age-Related Endothelial Dysfunction through Modulation of eNOS Phosphorylation**


**Background:** Development of chronic kidney disease (CKD) is closely related to aging. Both glycative stress and endothelial dysfunction are linked to aging-associated changes including CKD. To elucidate the mechanisms for CKD progression in elderly patients, we investigated how glycative stress alters endothelial function with aging, using experimental anti-glycation model rats with systemic overexpression of glyoxalase I (GLO1), which determines a representative anti-glycation precursor methylglyoxal (MG). We studied in pre-dialysis patients. To investigate the mechanism on the change of endothelial function, we studied nitrotyrosine formation, protein expression and post-translational modification of endothelial nitric oxide synthase (eNOS).

**Methods:** Four groups of rats were examined, namely young (13-week-old) and mid-age (53-week-old) wild type (WT) and GLO1 transgenic (Tg) rats. Endothelial glycation level was evaluated by immunohistochemistry for MG-modified proteins. Age-related changes in endothelial-dependent and independent vasorelaxation were assessed by vascular functional studies. To investigate the mechanism on the change of endothelial function, we studied nitrotyrosine formation, protein expression and post-translational modification of endothelial nitric oxide synthase (eNOS).

**Results:** Accelerated MG-modification of proteins by aging was significantly attenuated in Tg endothelium. Age-related impairment of endothelium-dependent vasorelaxation was attenuated in Tg rats, whereas vasorelaxation independent of endothelium was identical between WT and Tg rats. While total and dimeric form of eNOS did not differ between WT and Tg rats, inhibitory eNOS phosphorylation on Thr495, which regulates a representative glycation precursor methylglyoxal (MG), was significantly reduced in Tg rats.

**Conclusions:** GLO1 attenuated age-related glycation stress and endothelial dysfunction in endothelium, with decreased eNOS phosphorylation on Thr495. Our study strongly suggests that regulation of glycative stress present a promising strategy for the prevention of aging and CKD.

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

**TH-PO166**

**Impact of Vascular Calculations Assessed by Simple Radiography in the Prognosis of Non-Dialysis Chronic Kidney Disease Patients: Results of the 3-Year Observational OSERCE-II Study**

Jose L. Gorriz, Pablo Molina, Jordi Bover, Javier Nieto, Alberto M. Martinez-Castelao, Angel Luis M. De Francisco, Guillermina Barril, Maria angeles Guerrero-Riscos, Luis Miguel Molinero.

**Background:** Whereas the poor prognosis effect of the presence of vascular calcifications (VC) has been clearly defined in dialysis patients, their impact in the earlier stages of chronic kidney disease (CKD) is not well established. The present study evaluated the prevalence of the VC in non-dialysis CKD patients, its correlation with other cardiovascular risk factors, and its value for the prediction of death, hospitalizations and renal and cardiovascular events.

**Methods:** OSERCE-II is a multicenter, observational, prospective, study which enrolled 722 non-dialysis CKD subjects (3-stage: 40%; 4-stage: 46%; 5-stage:14%; mean age:66±13 years; women:35%; diabetes mellitus:37%) attending 39 hospitals in Spain from 2009 to 2012. VC were assessed by the Atdrago score (50% of ribs and hands) and the Kauppi score (KS;X:y lateral lumbar spine). Ankle-brachial index, blood pressure and biochemical parameters were measured. Cardiovascular and renal events and hospitalization episodes were assessed.

**Results:** VC were present in 79% of patients, being prominent in 47% (AS:3±3; KS:6±31%). During an observational period of 3 years there were 74 deaths(10%), 174 patients(24%) needed hospitalizations and 154 patients(21%) started dialysis treatment. Cardiovascular was the most common cause of death (42%). By multivariate analysis, the factors independently associated with mortality were age [OR:1.037(1.003-1.071); p<0.001], diabetes [OR:1.738(1.003-3.012); p=0.049] and AS ≥3 [OR:2.130(1.222-3.712); p=0.008]. Diabetes [OR:1.880(1.319-2.681);p<0.001], low albumin levels [OR:6.61(1.8-23.861); p<0.005] and KS≥6 [OR:1.524 (1.056-2.199); p=0.024] were independent predictors of hospitalization. Patients with VC didn't showed higher risk for need to start dialysis.

**Conclusions:** VC detected by plain radiography is highly prevalent in CKD patient. AS and KS represent a reliable and inexpensive tool for the assessment of death and hospitalization risks in these patients.

**TH-PO167**

**Histopathology of Peripheral Arterial Disease in Chronic Kidney Disease**


**Background:** Peripheral arterial disease is a serious problem in patients with end-stage renal disease (ESRD) and chronic kidney disease (CKD) but the underlying pathology, its relationship to vascular calcification, and whether it differs from that in patients without kidney disease is unclear.

**Methods:** A total of 175 arteries (45 above the knee and 130 below the knee) in lower limb amputations performed for critical limb ischemia in 60 patients were examined retrospectively by reviewing sections stained with hematoxylin and eosin.

**Results:** ESRD was present in 21 patients, CKD in 21, and no CKD (defined as a serum creatinine < 1.0) in 18. Mean age was 65.0 +/- 1.9 years and 56% had diabetes, which did not differ between groups. The serum creatinine was 1.6 +/- 0.1 and 0.80 +/- 0.03 in patients with and without CKD. Of the 15 patients using warfarin, 7 had ESRD and 6 had CKD. Intimal thickening was present in 92% of arteries but lipid accumulation and inflammation were each apparent in only a third of these. This did not differ between patients with ESRD, CKD, or no CKD. The prevalence of medial calcification was similar in CKD and non-CKD arteries (63%) but increased to 86% in ESRD arteries (<0.01). The prevalence of intimal calcification increased from 29% to 43% to 52% in non-CKD, CKD, and ESRD respectively, but this was not significant. Both medial and intimal calcification were present in 35% of arteries and 46% of calcified arteries but the intimal calcification was almost always less extensive than the medial calcification. Arterial pathology was similar in diabetic vs. non-diabetic arteries, and warfarin use did not alter the prevalence of severity of either medial or intimal calcification.

**Conclusions:** The principal arterial lesions in ESRD and CKD patients with critical limb ischemia are non-atherosclerotic intimal thickening and medial calcification. Except for a greater prevalence of medial calcification in ESRD arteries, the histopathology did not differ from that in patients without CKD and was unaffected by diabetes or warfarin use. Most of the vascular calcification in lower extremities is medial rather than atherosclerotic.

**TH-PO168**

**High Ankle Brachial Index Is Associated with Vascular Calcification in Chronic Kidney Disease**


**Background:** The ankle brachial index (ABI) is a noninvasive measure of subclinical CVD and atherosclerosis of the lower extremities. Recently, data suggested that high ABI was associated with cardiovascular mortality and vascular calcification in dialysis patients. However, the association of the spectrum of vascular calcification and high ABI is not well studied in pre-dialysis patients.

**Methods:** We investigated the association of vascular calcification with risk of high ABI (≥1.4) in 243 patients with chronic kidney disease (CKD). Vascular calcification was assessed using electron-beam computed tomography (EBCT) and coronary artery calcification (CAC) Agatston score was calculated.

**Results:** CAC was classified as none (0), moderate (>0-100) or severe (>100) according to Agatston scores. Compared to those without CAC, the patients with moderate and severe CAC had increased risk of having high ABI. For example, the odds ratio (95% confidence interval) associated with moderate and severe CAC was 7.5 (1.0, 58.3) and 18.3 (2.6, 128.4) for ABI ≥1.4, respectively, after adjustment for age, gender, race, high-school education, physical activity, current cigarette smoking, weekly alcohol drinking, body mass index, LDL-cholesterol, plasma glucose, mean arterial pressure, estimated glomerular filtration rate, and history of cardiovascular disease.

**Conclusions:** These data indicate that CAC may be associated with risk of high ABI in patients with CKD independent of the risk factors for arteriosclerosis.

**Funding:** Other NIH Support - the National Center for Research Resources, National; Institutes of Health, Bethesda, MD.
Calcification Is a Risk Factor for Intraplaque Hemorrhage in Coronary Atherosclerosis of Patients with Chronic Kidney Disease: The Hisayama Study

Toshihiko Nakano,1,2 Toshishiru Ninomiya,1 Kazuhiiko Tsunyua,1 Yutaka Kiyohara,1 Takarari Kitazono.1
1 Department of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; 2Pathophysiological and Experimental Pathology, Kyushu Univ, Fukuoka, Japan; 3Department of Environmental Medicine, Kyushu Univ, Fukuoka, Japan.

Background: People with chronic kidney disease (CKD) are at the increased risk of coronary heart disease. A previous study reported that CKD was associated with severity of atherosclerosis and frequencies of intraplaque hemorrhages in coronary arteries (Am J Kidney Dis 2010;55:21-30, Kidney Int 2013 doi:10.1038/ki.2013.111). The aim of this study is to investigate the risk factors for intraplaque hemorrhage in coronary atherosclerosis in patients with CKD.

Methods: We randomly selected 126 subjects from 844 consecutive autopsy samples of residents of the town of Hisayama, Japan, and examined the frequencies of calcified lesions and intraplaque hemorrhages in coronary arteries. The three main coronary arteries were evaluated in each subject. The subjects were classified into four categories based on estimated glomerular filtration rate (eGFR): ≥ 60, 45-59, 30-44, and < 30 ml/min/1.73 m². The risk factors for intraplaque hemorrhage incidence were analyzed using logistic regression analysis.

Results: The frequencies of intraplaque hemorrhage increased gradually with lower eGFR levels (p for trend =0.01), and were higher in subjects with coronary calcification than those without it for each eGFR level (with calcification: 7.7%, 12.5%, 12.8%, 18.8%, without calcification: 1.47%, 0%, 1.69%, 9.5% for eGFR ≥ 60, 45-59, 30-44, and < 30 ml/min/1.73 m², P=0.037, χ² test). The likelihood of intraplaque hemorrhages increased with lower eGFR (OR 1.29 [95% CI, 1.03-1.62]), lower HDL cholesterol (OR 1.45 [1.09-1.92]), and the presence of coronary calcification (OR 7.68 [2.57-22.95]) in univariate analysis. In multivariate analysis, coronary calcification was significantly associated with a greater risk of the presence of intraplaque hemorrhages (OR 8.78 [2.71-28.44]).

Conclusions: Our findings suggest that coronary calcification is a risk factor for the presence of intraplaque hemorrhages in coronary atherosclerosis. Patients with CKD have frequent coronary calcification, which possibly lead to vulnerable plaques.

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

Parathyroid Hormone-Mediated Chondrocyte Transition of Endothelial Cells Promotes Media Calcification in Experimental Secondary Hyperparathyroidism

Min Wu, Rining Tang, Hong Liu, Dan Li, Bi-Cheng Liu. Institute of Nephrology, Southeast Univ, Nanjing, China.

Background: Secondary hyperparathyroidism (SHPT) is closely associated with development of media calcification in patients with chronic kidney disease. Studies have demonstrated that heterotopic chondrogenesis contributes to AM. And recent investigations suggest that the potential of endothelial cells to transdifferentiate into chondrocytes. Thus, the purpose of this study is to investigate whether elevated PTH could induce the transition of endothelial cells into chondrocyte-like cells in experimental SHPT.

Methods: Ureaemia-related SHPT was induced by feeding rats an adenine diet (0.75%) for 4 weeks followed by high phosphorus diet (1.03%) until they were euthanized. Cultured human aortic endothelial cells (HAECs) were treated with PTH. Endothelial, mesenchymal and chondrocyte markers were examined by immunohistochemistry, immunofluorescent staining, real-time PCR and western blot.

Results: After 4 weeks of an adenine diet, serum creatinine, BUN and PTH concentrations significantly increased compared with control rats (p<0.05), reflecting the installation of uremia-related SHPT. At 8 weeks after the establishment of uremia, von Kossa staining showed severe media calcification in the aorta. Western blot showed that downregulation of endothelial marker CD31 and the upregulation of mesenchymal markers (α-SMA and FSP1) and chondrocyte markers (SOX9 and COL2A1). Confocal microscopy further revealed the co-localization of CD31 and SOX9 in the aortic media of SHPT group. Besides, exposure of cultured HAECs to PTH upregulated the expressions of FSP1 and α-SMA and downregulated the levels of CD31 in concentration-dependent and time-dependent manners (P<0.05). And a western blot analysis indicated that expressions of SOX9 were significantly increased in PTH-treated cells compared with the control.

Conclusions: Elevated PTH could induce the transition of HAECs into chondrocyte-like cells via EndMT, which might be involved in media calcification in uremia-related SHPT.

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

Chronic Kidney Disease Is an Independent Factor for Atheromatosis Disease

Angels Betriu,1,2 Monserrat Martinez-Alonso,1,2 M. Vittoria Arcidiacono,1,2 Merce Borras,1,4 Jose M. Valdivielso,1,4 Elvira Fernandez,1,4,5 Nephrology, Univ Hospital Arnau de Vilanova, Lleida, Spain; 2Biostatistics Unit, IRBLleida, Lleida, Spain; 3Experimental Nephrology, IRLLeida, Lleida, Spain; 4NEFRONA Group.

Background: Although cardiovascular (CV) mortality in patients with chronic kidney disease (CKD) is well known, it is still questioned if CKD per se is a promoting factor of the atheromatosis process. Therefore, the aim of the study was to study the impact of CKD on atheromatosis from early to late stages: 3 (E3); 4-5 (E4-5) and 5D (E5D) in comparison with the progression of CV. fH modulation by AHT therapy suggests a further non-traditional role for both AHT therapy and possibly the choice of agents used.

Methods: We analyzed 2445 CKD patients (CKD3: 937; CKD4:5-5: 280; CKD5: 688) and 559 controls, 18 to 75 years old without previous cardiovascular events (NEFRONA study). CV risk was measured by SCORE charts. Carotid (common, bulb, internal and external) and femoral (common and superficial) arteries were explored with B-mode ultrasound to detect atheromatous plaques. The estimation of atheromatous plaques presence was calculated by a multivariate logistic regression model by gender, age and diabetes; plaque prevalence was stratified by the same variables.

Results: CKD patients were 61.7% men, 57.9 years old, and 25.7% of them were diabetic. While control subjects were 53.3% men, 54.6 years old and 10.7% of them were diabetic. CKD patients presented a higher prevalence of plaque compared to that observed in control subjects (70% vs 51%; p<0.001). Moreover, plaque presence was higher as the age of patients increased, in men and diabetic subjects. Importantly, plaque prevalence increased in parallel with CKD severity with the highest value at 5D stage. This trend was

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author/disclosure.
observed in both genders, for all the age ranges and presence or absence of diabetes. In contrast, SCORE values were higher in E3 and decreased with CKD severity and plaque presence (P=1.4, E3:2.6, E4-5.2:2.2, E5-3:1.3).

Conclusions: CKD per se is a cause of atheromatosis and the process is exacerbated by the severity of the disease, age and diabetes. Importantly, B-mode ultrasound of the carotid and femoral arteries is a better predictor of CV disease than SCORE charts.

Funding: Pharmaceutical Company Support - ABBVIE

TH-PO174

Chronic Kidney Disease Promotes Carotid Adventitial Neovascularization
M. Vittoria Arcidiacono,1 Mercè Borras,2 Ana Vilar,3 M. Lusia Martin-Conde,1 Belart Montserrat,1 Lourdes Craver,2 Ángels Betria,2 Elvira Fernandez,1,2 1Experimental Nephrology, IRBLleida; 2Nephrology, Univ Hospital Arnau de Vilanova; 3Sistemes Renals, Lleida, Spain.

Background: Plaque vulnerability is strongly associated with the presence of Vasa Vasorum (VV) coming from the adventitial layer. Detection of the increases of carotid adventitial VV could be a good tool for early detection of the atheromatosis. Knowing that chronic kidney disease (CKD) patients are prone to develop atheromatosis, we studied the adventitial VV in CKD and healthy patients, and its association with causes of neangiogenesis. Moreover, the right common carotid artery is less subject to hemodynamic factors, therefore we studied separately the left and right carotid arteries.

Methods: Forty-two healthy patients with none of the classical atheromatous risk factors were compared with 89 CKD patients (3-4: 44, 5D:45), age<75 years and without previous cardiovascular events. Anthropometric, blood pressure, and analytical data (at fasting: lipid profile, C-reactive protein, glucose, calcium, phosphorous, PTH and Vascular Endothelial Growth Factor (VEGF)) were collected. Contrast-enhanced ultrasound (CEUS) was performed to evaluate adventitial VV in plaque-free common arteries, and B-mode ultrasound was performed to evaluate the intima-media thickness (IMT) and plaque presence.

Results: Control and CKD patients did not differ in age and gender. CKD patients showed a higher right adventitial VV and a higher right IMT than those observed in control patients (p=0.01; p=0.006), while the left carotid did not differ. Moreover, the right adventitial VV only correlates with the relative IMT (p=0.04) and with total cholesterol (p=0.01; p=0.006), while the left carotid did not differ. Moreover, the correlation between VEGF levels and adventitial VV was no correlation between VEGF levels and adventitial VV . (p=0.03). Besides higher levels in CKD patients than in control patients (p=0.005), there was no correlation between VEGF levels and adventitial VV in plaque presence.

Conclusions: The differences between the left and right carotid arteries in VV increases, suggest that is mandatory to study separately the two arteries. Moreover, the correlation with IMT and cholesterol levels, a well known cardiovascular risk factor, suggest that CES imaging is a good tool in exploring the eutopogenesis of atheromatosis in CKD patients.

Funding: Pharmaceutical Company Support - ABBVIE

TH-PO175

ADAM17 Inhibition by the Calcimimetic R568 and Its Combination with Vitamin D Attenuates Systemic Inflammation, Renal Damage and Motor-Neuron Dysfunction in Experimental Kidney Disease
M. Vittoria Arcidiacono,1 Sabrina Degaspari,1 Petya Valcheva,1 Sandra De La Fuente,2 Elvira Fernandez,1,2 Adriana S. Dusso,1,2 1Experimental Nephrology, IRBLleida; 2Nephrology, HUAFT, Lleida, Spain.

Background: ADAM17 causes systemic inflammation, renal and cardiovascular damage through the cleavage and release to the circulation of the inflammatory cytokines TNFα, ICAM-1 and VCAM-1, and impairs motor-neuron function through the cleavage of pentraxin, essential for neuronal synapsis. Vitamin D inhibition of ADAM17 and induction of Klotho contribute to renal and cardiovascular protection. Because high dietary calcium prevents the parathyroid hyperplasia caused by enhanced ADAM17-TGF-β/GDFR signals, this study examined the efficacy of the calcimimetic R568 and its synergy with vitamin D in attenuating renal, cardiovascular and motor-neuron dysfunction in mouse kidney disease.

Methods: Two months after 75% nephron reduction, mice were treated with either R568 (s.c. 60 mg/kg body weight), 25-hydroxyvitamin D (i.p. 80 ng weekly) or paricalcitol (i.p. 16 ng thrice weekly) or the combination for 6 weeks.

With treatment with R568, at doses ineffective to suppress PTH, prevented the progression of renal damage (BUIN=0; p=0.01 ), while the R568-Vitamin D combination improved renal function (ABUN=0; p<0.05). The reversal of renal damage could be partially accounted for by vitamin D prevention of reductions in renal klotho, the longevity gene also cleared by ADAM17. R568 alone or its combination with vitamin D elicited similar efficacy in preventing the loss of motor-neuron function assessed in Ladder rung walking and Rotarod tests, an effect associated to parallel reductions in monocyte ADAM17 expression (p=0.05), a marker of systemic inflammation. Despite the absence of vascular calcification in these uremic mice, serum VCAM-1, a marker of vascular damage, correlated directly with the degree of renal damage.

Conclusions: Thus, the efficacy of R568 or its combination with vitamin D to prevent the impairment of motor-neuron function in CKD parallels their ability to inhibit monocyte and/or renal ADAM17 and to attenuate renal klotho loss in the course of CKD.

Funding: Pharmaceutical Company Support - Amgens

TH-PO176

Evaluation of Cardiac Troponin I in Patients with Chronic Kidney Disease
Om Parkash Kalra, Nithyanganthan Peramanathan, Sunil Agarwal, Ashok K. Tripathi, Anil Kumar Yadav. Univ College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India.

Background: Elevated levels of cardiac troponin I (cTnI) have been reported in patients with chronic kidney disease (CKD) even in the absence of acute coronary syndrome (ACS). Elevated levels of cTnI may predict future development of cardiovascular events. In this study, we assessed the cTnI levels in patients with CKD and correlated them with the structural and functional abnormalities of left ventricle (LV).

Methods: This cross-sectional study involved 90 subjects in the age group 31 to 60 years, divided into three groups (30 in each). Group I: Healthy controls (HC), Group II: Patients with CKD stages 3 – 5 not on hemodialysis, Group III: Patients with acute myocardial infarction (AMI) without CKD. cTnI was measured using a highly sensitive ELISA test in all groups and 2D echocardiography was done in patients with CKD to assess the following parameters: LV mass (LVM), LV mass index (LVMi) and LV systolic as well as diastolic functions.

Results: The mean cTnI levels in patients with CKD (142.83 pg/mL) were significantly higher (p<0.001) than healthy controls (75.22 pg/mL) and significantly lower (p<0.001) when compared with patients having AMI (456.16 pg/mL). The prevalence of elevated cTnI levels (>122.21 pg/mL, i.e., >999 percentile value of cTnI in healthy controls) in patients with CKD was found to be 43.3%. In patients with CKD, there was significant positive correlation (p<0.01) between cTnI and various parameters, such as LVM, LVMi and E/E' (r=0.470, 0.500 and 0.461 respectively); however, correlation between cTnI and LV ejection fraction was not significant (r=-0.276, p=0.14).

Conclusions: In patients with CKD, cTnI levels were elevated even in the absence of AMI. The prevalence of elevated cTnI levels in patients with CKD stages 3-5 not on hemodialysis was found to be 43.5%. The elevated levels of cTnI were associated with the presence of LV hypertrophy and diastolic dysfunction in patients with CKD. Elevated cTnI levels may help in identifying patients with CKD at increased risk for future cardiovascular events, so that these patients may be subjected to more aggressive and targeted intervention.

Funding: Government Support - Non-U.S.

TH-PO177

Renalase Is Removed by Kidneys and during Dialysis – Excess Related to CKD Complications?
Jolanta Malyszko, Ewa Koc-Zorawski, Jacek S. Malyszko. Nephrol. Dept, Med Univ, Białystok, Poland.

Background: Hypertension and cardiovascular complications are very common in CKD. Renalase could be synthesized not only by the kidney but also by cardiomyocytes, liver, and adipose tissue. Renalase deficiency was claimed to be present and reponsible for hypertension and cardiovascular complications and complications in CKD. Data on renalase levels in serum were conflicting with low activity and high levels reported in patients with hypertension and CKD. We aimed to assess the renalase levels in patients after unilateral (CKD) and bilateral nephrectomy (HD), in HD as well as in urine, ultrafilterate in HD patients. We also assessed the effect on HD session on renalase levels.

Methods: Renalase (plasma, ultrafiltrate, urine) in 100 HD patients were studied using commercially available assays. Renalase was also assessed in 17 HD patients and 24 healthy controls. We also studied renalase presence using Western Blot analysis.

Results: Renalase was present in ultrafilterate in HD patients and was not affected by type of dialysers (high-flux vs low-flux). Urine renalase in HD patients (n=60) was lower than in healthy volunteers (n=24). Patients with residual renal function had lower renalase relative to anuric patients (p<0.01). In univariate analysis, plasma renalase correlated with urinary renalase (r=−0.28, p<0.05) and renalase in the ultrafilterate (r=−0.31, p<0.05) in HD patients and with urinary renalase in healthy volunteers (r=0.61, p<0.01). Urinary renalase correlated with residual renal function. HD session lower slightly renalase and type of heparin has no effect. HDF patients has significantly lower renalase than HD patients. In Western blot we found that patients after bilateral nephrectomy had the highest renalase, followed by unilateral nephrectomy.

Conclusions: Renalase is cleared by kidneys and it seems that renalase excess not deficiency might contribute to the observed cardiovascular complications in CKD.

Funding: Government Support - Non-U.S.
In Chronic Kidney Disease Signal Regulatory Protein-α Not Only Impairs Insulin Signaling in Skeletal Muscle but also Contributes to Fibrosis

**Background:** Insulin resistance in chronic kidney disease (CKD) begins as early as a serum creatinine 1.0 mg/dL impairing insulin signaling with loss of muscle mass. We have demonstrated for the first time that signal regulatory protein alpha (SIRPs) is upregulated in CKD and adversely influences insulin signaling by forming an immunocomplex with the insulin receptor and insulin receptor substrate-1. This results in tyrosine dephosphorylation of the insulin receptor and IRS-1 downregulating p-Akt causing muscle protein loss.

**Methods:** Western blot analysis was performed based on C2C12 cell lysates and C6/1 variety of aged matched controls. Overexpression of SIRPs in muscle cells stimulates expression of p-Smad3, a transcription factor initiating and TGFβ signaling, and expression of the fibrosis marker alpha smooth muscle actin (α-SMA). Silencing SIRPs in muscle cells treated with a cytokine mixture similar to that which is found in CKD patients, caused a decrease in expression of p-Smad reducing expression of α-SMA. To determine if SIRPs influences p-Smad3 via a PI3/Akt dependent pathway, we silenced SIRPs in skeletal muscle cells that were infected with Ad-AKT-AAA-A. In SIRPs silenced muscle cells that had been infected with Ad-AKT-AAA-P, p-Akt was upregulated and phosphorylated in diabetic nephropathy through inhibition of TGF-[β] pathway. The present study aimed to identify the role of KCa3.1 in the inflammatory responses of diabetic nephropathy.

**Results:** There is a 3.8-fold increase of SIRPs in skeletal muscle samples of patients with advanced CKD vs. aged matched controls. Overexpression of SIRPs in muscle cells treated expression of p-Smad3, a transcription factor initiating and TGFβ signaling, and expression of the fibrosis marker alpha smooth muscle actin (α-SMA). Silencing SIRPs in muscle cells treated with a cytokine mixture similar to that which is found in CKD patients, caused a decrease in expression of p-Smad reducing expression of α-SMA. To determine if SIRPs influences p-Smad3 via a PI3/Akt dependent pathway, we silenced SIRPs in skeletal muscle cells that were infected with Ad-AKT-AAA-A. In SIRPs silenced muscle cells that had been infected with Ad-AKT-AAA-P, p-Akt was upregulated and phosphorylated in diabetic nephropathy through inhibition of TGF-[β] pathway. The present study aimed to identify the role of KCa3.1 in the inflammatory responses of diabetic nephropathy.

**Conclusion:** These results imply that SIRPs increases p-Smad3 by a mechanism that is dependent on the PI3/Akt pathway, suggesting that SIRPs influences muscle fibrosis via a new pathway in chronic kidney disease.

**Funding:** Other NIH Support - T32 Training Grant

---

**TH-PO178**

**Circling dp-ucMGP: Modifiable Risk Marker in Chronic Kidney Disease**

**Elke Theuwissen,1 Elke Magdeleyns,1 Heather Pham,2 Cees Vermeer.1 Cardiovascular Research Institute, Maastricht Univ, VitaK, Maastricht, Netherlands; 2Immunodiagnostics Systems, Boldon, United Kingdom.

**Background:** Vascular calcification is a major burden in chronic kidney disease (CKD), associated with increased morbidity and mortality. Matrix Gla-protein (MGP) is primarily expressed by vascular smooth muscle cells and acts as an inhibitor of vascular calcification; its activity depends on vitamin K-dependent γ-glutamyl carboxylation. Vascular K insufficiency leads to the formation of inactive undercarboxylated MGP. Circulating inactive desphospho-uncarboxylated MGP (dp-ucMGP) is a recognized marker for vascular vitamin K status.

**Methods:** Circulating dp-ucMGP was measured with our lab-developed sandwich dual-antibody ELISA. The capture antibody was directed against the non-phosphorylated MGP sequence 3–15 and the detecting antibody directed against the uncarboxylated MGP sequence 35–49. MGP. Circulating dp-ucMGP was measured with our lab-developed sandwich dual-antibody ELISA. The capture antibody was directed against the non-phosphorylated MGP sequence 3–15 and the detecting antibody directed against the uncarboxylated MGP sequence 35–49.

**Results:** There is a 3.8-fold increase of SIRPs in skeletal muscle samples of patients with advanced CKD vs. aged matched controls. Overexpression of SIRPs in muscle cells treated expression of p-Smad3, a transcription factor initiating and TGFβ signaling, and expression of the fibrosis marker alpha smooth muscle actin (α-SMA). Silencing SIRPs in muscle cells treated with a cytokine mixture similar to that which is found in CKD patients, caused a decrease in expression of p-Smad reducing expression of α-SMA. To determine if SIRPs influences p-Smad3 via a PI3/Akt dependent pathway, we silenced SIRPs in skeletal muscle cells that were infected with Ad-AKT-AAA-A. In SIRPs silenced muscle cells that had been infected with Ad-AKT-AAA-P, p-Akt was upregulated and phosphorylated in diabetic nephropathy through inhibition of TGF-[β] pathway. The present study aimed to identify the role of KCa3.1 in the inflammatory responses of diabetic nephropathy.

**Conclusion:** These results imply that SIRPs increases p-Smad3 by a mechanism that is dependent on the PI3/Akt pathway, suggesting that SIRPs influences muscle fibrosis via a new pathway in chronic kidney disease.

**Funding:** Other NIH Support - T32 Training Grant

---

**TH-PO179**

**Restoration of Repressed Estrogen Receptor α in Post-Menopausal Women and Female Mice with Diabetic Kidney Disease**

**Elena M. Yubero-Serrano,1 Shobha M. Swamy,1 Jaime Uribarri,1 Mark Woodward,2 Helen Vlassara,3 Gary E. Striker.1 Mount Sinai School of Medicine, New York; 2George Institute for Global Health, Sidney, Australia.

**Background:** Estrogens reduce expression of proinflammatory markers described above in diabetic eNOS−/− mice compared to diabetic vehicle groups. Furthermore, blocking the KCa3.1 channel in both animal models led to the reduction of phosphorylation of NF-κB.

**Conclusions:** KCa3.1 mediated renal inflammation under diabetic condition through the NF-κB pathway.

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

---

**TH-PO180**

**Normalization of AMPK Activity Corrects Renal Insulin Resistance in Non-Diabetic CKD**

**Aihua Deng, Roland C. Blantz. Renal Lab, Kolling Institute of Medical Research, Univ of Sydney, Sydney, NSW, Australia.

**Background:** AMPK activation can correct such insulin resistance.

**Funding:** NIDDK Support, Veterans Affairs Support

---

**TH-PO181**

**Blockade of KCa3.1 Attenuates Renal Inflammation in Diabetic Mice**

**Chunling Huang, Xinning Chen, Aihua Deng, Roland C. Blantz. Renal Lab, Kolling Institute of Medical Research, Univ of Sydney, Sydney, NSW, Australia.

**Background:** Inflammation plays a key role in the development and progression of diabetic nephropathy. KCa3.1, a potassium channel protein, is associated with vascular inflammation, atherogenesis, and proliferation of endothelial cells, macrophages, and fibroblasts. We previously demonstrated that blockade of KCa3.1 ameliorated renal fibrosis in diabetic nephropathy through inhibition of TGF-[β] pathway. The present study aimed to identify the role of KCa3.1 in the inflammatory responses of diabetic nephropathy.

**Methods:** Two animal models of diabetes induced with streptozotocin were used in this study: (1) wild type versus KCa3.1−/− mice, and (2) diabetic eNOS−/− mice treated with or without a selective inhibitor of KCa3.1 (TRAM34). After mice were sacrificed, the expression of proinflammatory cytokines Chemokine (C-C motif) ligand 20 (CCL20), IL-6 and TNF-α were examined by real time PCR and immunohistochemistry staining.

**Results:** Both mRNA and protein levels of CCL20, IL-6 and TNF-α significantly decreased in kidneys of diabetic KCa3.1−/− mice compared to diabetic wild type mice. Similarly, TRAM34 reduced the expression of inflammatory markers described above in diabetic eNOS−/− mice compared to diabetic vehicle groups. Furthermore, blocking the KCa3.1 channel in both animal models led to the reduction of phosphorylation of NF-κB.

**Conclusions:** KCa3.1 mediated renal inflammation under diabetic condition through the NF-κB pathway.

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

---

**TH-PO182**

**SevCarb treatment of T2DM/DKD women showed a robust increase in ERα levels compared to DB or D/E+EN mice.**

**Funding:** SevCarb reduced HbA1c, AGEs, Nrf2 and total cholesterol. These changes were absent after CaCO3 treatment. PYR+EN treatment increased ERα levels compared to DB or D/E+EN mice.

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

Underline represents presenting author/disclosure.
Conclusions: Sevelamer carbonate, but not CaCO3, reduced AGE levels in PMP prone mice with DKD and restored ERα blockers and paricalcitol. Both mono and combination therapy attenuated tubulointerstitial fibrosis (V: 5.69±0.8, Irb: 3.72±0.41, Irb+PPG: 4.10±0.7 %/area) and glomerulosclerosis (V: 1.37±0.13, Irb: 0.52±0.08, Irb+PPG: 0.66±0.13), along with improved glomerulomegic infiltration rate (V: 0.43±0.13, Irb: 0.91±0.12, Irb+PPG: 0.90±0.16 ml/min/kg) when compared with vehicle treated in 5/6 renal ablated rats.

**Funding:** Pharmaceutical Company Support - Sanofi Pharmaceuticals

**TH-PO183**

Atrasentan Does Not Significantly Impact Thoracic Bioimpedance in Patients with Type 2 Diabetes and Nephropathy

**Hans-Henrik Parving,3 The Radar Steering Committee.4**

**Conclusions:** In conclusion, the combination of these 3 drugs greatly improved renal function and histology, proteinuria, IV hypertrophy and cardiac oxidative stress in uremic rats.

**Funding:** Pharmaceutical Company Support - Abbott Pharmaceutical

**TH-PO186**

Protective Effects of Enalapril, Atrasentan, and Paricalcitol on Glomerulosclerosis, Proteinuria, and Cardiac Oxidative Stress in Uremic Rats

**Eduardo Slatopolsky,1 Cynthia S. Ritter,1 Jane L. Finch,1 Helen Liapis,1 Edu Suarez,2 Leon Ferder,2 James A. Delmez,1 Sarah Zhang.1**

**Conclusions:** Blockade of Angiotensin II Type I Receptor (AT1) and CC Chemokine Receptor 2 (CCR2) Heteromers in 5/6 Renal Ablation Model

**Yuan Zhang,1**

**Conclusions:** In conclusion, the combination of these 3 drugs greatly improved renal function and histology, proteinuria, IV hypertrophy and cardiac oxidative stress in the uremic rat.

**Funding:** Pharmaceutical Company Support - Abbott Pharmaceutical

Blockade of Angiotensin II Type I Receptor (AT1) and CC Chemokine Receptor 2 (CCR2) Heteromers in 5/6 Renal Ablation Model

**Yang Zhang,2 Hans-Henrik Parving,1**

**Conclusions:** Blockade of the AT1-CCR2 heteromer with Irbesartan and Propargamum (CCR2 pathway inhibitor) would have an additive benefit on progressive renal injury in 5/6 renal ablated rats.

**Methods:** 5/6 renal ablated rats (n=12) were randomly assigned to receive daily either Irbesartan (Irb; 10mg/kg) or a combination of Irb (10mg/kg) and Propargamum (PPG; 30mg/kg) or vehicle (V) for 12 weeks. In addition to renal function and histopathology examination, podocyte loss and the concentration of urinary MCP-1 were also measured.

**Results:** Without affecting body weight and blood pressure, the combination of Irb and PPG therapy in 5/6 renal ablated rats was associated with significantly less proteinuria (V: 3.72±0.52, Irb: 287±32, Irb+PPG: 136±16 mg/dm), urinary MCP-1 (V: 4048±587, Irb: 2533±409, Irb+PPG: 2105±538 pg/ml) and podocyte loss (V: 9.0±8.8, Irb: 10±6.6, Irb+PPG: 13.0±13.3 podocytes/glomeruli when compared to vehicle or Irb treatment.

Both mono and combination therapy attenuated tubulointerstitial fibrosis (V: 5.69±0.8, Irb: 3.72±0.41, Irb+PPG: 4.10±0.7 %/area) and glomerulosclerosis (V: 1.37±0.13, Irb: 0.52±0.08, Irb+PPG: 0.66±0.13), along with improved glomerulomegic infiltration rate (V: 0.43±0.13, Irb: 0.91±0.12, Irb+PPG: 0.90±0.16 ml/min/kg) when compared with vehicle treated in 5/6 renal ablated rats.

**Conclusions:** Blockade of the AT1-CCR2 heteromer with Irbesartan and Propargamum was superior to Irbesartan alone in reducing proteinuria and podocyte loss in the 5/6 renal ablation rat model of CKD.

**Funding:** Pharmaceutical Company Support - Dimerix Bioscience, Perth, Australia

**TH-PO185**

Chronic Nicotine (Ch-NIC) Induced Exacerbation of Subpressor Angiotensin-II (SP-AngII) Induced Renal Dysfunction and Chronic Kidney Disease (CKD) Is Partially Mediated through the Endothelin-A (ET-A) Receptor

**Kiran B. Chandrashekar,1 Istvan Arany,2 Arnaldo F. Lopez-Ruiz,1 Andrea P. Solijanic,1 RuiSheng Liu,2 Luis A. Juncos,2 **Nephrology, Univ of Miss Medical Center; 3Pediatrics, Univ of Miss Medical Center.

**Conclusions:** Before we reported previously that Ch-NIC worsens SP-AngII induced renal dysfunction despite insufficient blood pressure (BP) changes and also that it incites renal vascular remodeling which partly contributes to SP-AngII induced CKD. Smoking (Ch-NIC) increases plasma endothelins which damage microcirculation by regulating vascular growth-promoting factors and inducing microvascular remodeling. We hypothesized that ET-A receptor blockade protect against Ch-NIC induced renal dysfunction in SP-AngII induced CKD.

**Methods:** SD rats received saccharine or nicotine with or without SP-AngII. Separate groups were pretreated with ABT-627 (selective ET-A antagonist).

**Results:**

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

Underline represents presenting author/disclosure.

**References:**

1The Univ of Melbourne; 2Dimerix Bioscience; 3Pediatrics, Univ of Miss Medical Center; 4The Radar Steering Committee.4

**Funding:** Other NIH Support - NIH DK073401
TH-PO187

Inverse Correlation of Epidermal Growth Factor and Lipocalin-2 in Patients with Chronic Kidney Disease
Shahaan Smith,1 Vijii Nair,1 Felix H. Eichinger,1 Ivan Formentini,2 Maria Bobadilla,3 Maria Chiara Magnone,2 Keith A. Bellovich,1 Susan P. Steigerwald,1 Matthias Kretzler,1 Wenjun Ju.1

Background: Epidermal growth factor (EGF) and neutrophil gelatinase-associated lipocalin (LCN2) are potential urinary biomarkers for CKD. Therefore, it is important to understand the mechanism linking these two tubular markers to CKD. A study using LCN2 deficient mice demonstrated a critical role of LCN2 in renal failure, and their in vitro data suggested that EGF might activate LCN2 expression. However, if LCN2 is a down-stream target that links EGF to CKD progression in humans remains unknown. This prompted us to study the relationship between EGF and LCN2 in patients with CKD in cohort studies from Europe (European Renal cDNA Bank, ERCB) and North-America (Michigan O'Brien Renal Center P30, ERCB Consortium).

Methods: Renal RNA levels were derived from gene expression profiling performed on tubulointerstitial compartment of micro-dissected renal biopsy tissue from two independent cohorts: 164 ERCB subjects and 42 CPROBE subjects. Pearson correlation was used to correlate marker levels with kidney function, assessed by estimated glomerular filtration rate (eGFR) using the MDRD equation. Urinary EGF and LCN2 were measured by ELISA.

Results: Our study shows that intra-renal RNA levels of EGF and LCN2 in tubulointerstitial compartment are significantly correlated with eGFR-MDRD in ERCB (r=0.66, and r=-0.48, respectively), and in CPROBE (r=0.42, and r=-0.63, respectively). A significant inverse correlation was observed between EGF and LCN2 RNA level in both study cohorts (r=-0.54, and r=-0.61, respectively). The inverse correlation is retained at the urine marker protein level in CPROBE patients (r=-0.46, p<0.007).

Conclusions: The consistent association between reduced EGF level and increased LCN2 expression in CKD patients supports that LCN2 may be one of the paths that mediate the role of EGF in CKD progression. Future studies will focus on determining the signaling mediators between EGF and LCN2 in human tubular cells.

Funding: NIDDK Support, Pharmaceutical Company Support - Hoffmann-La Roche

TH-PO188

Uric Acid and Risk of Chronic Kidney Disease Progression in a United Kingdom Cohort
Matthew Denker,1 Jason Roy,1 Harold I. Feldman.2 Medicine, Univ of Pennsylvania, Philadelphia, PA.

Background: Uric acid (UA) is a potential risk factor for CKD progression, supported by some but not all observational studies. We aimed to identify patients with CKD with varying degrees of kidney dysfunction in order to test whether the association between UA and CKD progression differs by baseline CKD severity.

Methods: We conducted a retrospective cohort study using UK’s The Health Improvement Network (THIN) database to identify adult patients with CKD who had a UA recorded after meeting CKD criteria, a corresponding serum creatinine (Cr), and at least 1 Cr subsequent to both UA and latter Cr. Those with ESRD prior to UA or with <1 year follow-up were excluded. Linear mixed effects models were fit to model slope of ΔeGFR over time, adjusted for baseline covariates including age, sex, BMI, BP, eGFR, hemoglobin, albuminuria, RAAS-blockers, diuretics, and hypouricemic agents. Censoring occurred at the earliest of dialysis initiation, kidney transplant, death, or January 2012.

Results: We identified 21,478 patients: 47% men, median age 73.9 yrs, mean baseline eGFR (beGFR) 53 ml/min/1.73m². Median follow-up was 3.7 yrs.

<table>
<thead>
<tr>
<th>Mean eGFR (ml/min/1.73m²)</th>
<th>61.3</th>
<th>56.5</th>
<th>53.4</th>
<th>49.7</th>
<th>43.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout (%)</td>
<td>15.4</td>
<td>16.4</td>
<td>23.5</td>
<td>37.6</td>
<td>46.3</td>
</tr>
<tr>
<td>Median uric acid (mg/dl)</td>
<td>4.4</td>
<td>5.7</td>
<td>6.8</td>
<td>8.0</td>
<td>9.7</td>
</tr>
</tbody>
</table>

The association between UA and CKD progression differed by beGFR (test for interaction p<0.001). In patients with more preserved kidney function, higher UA was associated with faster loss of eGFR (p<0.001). No association with progression was observed in those with beGFR<45.

Funding: NIDDK Support

TH-PO189

Effects of Febuxostat versus Allopurinol in Reducing Serum Urate in Subjects with Hyperuricemia and CKD Stage 3-5: One Year, Randomized Trial
Nobuhito Hirawa,1 Keisuke Yatsu,1 Mari Katsumata,2 Akira Fujivara,3 Sanee Saka,1 Yoshiyuki Toya,1 Gen Yasuda,1 Satoshi Umemura,2 1Dept of Nephrology and Hypertension, Yokohama City Univ Medical Center, Yokohama, Kanagawa, Japan; 2Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Kanagawa, Japan.

Background: Febuxostat (Feb), an orally administered non-purine selective inhibitor of xanthine oxidase, was developed recently. Compared to allopurinol (Allo), Feb directly inhibits xanthine oxidase and is metabolized by liver, partly. Thus, Feb may be easy to use in patients with renal impairment. In this study, to clarify the urate-lowering efficacy and safety of Feb, we compare the effectiveness of Feb and Allo in subjects with hyperuricemia and CKD stage 3-5 for one year.

Methods: Forty patients with CKD stage 3-5 and hyperuricemia (serum urate levels > 8mg/dl) were randomized to receive once-daily Feb (10mg) or Allo (50mg) for four weeks. At that, Feb and Allo were permitted to increase the dose until 40mg/day (Feb) in all participants, and 100 mg (Allo) in CKD stage 3. The 1st endpoint was the UA values at one year. Furthermore, we examined the effects on renal function and investigated the safety of Feb and Allo treatments in CKD stage 3-5 patients.

Results: The average age and eGFR of the participants were 63 years old and 22 ml/min/1.73m². There were no differences in BP, Cr, UA values between Feb group and Allo group in the control period. Feb and Allo significantly decreased the serum UA levels at 2 weeks after treatments. The UA level of Feb group was significantly lower than Allo group in 12 weeks, 24 weeks and one-year of treatments (p<0.01). There was no difference in serum creatinine and eGFR by two treatments. The changes of the slope of 1/Cr were negatively correlated with the alterations of the serum UA (P<0.05). Using the multivariate analysis, the UA values of one-year treatment were associated with Feb use, baseline UA value, but not with baseline eGFR. Obvious side effects were not recognized in Feb treatments.

Conclusions: Febuxostat is effective and safe in patients with hyperuricemia and CKD stage 3-5 for one-year treatment.

TH-PO190

Interaction between Hyperuricemia and Smoking on Renal Arteriopathy in Chronic Kidney Disease Patients
Kentarou Kogahara,1 Tsuyoshi Miyagi,1 Masahiko Kouchi,1 Yuuake Ohya,1 Kunitoshi Ikeda,1 Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyus, Nishihara-Cho, Okinawa, Japan; 2Dialysis Unit, Univ of the Ryukyus, Nishihara-Cho, Okinawa, Japan.

Background: We have recently reported that hyperuricemia (HU) was associated with renal arteriopathy in chronic kidney disease (CKD) patients. Smoking (SMK) is also potential risk factor for renal arteriopathy. However, the effect of combination SMK and HU on renal arteriopathy is unknown.

Methods: We examined the cross-sectional association between HU and renal arteriopathy with or without SMK (current or past) using renal biopsy specimen. Arteriolar hyalinosis and wall thickening were assessed by semi quantitative grading for arterioles among 167 patients with CKD (mean age, 43.4 yrs; 88 men and 81 women).

Results: Subgroup analysis showed that HU+/SMK+ group had highest grade of arteriopathy followed by HU-/SMK+, HU-/SMK- group. Interaction between HU and SMK on index of renal arteriopathy was significant (p<0.003). That is, effect of HU on renal arteriopathy was significantly augmented by coexistence of SMK. Multiple logistic analysis adjusted for age hypertension and diabetes mellitus showed that HU+/SMK+ was significantly associated with higher risk for the presence of higher-grade renal arteriolar
hyalineosis and wall thickening compared with HU+/SMK- as a reference, but HU-/SMK- was not. The adjusted odds ratios (95% CI) of hyalineosis and wall thickening were 4.2 (1.1 to 15.9) and 12.4 (1.0 to 15.7), respectively.

Conclusions: In conclusion, significant interaction between HU and SMK on renal arteriopathy was observed in CKD patients. Further prospective study is needed to determine whether CKD patients in hyperuricemia who have smoking habit show rapid decline in eGFR.

TH-PO191
Effect of Cholecalciferol on Proteinuria in Patients with Chronic Kidney Disease
Subir K. Paul, Shejuti Paul, Rajesh Boorgu, Narasimha R. Boorgu, Jamie N. Cockrell. Shocks Kidney and Hypertension Center, Florence, AL.

Background: Proteinuria is well-known to be associated with adverse cardiovascular outcome. When angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) are contraindicated, poorly tolerated, or have inadequate effects, the therapeutic choice for proteinuria in chronic kidney disease (CKD) patients becomes mostly limited to optimum blood pressure control. Recently, Vitamin D receptor activation has shown to reduce proteinuria in diabetic nephropathy. The effect of nutritional Vitamin D on proteinuria in CKD is unknown. This study examines the effects of cholecalciferol (CHO) on proteinuria in patients with CKD.

Methods: 61 patients with stage 3 and early stage 4 CKD with urine protein creatinine ratio (UPCR) of 0.5 or more and 25 OH Vitamin D (25OHD) level of less than 32 ng/mL were studied. 31 patients were treated with an average dose of 2050 mg of CHO daily for 3 to 9 months. 30 patients did not receive CHO treatment. Patient characteristics including age, race, gender, estimated GFR, presence of diabetes, hypertension, glomerulopathy, number of patients on ACEI or ARB, control of hypertension and diabetes were similar in both groups. Comprehensive metabolic profile, UPCR, and 25OHD levels were measured at baseline and during 4 to 9 months.

Results: Baseline 25OHD level for treated and untreated patients was 20.03 ng/mL and 21.73 ng/mL respectively (P=0.32). 25OHD level increased to 36.4 ng/mL (P<0.0001) following therapy in treated group and remained similar at 21.8 ng/mL (P=0.96) in untreated group. Baseline UPCR in treated and untreated group was 3.91 and 3.55 (P=0.74) respectively. While in treated group, UPCR decreased from 3.91 to 1.64 (P=0.003), UPCR mildly increased from 3.55 to 4.07 (P=0.06) in untreated group. Baseline serum albumin was 3.71 g/dL and 3.71 g/dL (P=0.98) in treated and untreated patients respectively. Serum albumin increased from 3.71 g/dL to 3.97 g/dL (P=0.01) in treated group but was unchanged from 3.71 g/dL to 3.72 g/dL (P=0.91) in untreated group.

Conclusions: We confirm that CHO therapy may ameliorate proteinuria in patients with CKD. Large randomized trials are warranted.

TH-PO192
Endothelial Glycoalyx Perturbation Accompanies Renal Failure
Martin Dang,1,3 Meriem Khairoum,1 Bernard Van Den Berg,1 Duc Hyen Lee,1 Margien G.S. Boeck,1 Angelique Rops,2 Johan Van der Vlag,1 Hans Vink,1 Anton Jan Van Zonneveld,1 Marlies Reinders,1 Tom J. Rabelink,1 Nephrology, LUMC, Leiden, Netherlands; 2Nephrology, RUNMC, Nijmegen, Netherlands; 3Physiology, MUMC, Maastricht, Netherlands.

Background: End-stage renal disease (ESRD) is accompanied by endothelial dysfunction. Since the endothelial glycoalyx (endothelial surface layer, ESL) governs interactions between flowing blood and the vessel wall, perturbation could influence disease progression. In this study we used non-invasive sidestream darkfield (SDF) imaging to investigate whether renal failure is associated with perturbation of the ESL. To this end we measured the accessibility of red blood cells to the endothelial surface in the microcirculation (perfusion boundary region, PBR).

Methods: The PBR was measured in patients with ESRD (n=23), after a successful living donor kidney transplantation (n=12), in patients who developed interstitial fibrosis / tubular atrophy after kidney transplantation (IFTA, n=10) and healthy controls (HC) (n=10). In addition, the endothelial activation marker Angiotropin-2 (Ang2) and the shed ESL components syndecan-1 and soluble thrombomodulin (STM) were measured using ELISA. All differences shown have a P-value of <0.05.

Results: ESRD patients showed an increased PBR compared to controls (2.05 ± 0.25 vs. 1.82 ± 0.16 μm), which was accompanied by increased circulating levels of tST (19.9 ± 8.2 ng/mL vs. HC 7.1 ± 1.2 ng/mL) and syndecan-1 (107.5 ± 51.1 ng/mL vs. HC 49.8 ± 21.73 ng/mL respectively (P=0.96) in untreated group. Baseline serum albumin was 3.71 g/dL and 3.71 g/dL (P=0.98) in treated and untreated patients respectively. Serum albumin increased from 3.71 g/dL to 3.97 g/dL (P=0.01) in treated group but was unchanged from 3.71 g/dL to 3.72 g/dL (P=0.91) in untreated group.

Conclusions: We confirm that CHO therapy may ameliorate proteinuria in patients with CKD. Large randomized trials are warranted.

TH-PO193
Activation of Coagulation during Chronic Kidney Disease Is Counterbalanced by Defective Platelets Adhesion: An Intravital Videomicroscopy Analysis
Stephanie Baryte, Stéphane Poitevin, Roxane Darbouset, Bertrand Gondouin, Christophe Dubois. UMR_S1076, Aix-Marseille Univ, Marseille, France.

Background: Patients with chronic kidney disease (CKD) have an increased risk of thrombosis and an increased risk of hemorrhage. The pathophysiology of this counterintuitive association is unknown. We identified indolic solutes as critical in the induction of tissue factor (TF) expression and procoagulant activity. We hypothesize that TF could play an important role in vivo to promote clot formation.

Methods: To confirm it we used a well described in vivo live imaging of thrombi formation dependant of TF. Endothelial cells of the cremenarteries in anesthetized mouse were labeled by laser-dye. Platelets aggregation and fibrin formation at the lesion site were imaging by intravital videomicroscopy. The fibrin and the platelets were revealed by labels antibodies. The kinetics of thrombi was analyzed in more than 30 thrombi in five C57/b6 mice with renal failure induced by 5/6 nephrectomy (Nx) and four control mice.

Results: In mice with 5/6 Nx the fibrin formation began earlier. The same mean fluorescence intensity (5AU, 10 AU and 20 AU) was observed 50±10 seconds earlier in mice with renal failure than in control mice. At time 300s, the fibrin formation at the lesion site is more important in 5/6 Nx mice (30 AU) than in control mice (20 AU) (P<0.0001).

Conclusions: We confirmed in vivo the association of activated coagulation and defective platelets adhesion in a mouse model of renal failure. The coagulation activation is dependant of TF. This association could explain the increased risk of thrombosis observed in human combined with increased bleeding risk. The intravital videomicroscopy give us the opportunity to identify the mechanisms leading to the paradoxical hemostatic state observed in CKD.

TH-PO194
Vascular Injury Promotes Glomerulotubular Junction Abnormalities (GTJA) which May Progress Chronic Kidney Disease (CKD): Three-Dimensional (3D) Inspection of Vascular-Glomerular Alternations
Norkio Uesugi,1 Yoshihito Shimazu,2 Takaaki Aoba,3 Michio Nagata,1 1Pathol., Tsukuba Univ, Tsukuba, Japan; 2Pathol., Nippon Dental Univ, Tokyo, Japan.

Background: GTJA including atubular glomeruli (AG) has been identified as a cause of nephron loss in number of glomerulare diseases. GTJA is 3D event and was likely underappreciated because of difficulties of morphologic recognition. To verify the hypothesis that vascular injury by hypertension(HT) concern occurrence of GTJA promoting nephron loss in CKD, we investigated three-dimensional vascular-glomerular architectures of GTJA in human kidney with CKD stage 1-3.

Methods: Kidney tissue was obtained from 23 samples of surgically removed non-tumor parts of renal carcinoma in Japanese (Male 18, Female 5; age: 45-86; without proteinuria, 13 with HT). The prevalence of GTJA in CKD was first surveyed on 500 serial sections in 3mm² size with double staining by PAS and Elastic. On that basis, we selected 7 cases for 3D reconstruction, in which 120 serial sections were double or triple-stained in combination with CD10 (anti-proximal tubular marker), CD34 (anti-endothelial marker), and smooth muscle actin (SMA; anti-vascular medial marker). Individual immunostained images of a whole histological section were acquired with virtual slide system and 3D reconstruction were conducted using Image-J software.

Results: High resolution 3D reconstruction images from interlobular arteries to glomerular with proximal tubular image was successfully obtained. GTJA was noticed in 4.3±5.2% in HT cases and 0.7±0.3% in non-HT cases (p=0.09). Severe GTJA including AG showed complete disconnection of vascular pole and afferent arterioles (AA) associated with severe interstitial fibrosis. Occlusion of near interlobular arteries (AA) was found in some cases. Other GTJA showed marked narrowing of AA by intimal fibrosis and long distance convoluted running of AA with opened lumina. Loss of CD10 expression was often noticed in atrophic tubules.

Conclusions: In the pathogenesis of CKD, arteriolarlesclerosis caused by HT likely promote development of GTJA, resulting in nephron loss. Anomalous vasculo-glomerular architecture in CKD kidney can be monitored in 3D reconstruction.

Funding: Government Support - Non-U.S.

TH-PO195
Chronic Kidney Disease and Fracture Risk in the Action to Control Cardiovascular Risk in Diabetics Trial
Timothy Craven,1 Julia J. Scialla,1 Huihui Xie,1 Thomas L. Nickolas,2 Adrian Schnall,3 Joshua Barzilay,4 Ann Schwartz,2 1Univ of Miami Miller School of Medicine; 2Wake Forest School of Medicine; 3Columbia Univ Medical Center; 4CWRU School of Medicine; 5Emory Univ School of Medicine; 6UCSF School of Medicine.

Background: Large epidemiological studies demonstrate that type 2 diabetes independently increases fracture risk. One mechanism that could explain this increased risk is the higher prevalence and incidence of chronic kidney disease (CKD) that is associated with type 2 diabetes.

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

Underline represents presenting author/disclosure.
Methods: In secondary analysis of 6661 participants included in an ancillary study of fractures in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, we used logistic regression to examine the relationships between different definitions of CKD and centrally adjudicated non-vertebral fracture rates over a median follow up time of 4.9 years. Results: We found that definitions relying on baseline estimated glomerular filtration rate (eGFR) and/or albuminuria were not associated with fracture risk.

Results: We found that definitions relying on baseline estimated glomerular filtration rate (eGFR) and/or albuminuria were not associated with fracture risk.

Conclusions: Many men and women with chronic kidney disease will fracture. These results can be used for simple bedside prognostication and to guide sample size requirements for future fracture prevention trials.

Funding: Government Support - Non-U.S.

TH-PO197
Toll Like Receptor 2 / 4, MYD88, TNF-α and IL-6 Expression in Leukemoid of Hemodialysis and Pre-Dialysis Patients
Caren Cristina Grabulosa,1 Edgar Ferreira Cruz,2 Jose Tarcisio Carvalho,3 Aline Trevisan Peres,3 Beata Maria Redublo Quinto,1 Lilian Cappuri,1 Maria Dalboni,1 1Universidade Federal de Sao Paulo; 2Tufs-New England Medical Center.

Background: Toll-like receptors (TLR) are involved in mechanisms of immunity response. There are few studies that describe TLRs expression in leukocytes from chronic kidney disease patients. However, to evaluate TLR-2, TLR-4, MYD88, TNF-α and IL-6 expression in neutrophils (PMN), monocytes (MN) and lymphocytes (LYM) from HD and PD patients.

Methods: Blood samples from 38 hemodialysis (HD) patients, 33 pre-dialysis (PD) and 43 age- and gender-matched healthy volunteers (CONT) were analyzed for TLR2, TLR4, MYD88, TNF-α and IL-6 expression on PMN, MN and LYM. Besides, we studied PMN and MN from PD patients unstimulated and stimulated by lipopolysaccharide (LPS) and peptidoglycan (PG), by flow cytometry.

Results: PMN from PD patients without stimulus exhibited significant upregulation of TLR2 (4446±2426 vs 285±79; p=0.001), TLR4 (4749 ±2189 vs 317±293; p=0.001) and MYD88 (1018±670 vs 374±44; p=0.001) expression compared to CONT and HD groups. HD patients showed upregulation only for PMN TLR2+ MYD88+ expression compared to CONT and PD groups. We observed in PMN TLR2+ and PMN TLR4+ a positive correlation with TNF-α, IL-6 and MYD88 expression stimulated by LPS and PG in all groups (r = 0.40, p<0.05 and r = 0.37, p<0.05, respectively). PD neutrophils stimulated by LPS and PG showed a higher expression of TLR2 and TLR4 compared to unstimulated PD neutrophils: TLR2 (unstimulated: 4446±2426; LPS: 5755±1445 and PG: 7706±1419; p<0.01) and TLR4 (unstimulated: 4786±2558; LPS: 4334±2141 and PG: 5775±4202; p<0.01). In contrast, PD stimulated by LPS and PG were significantly lower than unstimulated monocytes (unstimulated: 170±161; LPS: 111±35 and PG: 109±30; p<0.05).

Conclusions: It is possible that the activation of PMN from PD patients (more TLR2 and TLR4 expression) probably reflected the effect of high serum levels concentration of uremic toxins. Moreover, the positive correlations between TLR2/4 and MYD88 with cytokines from leukocytes unstimulated and stimulated confirm the role of this mechanism in CKD inflammatory response.

Funding: Government Support - Non-U.S.

TH-PO198
Kidney-Brain Crosstalk during Sepsis
Misako Asada, Motoko Yanagita.
Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Background: Patients with chronic kidney disease (CKD) have a higher prevalence, severity, and mortality of sepsis. However, the mechanism that CKD influences the outcome of sepsis remains unclear. The main cause of death in septic patients is multi-organ failure, and increasing evidences support the presence of crosstalk between kidney and other distant organs via soluble and cellular inflammatory mediators. Here we investigated the influences of CKD on kidney-brain crosstalk in the context of systemic inflammation.

Methods: We divided C57BL/6J male mice (8~9week) into 4 groups: sham-operated mice injected with vehicle (sham/vehicle mice), mice operated with unilateral ureter obstruction (UUO) and injected with lipopolysaccharides (sham/LPS mice), mice operated with unilateral ureter obstruction (UUO) and injected with lipopolysaccharides (UUO/LPS mice). Mice were sacrificed 5 days after the operation, and organs were subjected to histological analysis and quantitative reverse transcription polymerase chain reaction (qPCR).

Results: The expression of IL-6, IL-1β, IL-10 and TNF-α was significantly up-regulated in both kidneys of UUO/LPS mice compared to sham/vehicle mice, while there was no difference between sham/LPS mice and UUO/vehicle mice. In the brain, we observed a significant decrease in the expression of IL-6, IL-1β and IL-10 in both sham/vehicle and UUO/vehicle mice compared to UUO/LPS mice.

Conclusions: Many men and women with chronic kidney disease will fracture. These results can be used for simple bedside prognostication and to guide sample size requirements for future fracture prevention trials.

Funding: Government Support - Non-U.S.

TH-PO199
Race and Severity of Kidney Disease Modify the Associations between Hyponatremia and Death
Sankar D. Navaneethan,1 Jesse D. Schold,2 Jonathan T. Halter,1 Susana Arrigain,2 Stacey Jolly,3 James F. Simon,1 Joseph V. Nally,1 1Nephrology; 2Quantitative Health Sciences; 3Medicine, Cleveland Clinic.

Background: Hyponatremia is associated with falls and higher risk for death in elderly population. We studied the associations between hyponatremia and death among chronic kidney disease (CKD) patients.

Methods: The risk for development of hyponatremia and association with death was examined using logistic regression and Cox proportional hazard models. We studied 2-way interactions between serum sodium and the following covariates in the adjusted model: age, gender, race, diabetes, heart failure and eGFR.

Results: We found that definitions relying on baseline estimated glomerular filtration rate (eGFR) and/or albuminuria were not associated with fracture risk.

Conclusions: Many men and women with chronic kidney disease will fracture. These results can be used for simple bedside prognostication and to guide sample size requirements for future fracture prevention trials.

Funding: Government Support - Non-U.S.
Results: Out of 45.021 CKD patients, 3.6% (n=1645) had hyponatremia (sodium <135 mEq/l in men and <132 mEq/l in women). Male gender, presence of diabetes and malignancy were associated with increased risk for hyponatremia while higher age, eGFR and BMI were associated with lower risk for hyponatremia. After covariate adjustment that included heart failure, kidney and liver function, hyponatremia was associated with a 47% increased risk (95% CI 1.36, 1.60) for death. Caucasians but not blacks had higher risk for death with hyponatremia. The association between hyponatremia and death was pronounced among those with stage 3 CKD and younger patients.

Similar results were noted in a subset of patients (n=8,205) when adjusted for LVEF (instead of clinical diagnosis of heart failure).

Conclusions: Hyponatremia is associated with death among those with CKD. Caucasians and those with stage 3 CKD sustain higher risks for death than African Americans and those with advanced kidney disease. Future studies should explore the reasons for the modified effects noted in our study.

TH-PO200

Association of Anemia and Mineral and Bone Disorders with Health-Related Quality of Life in Predialysis Patients

Priscilla P. How,1 Jun Jie Benjamin Seng,1 Jia Jia Lee,1 Hwce-Lin Wec,1 Pallavi Tyagi,1 Vathisala Anathanam.1
1Pharmacy, National University of Singapore, Singapore, Singapore; 2Medicine (Div of Nephrology), National Univ Hospital, Singapore, Singapore.

Background: Chronic kidney disease (CKD) patients have poor health-related quality of life (HRQoL), which has been associated with increased morbidity and mortality. Compared with dialysis patients, the impact of CKD-related complications such as anemia and, mineral and bone disorders (MBD), on HRQoL in predialysis patients is less well-studied. This study aimed to examine the association of anemia and MBD with HRQoL in predialysis patients.

Methods: A cross-sectional study involving predialysis patients from the National University Hospital, Singapore, outpatient renal clinic was conducted. Patients’ HRQoL were assessed using the Kidney Disease Quality of Life Short Form (KDQOL-SF)1) and EuroQol 5 Dimensions—3 levels (EQ-5D-3L). Psychosocial variables were evaluated using the Medical Outcomes Family Functioning Measure questionnaire. Separate hierarchical multiple linear regressions were performed using HRQoL scales as dependent variables, with adjustment for socio-demographic, clinical and psychosocial variables, to determine associations.

Results: Among 246 patients who completed the study, 227 and 225 patients possessed the relevant data for the anemia and MBD analyses, respectively. Eighty-four (37.0%) patients had anemia while 96 (42.7%) patients had MBD. After adjusting for potential confounders, anemia was associated with poorer physical component summary (β=−3.95, p=0.006) and mental component summary scores (β=−4.05, p=0.003), but better EQ-5D-3L visual analogue scale scores (β=6.64, p=0.021). Anemia was not associated with EQ-5D-3L utility scores. Although no association was found between MBD and the four summary HRQoL scales, it was associated with poorer scores in other disease-specific HRQoL domains such as symptoms (β=−22.30, p=0.001).

Conclusions: Anemia and MBD were associated with poorer HRQoL in predialysis patients. Future research should explore the impact of optimal anemia and MBD treatment on improving patients’ HRQoL.

TH-PO201

Daily Patient Reported Outcome Reporting Is Practical and Demonstrates Differential Patient Experience

Zoe C.L. Pittman,1 Stephen G. John,1 Chris W. Jutleyreyc.1 2Royal Derby Hospital, United Kingdom; 3Uni of Nottingham, United Kingdom.

Background: Patient reported outcomes (PRO) are increasingly recognized as a critical metric in chronic disease. Whilst a variety of generic and disease specific PRO measures (PROMs) have been used in CKD, studies are mainly cross-sectional with limited longitudinal data. None of the available PROMs are designed for iterative application. We designed and implemented a CKD specific online dynamic PROM for daily use.

Methods: PRO selection was informed by published data on symptom burden and a brain and cerebrospinal fluid status, admissions and differing scores dependent on dialysis or non-dialysis day.

Conclusions: No large studies exist regarding the prevalence of depression in pediatric chronic kidney disease (CKD). Using CKD data, we assessed the factors associated with depression.

Results: Depression was defined as a score ≥ one standard deviation above the mean on the Children’s Depression Inventory (CDI) or a history of depression concurrent with active treatment. Associated factors were determined by multivariate linear and logistic regression analyses. Separate models assessed clinical/demographic factors and cognitive/ psychosocial factors.

Conclusions: Results: 344 children (median age 13 years [IQR 10, 15], completed the CDI; 18 had elevated depression scores and 7 had normal scores and were undergoing treatment for depression. Higher maternal education and higher height z-score were protective for depression. There was a trend towards more depression in patients with congenital CKD. Depression subjects had lower academic achievement scores (WIAT-II) (p=0.06) and lower quality of life scores (PedsQL) (p>0.001).

Future research should explore the impact of optimal anemia and MBD treatment on improving patients’ HRQoL.

TH-PO203

Advanced Glycation End Products (AGEs) Increase the Risk for Cognitive Decline in Aging Mice with Chronic Kidney Disease (CKD)

Shobha M. Swamy, Elena M. Yubero-Serrano, Jaime Urribarri, Helen Vlassara, Gary E. Striker. Mount Sinai School of Medicine, New York, NY.

Background: Cognitive decline in CKD has been associated with elevated inflammation and reactive oxygen species (ROS) and decreased SIRT1. Accumulation of glyoxal (glyoxylate) (AGEs) has been implicated in the increased inflammation/ROS, leading to the complications of aging, including cognition and CKD. We recently reported that high levels of circulating MG-derivatives (very reactive AGEs) were associated with higher brain and cerebrospinal fluid (CSF) AGE levels and a significantly faster rate of cognitive deterioration revealed in non-diabetic elderly subjects. Here we asked if there was an effect of methylglyoxal on motor co-ordination, learning and memory in aged mice with CKD fed with an AGE-enriched diet, compared to isocaloric pair-fed controls.

Methods: C57BL6 mice (18-19 month old) fed a Low AGEs diet supplemented with MG (+) diet for 10 generations developed insulin resistance and CKD, whereas mice pair-fed a Low AGEs (MG-) were unaffected. AGE-induced cognitive changes were assessed by Rotarod and object recognition tests.

Results: Despite repeated learning sessions MG+ mice showed a significant decrease in the latency (time to fall from the Rotord) (Fig. A) at lower speed and shorter distance, compared to MG- mice. MG+ mice showed poor recognition ability with significantly lower discriminatory capacity between novel and a familiar object. Compared to MG- mice, MG+ mice showed poor recognition ability with significantly lower discriminatory capacity between novel and a familiar object, compared to MG- mice (Fig. B).

Conclusions: The prevalence of depression in this pediatric CKD cohort was lower than in other reports. Few clinical factors predicted depression. The association with congenital CKD without an association with duration of disease suggests that there may be a common pathway linking congenital CKD to the occurrence of depression. Depression may be a modifiable factor contributing to academic achievement and quality of life in these patients.

Funding: NIDDK Support
Conclusions: As in aging humans, the motor and memory dysfunction in the current study of C57Bl/6 mice with CKD appear to be due to increased ROS and inflammation secondary to the accumulation of AGEs in the brain. Littermates pair-fed a low AGE diet did not show these changes. Clinical studies will need to be conducted to determine if reduction of dietary AGEs may protect against cognitive decline in CKD patients.

TH-PO206
Glycosuria under Normoglycemia May Be an Unrecognized Characteristic of Chronic Kidney Disease
Takahito Ito, Yoko Shima, Naoko Morikage, Ryuta Fujimura, Chisako Nakano, Akira Wada, Masafumi Yamato. Div of Nephrology, Osaka National Hospital, Osaka, Japan.

Background: Normal nephrons do not lose glucose in the urine under normoglycemia. We studied the relation between chronic kidney disease and glycosuria.

Methods: From April 1/1 to October 31/2011, we had 5786 datasets in each of which urine dipstick glucose level, serum glucose concentration, serum ferritin concentration, and HbA1c were measured at the same time. If a subject was tested repeatedly in the period, the oldest data set was adopted. Finally, we used 1629 datasets of the different subjects (64.1±13.5 y, 1049 males) in the following analysis. None took pharmacological agents or propranolol which might result in a false-positive glycosuria.

Results: Glucose concentration and HbA1c were 113.0 mg/dL [IQR: 97.0-155.0] and HbA1c 5.70% [IQR: 5.00-6.60], respectively. When the presence of glucose in the urine (1-plus or more) was defined as glycosuria, the numbers of subjects with and without glycosuria were 523 (Group G) and 1106 (Group N), respectively. There was no significant difference of age or estimated glomerular filtration rate (eGFR) between Groups G and N. Using 596 subjects whose serum glucose and HbA1c were lower than their median values (glucose 5.17±2.06 and HbA1c 5.6, respectively), we performed two sub-analyses. (1) Subjects with and without glycosuria were re-classified into Group GG and NN, respectively. eGFR of Group GG (N=29) was significantly lower than that of Group NN (N=567) (30.9±13.7 vs. 68.9±27.4, P<0.001). Age was not significant. (2) We defined the subjects with eGFR lower than 60 as “CKD” (N=199) and compared them with “non-CKD” (N=397). The non-adjusted and age-adjusted odds ratios for glycosuria in “CKD” were 2.230 [95% CI: 1.050-4.767] and 2.256 [1.013-5.075], respectively. Even when a trace level of glucose in the urine was included in the definition of glycosuria, we obtained similar results.

Conclusions: Glycosuria under normoglycemia may be more common in CKD. This phenomenon may come from abnormal glucose transport, saturated glucose transport in the reduced number of nephrons, and/or delayed tubular fluid flow leading to the dissociation between blood and urinary glucose levels.

Funding: Clinical Revenue Support

TH-PO207
Modeled eGFR, eGFR Slope, and Mortality Risk among Adults with Moderate and Advanced CKD
Xiaoxin Tang,1 Robert M. Perkins,2 Ian D. Bucaloiu,1 H. Lester Kirchner.3 Geisinger Medical Center, Danville, PA; 2Bassett Medical Center, Cooperstown, NY.

Background: Single time-point eGFR estimates are used for risk prognostication among those with CKD. Various applications of longitudinal eGFR using linear models—to include time-independent slope and variability—have been shown to be independent predictors of mortality. We wished to extend these applications by modeling both longitudinal eGFR history—forming estimates of current value of eGFR and time-dependent slopes at any time point—and then test the independent association of these variables with mortality risk in an adjusted, joint survival model.

Methods: We retrospectively assembled a cohort of Geisinger primary care patients with stage G3 or G4 CKD (1/1/2001 to 6/30/2012) who had a minimum of 4 outpatient eGFR results and 6-months follow-up. Patients were excluded for prior history of dialysis or renal transplantation. Patients were followed through 12/31/2012 for death. eGFR trend was modeled using a random intercept and slope model with a flexible spline transformation of time to capture patient-specific, non-linear patterns. Time to death was modeled with Cox Proportional Hazard regression.

Results: A total of 16,773 patients met cohort entry criteria. The sample had mean age 69.4 years, 28% had diabetes, and mean baseline eGFR was 51 mL/min. During 98,075 person-years of follow-up, 3709 (22%) patients died. In fully adjusted models, each 5 mL/min/1.73m² decrease in current eGFR value was associated with a mortality hazard ratio(HR) of 1.05 (95% CI 1.03, 1.09). For the time-dependent slope of the eGFR trend, each 2 mL/min/1.73 m²/year decrement was associated with a HR of 1.09 (95% CI 1.05, 1.12). Both diabetes and gender modified these associations, such that the mortality risk was significantly greater among non-diabetics and females.

Conclusions: Modeled longitudinal eGFR and time-dependent eGFR slope each independently associate with mortality risk among patients with moderate and advanced CKD. Comparing results to baseline eGFR (HR=1.07 [95% CI: 1.05, 1.07]), the joint model may provide more prognostic value to predicting mortality.

TH-PO208
Mathematical Models for the Evaluation of eGFR Decline in CKD Patients: Linear versus Non-Linear
Jan A.J.G. van den Brand,1 Teerd Maartens-Hein Dijkstra,1 Arjan D. Van Zuijlen,2 Peter J. Blankenstijn,3 Jack F. Wetzels,3 Tom Reske,1 1Nephrology, Radboud Univ Medical Centre, Nijmegen, Netherlands; 2Nephrology, Univ Medical Centre Utrecht, Netherlands; 3Institute for Computing and Information Sciences, Radboud Univ, Nijmegen, Netherlands.

Background: We recently questioned the concept that eGFR decline is linear in patients with CKD (Li et al. AKJD 2012). We aimed to evaluate what proportion of CKD patients showed possible non-linear eGFR decline with a simpler technique.

Methods: We analyzed data of patient that participated in MASTERPLAN (Van Zuijlen et al. Nephron 2012). Kidney transplant patients were excluded. eGFR was estimated using the eGFR-Ckbd equation for serum creatinine. Ordinary least squares regression was used to obtain a linear model of eGFR over time. An optimal first order model was
selected from possible powers $x^1, x^2, x^{3}, \ln(x), x^3$, and $x^4$ using STATA's fractional polynomials (Statacorp, TX). The fit for both models was compared using Akaike’s Information Criterion (AIC). The probability that a linear fit was acceptable was calculated as $\exp[-(AIC_{fp}-AIC_{lin})/2]$.

**Results:** In total, 640 patients were included, 69% were male and mean age was 60 ± 12.6 years, baseline eGFR was 37 ± 15 mlln per 1.73m². The mean number of serum creatinine (eGFR) per patient was 14.0 ± 5.2 over the course of 4.2 ± 1.2 years. The histogram shows the proportion of patients by the probability of linearity (top left panel); the line plot shows the total proportion of patients with a linear eGFR decline by acceptance threshold probability for linearity (top left) and eGFR course for three patients as an example.

**Conclusions:** In most CKD patients eGFR decline is linear. However, even when accepting a low threshold (5%), eGFR decline is non-linear in 10% of patients. Our findings confirm previous work by Li et al. using a simpler technique.

**Funding:** Private Foundation Support

---

**TH-PO210**

The Validity of Doubling of Serum Creatinine as a Surrogate Marker for ESRD: A Systematic Review of Randomized Trials

**Background:** This systematic review assessed the validity of doubling of serum creatinine (DSC) as a surrogate for endstage renal disease (ESRD) in trials assessing the effects of blood pressure (BP) lowering in high-risk adults with diabetes, CKD stages 1-4 and/or renal transplantation.

**Methods:** MEDLINE, EMBASE, and the Cochrane Library were searched (1946-Jun 2012) for randomized trials reporting the effects of BP lowering on ESRD and DSC. Abstract review and data extraction was done independently by 2 reviewers. The association between treatment effects on DSC and ESRD was expressed as the “treatment effect ratio (TER)” (effect on ESRD/effect on DSC; ideal surrogate would have a TER close to 1). This test is a key element of Prentice’s operational criteria for validating surrogate markers. Treatment has a significant impact on surrogate and the true outcome(TO) surrogate has a significant impact on the TO; the full effect of treatment on the TO is captured by the surrogate).

**Results:** The systematic review yielded 7531 abstracts of which 9 BP lowering trials in 36500 patients with diabetes, hypertension and/or CKD 1-4 met the inclusion criteria. 1 trial had 3 arms and was treated as 2 trials. Majority of the trials showed a beneficial treatment effect on DSC and ESRD (80% for both).

**Conclusions:** These results show that in trials assessing the effects of BP lowering drugs in high-risk patients, DSC is a relatively good surrogate for ESRD. We assessed the validity of DSC according to only 1 of 3 elements of Prentice’s criteria for validation of a surrogate marker. Future studies will need to consider for the remainder criteria where possible.

**Funding:**-Aventis

---

**TH-PO209**

Predictors of Progression in European CKD Patients: The Tangri Model and Beyond

**Background:** Patients with CKD may progress to ESRD and benefit from early referral to nephrological care. However, treatment adds costs and may also have adverse effects. Therefore, adequate prediction of CKD progression is important. We validated the predictive models developed by Tangri et al. using a simpler technique.

**Methods:** MASTERPLAN is a controlled trial in patients with CKD. CKD progression was defined as ESRD (initiation of chronic dialysis or kidney transplantation) or a 50% increase in serum creatinine concentration. Patients who died before reaching an endpoint were censored. Clinical parameters and laboratory data at MASTERPLAN baseline were assessed as predicting factors for CKD progression, using univariate and multivariate Cox regression.

**Results:** We evaluated 788 patients (67% male, mean age 59 years, mean eGFR 36 ml/min). 330 patients showed CKD progression in univariate analysis treatment center, cause of kidney disease, diabetes mellitus, age, BMI, systolic blood pressure, current smoking, activity score, eGFR, protein creatinine ratio, and serum levels of hemoglobin, PTH, calcium, phosphate, albumin, bicarbonate, potassium, and uric acid were associated with CKD progression. Predictors of CKD progression in multivariate analysis are shown in the table.

**Conclusions:** We identified independent predictors of CKD progression in our MASTERPLAN cohort. We confirmed variables that were included in models by Tangri et al. The cause of kidney disease, blood pressure, current smoking, hemoglobin, and uric acid provided added value.

**Funding:** Pharmaceutical Company Support - Dutch Kidney Foundation (Nierstichting Nederland), Netherlands Heart Foundation (Nederlandse Hartstichting), Amgen, Genzyme, Pfizer, Sanofi-Aventis

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

Underline represents presenting author/disclosure.
**TH-PO211**

**Validity and Statistical Power of Alternative eGFR-Based Endpoints: A Report from an NKF FDA Workshop**

**Background:** Because the follow-up period required to observe the FDA approved doubling of serum creatinine (SCR) endpoint can be prohibitive, we investigated the performance of alternative endpoints defined by ESRD or confirmed reductions in eGFR of either 57% (approximate doubling of SCR), 40% or 30% on the validity and efficiency of CKD RCTs.

**Methods:** We used statistical simulation to determine the efficiency (defined as the required sample size [N] to achieve 90% power) and validity (defined as the Type 1 error for the eGFR-based endpoint when there is no treatment effect on time to ESRD) of alternative eGFR-based endpoints under different scenarios. Simulations were calibrated with data from 11,982 patients in 41 CKD RCTs.

**Results:** We simulated 800 repetitions for each endpoint over more than 800 scenarios. In the base case scenario, use of a 30% eGFR decline endpoint reduced the required Ns for 3 year RCTs by 19% to 54% compared to the required Ns for a 57% eGFR decline endpoint in trials with a moderate to high baseline eGFR for treatments with no acute effect. However, use of a 30% eGFR decline endpoint increased the required N and led to inflated Type 1 error for treatments with an acute effect of -1.5 ml/min/1.73m² in the opposite direction of the long term effect.

Conclusions: A moderate acute effect in the opposite direction from the long term treatment effect can lead to increased Type 1 error and/or increased required N when using smaller eGFR event thresholds. However, the endpoint of ESRD with 30% or 40% decline in eGFR may reduce the required sample size and thereby increase the efficiency of trials with moderate to high baseline eGFR when an acute effect is not expected.

Funding: Private Foundation Support

**TH-PO212**

**Longitudinal eGFR, eGFR Slope, and Incident Cardiovascular Events among Adults with CKD**

**Background:** Single time-point GFR estimates are used for risk prognostication among those with CKD. Various applications of longitudinal eGFR using linear models— to include time-independent slope and variability— have been shown to independently predict cardiovascular events. We wished to extend these applications by modeling both longitudinal eGFR— forming estimates of current eGFR value and time-dependent eGFR slope at any time point— and then test the independent association with incident cardiovascular event risk in an adjusted, joint model.

**Methods:** We retrospectively assembled a cohort of Geisinger primary care patients with stage G3-G4 CKD (1/1/2001 to 6/30/2012) who had a minimum of 4 outpatient eGFR and time dependent eGFR slope each visit and every 4 weeks during 24-weeks of treatment. At each visit three consecutive first morning void (FMV) urines were collected. The effect of paricalcitol 2 μg/day versus placebo, in subjects that submitted at each visit three first morning voids (N=137), was assessed as the geometric mean UACR change from baseline to week 24 and secondly as the geometric mean change considering all follow up visits. In both analyses, UACR was calculated based on 1, 2, or 3 consecutive FMV UACR measurements.

**Results:** We used statistical simulation to determine the efficiency (defined as the required sample size [N] to achieve 90% power) and validity (defined as the Type 1 error for the eGFR-based endpoint when there is no treatment effect on time to ESRD) of alternative eGFR-based endpoints under different scenarios. Simulations were calibrated with data from 11,982 patients in 41 CKD RCTs.

**Conclusions:** Clinical trials can be more efficiently designed if they take into account all albuminuria measurements collected over time rather than considering a change in albuminuria between two pre-determined time-points.

**Funding:** Private Foundation Support

**TH-PO213**

**Impact of the Number of Albuminuria Measurements on Sample Size Requirements for Clinical Drug Trials**

**Background:** Change in albuminuria is used as a surrogate endpoint in clinical trials of CKD progression. Yet, the number of urine samples (albumin measurements) needed to precisely quantify an anti-albuminuric drug effect is unknown. We assessed the impact of the number of urine samples (albumin measurements) needed for clinical trials.

**Methods:** Data from the Selective vitamin D receptor activation for albuminuria lowering (VITAL) trial were used. Urinary albumin:creatinine ratio (UACR) was measured at randomization and every 4 weeks during 24-weeks of treatment. At each visit three consecutive first morning void (FMV) urines were collected. The effect of paricalcitol 2 μg/day versus placebo, in subjects that submitted at each visit three first morning voids (N=137), was assessed as the geometric mean UACR change from baseline to week 24 and secondly as the geometric mean change considering all follow up visits. In both analyses, UACR was calculated based on 1, 2, or 3 consecutive FMV UACR measurements.

**Results:** The mean UACR reduction slightly varied according to the number of UACR measurements and was somewhat smaller when all UACR data over time were considered (Table 1). However, the precision of the treatment effect increased (decreased standard error) with increasing number of UACR measurements. Thus, a post-hoc power calculation showed that the number of patients required to obtain a significant treatment effect decreased with more UACR measurements and markedly decreased when all UACR measurements over time were considered.

**Conclusions:** Clinical trials can be more efficiently designed if they take into account all albuminuria measurements collected over time rather than considering a change in albuminuria between two pre-determined time-points.
Methods: We systematically searched MEDLINE Embase and Cochrane library for trials published between 1970 and November 2012. We included prospective randomised controlled trials assessing the effects of ACE inhibitors or ARBs on renal or cardiovascular outcomes in people with CKD. Summary estimates of relative risk (RR) used a random effects model.

Results: Overall 109 trials were included, providing data for 50,740 patients with CKD. As compared to placebo, ACE inhibitors reduced kidney failure (defined as doubling serum creatinine or end-stage kidney disease) by 38% (RR 0.62, 95% CI 0.53-0.72) and ARBs by 11% (0.89, 0.82-0.97). There’s significant difference on the kidney protection between ACE inhibitors and ARBs (p<0.001). Compared to other blood pressure lowering agents, both ACE inhibitors (0.78, 0.67-0.91) and ARBs (0.61-0.79) produced a better kidney protection without difference (p<0.001). ACE inhibitors and ARBs reduced the risk of major cardiovascular events in patients with CKD as compared to either placebo (RR 0.86, 95% CI 0.80-0.93) or antihypertensive agents (0.88, 0.79-0.97) without heterogeneity (p=0.22). ACE inhibitors also reduced the risk of death or cardiovascular death (0.89, 0.79-0.99) or all death (0.89, 0.79-0.99) while ARB didn’t. Adverse events were significantly increased by ACE inhibitors or ARBs, including hyperkalemia and cough compared to placebo. ARBs therapy was associated with greater risk of hyperkalemia as ACE inhibitors (p for heterogeneity=0.004).

Conclusions: ACE inhibitors or ARBs reduce the risk of kidney failure or cardiovascular events in the patients with CKD as compared to placebo or other blood pressure agents. ACE inhibitors showed more kidney protection as compared to ARBs and also reduced the death thus could be of the first choice in this population.

TH-P0216

Effects of Spironolactone in Combination with ACE Inhibitor or Angiotensin Receptor Blockers in Aldosterone Escape and Non-Escape Group of Patients with Proteinuria

Hy Yeon Kim, Yong Un Kang, Chang Seong Kim, Joon Seok Choi, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim. Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea.

Background: The present study was aimed to investigate whether add-on aldosterone blocker spironolactone has beneficial antiproteinuric effects in aldosterone escape and non-escape group, and to compare changes in proteinuria in patients according to estimated GFR (eGFR) in association with changes of vitamin D level.

Methods: In this prospective intervention trial, we studied the effects of spironolactone (25mg/day) in 219 patients who showed persistent proteinuria after ACE inhibitor or ARB medications for more than 3 months. Plasma aldosterone, potassium, eGFR and urine protein to creatinine ratio (UPCR) were determined at baseline and 6 months after spironolactone add-on treatment. Patients were divided according to their aldosterone level during ACE inhibitor/ARB treatment in an escape group (plasma aldosterone > 80 pg/ml), and a non-escape group (n=150, 68.5%).

Results: There was no decrease in UPCR in both groups (p=0.763 in aldosterone escape group, p= 0.528 in non-escape group). UPCR was significantly decreased with treatment of spironolactone in patients with eGFR ≥ 60 mL/min/1.73 m² (1.36±1.29 to 1.19±1.33 g/g Cr, p=0.042), not in eGFR <60 mL/min/1.73 m² (1.54±1.25 to 1.59±1.58 g/g Cr, p=0.712). Hyperkalemia (K ≥5.5mEq/L) was developed in 30 of the 103 patients with eGFR <60 mL/min/1.73 m² (29.8 %) and in 8 of the 120 patients with eGFR ≥ 60 mL/min/1.73 m² (7.1 %). In all patients, 25-Hydroxy vitamin D was increased after adding spironolactone (p=0.004 in aldosterone escape group, p <0.001 in non-escape group, p=0.003 in patients with eGFR ≥ 60 mL/min/1.73 m², p <0.001 in patients with eGFR < 60 mL/min/1.73 m²). UPCR was correlated with 25-Hydroxy vitamin D negatively (R= -0.222 p=0.008).

Conclusions: Change of proteinuria was not different between aldosterone escape and non-escape group after add-on spironolactone treatment. Proteinuria was significantly decreased by add-on spironolactone treatment in patients with eGFR ≥ 60 mL/min/1.73 m² but not in patients with eGFR < 60 mL/min/1.73 m².

TH-P0217

Renal Protective Effects by Rosuvastatin through the Amelioration of Intra-Renal Vascular Resistance

Keiko Fujimura, Shu Wakino, Koichi Hayashi, Hiroshi Inoh. Dept of Internal Medicine, School of Medicine, Keio Univ, Tokyo, Japan.

Background: Nephrosclerosis has been one of the common causes of renal insufficiency. One of the major clinical characteristics of nephrosclerosis is the increased intra-renal vessel resistance and the decreased renal blood flow. The effects of these renal anatomical changes were not clinically fully evaluated. A recent trial has shown that statin have renal protective effects in patients with CKD. By using Ultrasound pulse-doppler analysis (Doppler), we aimed to assess the effects of rosuvastatin treatment on the progression of CKD with nephrosclerosis.

Methods: We used our CKD cohort composed of the patients with nephrosclerosis with CKD whose eGFR levels were less than 60 mL/min/1.73m². The patients with diabetes and biopsy-proven nephritis were excluded. The relationship between various parameters of Doppler and biochemical parameters were examined. Among these subjects, we recruited 33 patients, treated them with rosuvastatin (Ros) at the dose of 2.5-5mg until the LDL-cholesterol (LDL-C) levels reached under 100mg/dl and observed for a year. We compared the change of various parameters including those of Doppler before and after Ros treatment.

Results: In regression analysis, resistance index (RI) and maximum velocity of renal blood flow(Vmax) were correlated with eGFR. Ros significantly lowered LDL-C (before vs. after; -5.5±4.5% vs. -17.7±6.7%, p<0.05). Although Ros did not suppress the increase in proteinuria, it alleviated the changes of renal tubular marker, it blunted the decline of eGFR (before vs. after; -4.2±2.0% vs. 4.2±2.4%,p<0.05). In Doppler analysis, Ros significantly suppressed the increase of RI (before vs. after;4.2±1.3% vs. -4.6±2.1%,p<0.05).

TH-P0218

Metformin Is Safe and Effective in Stage 3 and 4 Diabetic Chronic Kidney Disease Patients – A Randomized Trial


Background: In absence of evidence against use of metformin in CKD 3-4, we conducted clinical trial to study the use of metformin in diabetic CKD in stage 3 and 4. The aim of the study was to evaluate the efficacy of metformin in terms of glycomic control, incidence of lactic acidosis, episodes of hypoglycemia in patient with diabetic stage 3 and 4 CKD.

Methods: In a randomized open labeled clinical trial, a total of 218 patients were randomized by computer-generated table of random number in two groups - Insulin group (109) and Metformin group (109). Baseline characteristics of the patients in both groups were similar. During initial wash out period all the existing anti-diabetic medication were stopped. After the wash out phase, the patients were allocated to one of the two groups as per their randomization number. The OHA and Insulin were initiated and increased stepwise as per protocol. Patients were followed at 1 week, 2 weeks, 1 month and then monthly for six month. Blood analysis for acidosic and bicarbonate, serum creatinine, electrolyte, glucose profile, was measured in each visit. HbA1c was measured at 3 and 6 month. When targeted blood sugar was not achieved in metformin group sulfonylureas was added.

Results: Four patients from Insulin group and 5 patients from Insulin did not complete the study. Two patients on metformin were switched over to insulin due to intolerance to metformin.

The glycosylated hemoglobin decreased by 1.2% and 1.4% percent at 6 month in metformin and Insulin group respectively. There was no case of lactic acidosis in either group. One patient in metformin group showed increase serum creatinine that return to baseline on switching over to Insulin. There was no case of severe hypoglycemia in either group, though minor episodes hypoglycemia therapy was recorded in 3 and 7 patients in Metformin and Insulin group respectively.

Conclusions: Metformin is a safe and effective oral hypoglycemic agent in diabetic stage 3 and 4 CKD. Its use in this group of patients is not associated with lactic acidosis.

TH-P0219

Renoprotective Effect of Combining Pentoxiphylline with Angiotensin Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker in Moderate to Severe Kidney Disease

Ping-Min Chen, Ping Yu Chen, Tai-Shuan Lai, Wen-Chih Chiang, Shuei-Liong Lin. Dept of Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan; Dept of Internal Medicine, National Taiwan Univ Hospital, Bei-Hu Branch, Taipei, Taiwan.

Background: Several studies showed that pentoxifylline (PTX), a phosphodiesterase inhibitor, has beneficial antiproteinuric effects on proteinuria and chronic kidney disease (CKD). This study was to examine whether there was an add-on effect of combining PTX with angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB).

Methods: A single-center retrospective study was conducted, involving total of 697 patients with CKD stage of 3B-5 (age 18-80), to evaluate the effect of individual risk factor. Subgroup analysis was also performed by dividing the patients into lower and higher proteinuria groups (baseline urine protein/creatinine ratio < 1 g/g or ≥ 1 g/g).

Results: Addition of PTX with either ACEI or ARB showed a better renal outcome (p = 0.044). There were no between group differences regarding all-cause mortality or cardiovascular events. Subgroup analysis revealed that the protective effect of add-on PTX was demonstrated in the higher proteinuria group (p = 0.009), but not in the lower proteinuria group. Multivariate Cox regression model combined combination therapy had less chance of RRT again (HR 0.705, 95% CI 0.505 – 0.985, P = 0.040), especially in higher proteinuria group (HR 0.606, 95% CI 0.420 – 0.873, P = 0.007).

Conclusions: Combination treatment of PTX with ACEI or ARB showed a better renal outcome than single use of ACEI or ARB, especially in higher proteinuria patients. Large randomized control trials are needed to provide more evidence of the add-on effect of PTX in CKD patients.
Background: Heart failure (HF) is a major complication of chronic kidney disease (CKD). NT-proBNP and high sensitivity troponin T are associated with HF in the general population, but these associations remain unclear in the setting of CKD.

Methods: We studied 3,483 participants of the Chronic Renal Insufficiency Cohort (CRIC) Study (mean age: 58 years; 48% diabetic; 42% black; mean eGFR: 45 mL/min) who did not report HF at baseline. Incident HF hospitalizations were adjudicated using standard criteria. Associations of each biomarker with incident HF were assessed using Cox models after multivariable adjustment, and then additionally adjusted for both biomarkers.

Results: Median (IQR) NT-proBNP and troponin T was 135.3 (58.6-335.6) and 11.9 (5.4-21.8) pg/mL, respectively. Over a median of 4.7 years, 284 incident HF events occurred. Those in the highest (versus lowest) quintile of NT-proBNP had an 11-fold higher adjusted rate of incident HF (Table). Compared to those with undetectable troponin T, those in the highest quartile of detectable troponin T had a 4-fold higher adjusted rate of incident HF. Results did not change after adjustment for the alternative biomarker.

<table>
<thead>
<tr>
<th>NT-proBNP (ng/mL)</th>
<th>HR* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref: ≤ 247.6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt;247.6-95.8</td>
<td>3.3 (1.4-8.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;95.8-188.8</td>
<td>9.9 (4.6-19.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;188.8-428</td>
<td>3.2 (2.6-15.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;428</td>
<td>11.4 (4.7-27.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Troponin T (ng/mL)</th>
<th>HR* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref: undetectable</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≤ 3.7</td>
<td>1.4 (0.6-3.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;3.7-13.6</td>
<td>3.1 (2.0-5.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;13.6-24.4</td>
<td>2.6 (1.2-6.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;24.4</td>
<td>1.1 (0.8-1.5)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Troponin T and NT-proBNP, possibly reflecting subclinical myocardial stress and dysfunction, were significantly and independently associated with incident HF among a diverse cohort of CKD patients.

Funding: NIDDK Support

TH-PO221
Risk of Nephropathy Associated with Choice of Add-On Therapy for Diabetes Treatment after Metformin Adriana Hung,1 Christianne Roumieu,1,2 Robert Greevey,1,2 Xulei Liu,1,2 Carlos Grijalva,1,2 Harvey J. Murff,1,2 T. Alp Ikizler,1,2 Marie Griffin,1,2 Veterans Affairs, Nashville, TN; Vanderbilt Univ, Nashville, TN.

Background: Glycemic control reduces the risk of chronic kidney disease (CKD). The addition of a second agent is often needed when diabetes is sub-optimally controlled with metformin monotherapy. We compared the effectiveness of adding either insulin or sulfonylurea to metformin in preventing kidney function decline or death.

Methods: We assembled a national retrospective cohort of veterans who initiated diabetes treatment with metformin monotherapy between October 2001 and September 2008 and added either insulin or a sulfonylurea or a change in metformin dose to follow-up until an outcome, loss to follow-up, death or end of the study. The risk for the outcomes was compared between regimens using marginal structural Cox models. Stratified analyses included subgroups by eGFR (≥60 or <60 ml/min) and by HbA1c (<7, 7-9, and ≥9%).

Results: Among sulfonylurea monotherapy initiators, we identified 1857 patients that added insulin to sulfonylurea and 1581 that switched to insulin monotherapy. Patients' characteristics were similar between groups, median age was 64 years and 99% were men. There were 4.9 versus 5.2 renal composite events per 100 person-years among sulfonylurea + insulin versus insulin monotherapy users respectively ([aHR] 0.91 95% CI 0.73, 1.13). For the secondary outcome of an eGFR event, eGFR or death, the respective rates were 11.1 versus 13.1 renal composite events per 100 person-years ([aHR] 1.07 95% CI 0.93, 1.24). Results were similar by eGFR and HbA1c subgroups, and in analyses that required persistence on the intensifying regimen.

Conclusions: There were no differences in the risk of a sustained decline in eGFR, eGFR or death between patients who intensified their sulfonylurea regimens by adding insulin versus those that switched to insulin monotherapy.

Funding: Other NIH Support - AHRQ

TH-PO222
Comparative Effectiveness of Insulin versus Combination Insulin and Sulfonylurea in Preventing Renal Outcomes Adriana Hung,1 Christianne Roumieu,1,2 Robert Greevey,1,2 Xulei Liu,1,2 Carlos Grijalva,1,2 Harvey J. Murff,1,2 Marie Griffin,1,2 T. Alp Ikizler,1,2 Dept of Veterans Affairs, Nashville, TN; Vanderbilt Univ, Nashville, TN.

Background: Evidence based recommendations for the choice of diabetic regimen for prevention of renal outcomes among those with low GFR are lacking. We compared renal outcomes among diabetes patients who intensified their sulfonylurea monotherapy regimen by adding insulin versus those who switched to insulin monotherapy.

Methods: This retrospective cohort included veterans who initiated treatment with a sulfonylurea between 2001 and 2008 and then added or switched to insulin therapy through 12/2010. The primary outcome was a renal composite of a sustained decline of GFR of ≥35 mL/min. The secondary outcome was a composite of an GFR event, eGFR or death. Follow-up started at the time of addition or switching to insulin regimen and continued until an outcome, loss to follow-up, death or end of the study. The risk for the outcomes was compared between regimens using marginal structural Cox models. Time-varying covariates were: HbA1c, blood pressure, BMI, co-morbidities and medications. Stratified analyses included subgroups by GFR (≥60 or <60 ml/min) and by HbA1c (<7, 7-9, and ≥9%).

Results: Among sulfonylurea monotherapy initiators, we identified 1857 patients that added insulin to sulfonylurea and 1581 that switched to insulin monotherapy. Patients' characteristics were similar between groups, median age was 64 years and 99% were men. There were 4.9 versus 5.2 renal composite events per 100 person-years among sulfonylurea + insulin versus insulin monotherapy users respectively ([aHR] 0.91 95% CI 0.73, 1.13). For the secondary outcome of an eGFR event, eGFR or death, the respective rates were 11.1 versus 13.1 renal composite events per 100 person-years ([aHR] 1.07 95% CI 0.93, 1.24). Results were similar by eGFR and HbA1c subgroups, and in analyses that required persistence on the intensifying regimen.

Conclusions: There were no differences in the risk of a sustained decline in eGFR, eGFR or death between patients who intensified their sulfonylurea regimens by adding insulin versus those that switched to insulin monotherapy.

Funding: Other NIH Support - AHRQ

TH-PO223
Low Dose Aspirin for Prevention of Cardiovascular Events in Patients with Chronic Kidney Disease: A Propensity-Matched Study Ji Yong Jung,1 Han Ro,1 Chung Sik Lee,2 Sun Moon Kim,3 Ae Jin Kim,3 Hyung Soo Kim,1 Jae Hyun Chang,1 Hyun Hee Lee,1 Wooyong Chung,3 Div of Nephrology, Dept of Internal Medicine, Gachon Univ, Incheon, South Korea; Div of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Korea; Div of Nephrology, Dept of Internal Medicine, Chonbuk National Univ Hospital, Cheongju, Korea.

Background: Chronic kidney disease (CKD) is a powerful risk factor for development of cardiovascular disease (CVD). Previous trials have investigated the effect of low dose aspirin on prevention of CVD in patients with diabetes but not in CKD patients. In addition, the role of aspirin in diabetics is controversial and the available literature is contradictory. Therefore, we studied whether low dose aspirin would be beneficial in patients with chronic kidney disease (CKD) as high risk group for CVD.

Methods: Using propensity score matching, 191 low dose aspirin (100mg/day) recipients and 382 non-recipients were 1:2 paired for analysis from 2,624 patients with CKD. The primary endpoint was a composite of coronary arterial disease, ischemic stroke, and peripheral arterial disease. Secondary endpoints included death from any cause, bleeding events, and time to serum creatinine doubling and renal death.

Results: Low dose aspirin was prescribed for 8.9% of patients with CKD. The incidence of primary endpoint of any atherosclerotic CVD was not significantly different in the aspirin users than in the non-aspirin users after PS matching (hazard ratio = 1.025; 95% confidence interval = 0.642 – 1.637; P = 0.917). Secondary endpoints including all-cause mortality, time to serum creatinine doubling and renal death, hemorrhagic stroke and significant gastrointestinal bleeding events were not significantly different between the aspirin and non-aspirin users.

Conclusions: These results suggest that use of low dose aspirin did not reduce the risk of atherosclerotic CVD in CKD patients. Further randomized clinical trials are warranted to confirm the effect of low dose aspirin therapy on the development of CVD in these patients.
**TH-PO225**

**Diabetic Kidney Disease: Results from the Irbesartan Diabetic Nephropathy Trial (IDNT)**

*Jamie P. Dwyer,1 Julia Lewis,1 Tom Greene,2 Nan Hu,2 Edmund J. Lewis,1 The Collaborative Study Group,1 Vanderbilt Univ; 2Univ of Utah; 3Rush Univ.*

**Background:** The composite endpoint of time to of SCR (dSCR) or ESRD is accepted by the FDA and traditionally used to determine treatment effects on progression of chronic kidney disease (CKD) in contemporary clinical trials. However, the follow-up time required for these events can be substantial.

**Methods:** We assessed the accuracy of endpoints defined by smaller confirmed increases in SCR at either 12 months or 18 months for prediction of subsequent occurrences of ESRD using analyses of time dependent receiver operating characteristic (ROC) curves in the Irbesartan Diabetic Nephropathy Trial (IDNT) data base.

**Results:** Shown are time-dependent ROC curves with associated areas under the curve (AUC) for alternative early SCR endpoints relative to occurrence of ESRD by 33 months. We considered the following early SCR endpoints: a) Confirmed increase in SCR at 12 months; b) Confirmed increases in SCR at 18 months, and c) Three additional composite endpoints defined by confirmed increases in SCR by varying levels at 18 months OR a confirmed increase in SCR at 12 months by either 25%, 35% or 45%.

**Conclusions:** Warfarin treatment was associated with a decreased 1-year risk of death, readmission for MI, stroke and bleeding in consecutive MI patients with AFib. This association was not influenced by the severity of concurrent renal disease.

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

---

**TH-PO226**

**Urinary Albumin:Creatinine and Protein:Creatinine Are Prognostically Equivalent for CKD Progression: Results from CANPREDICT**

*Claudio Rigatto,1 Adeaer Levin,2 Catherine M. Clase,3 Brendan J. Barrett,2 Francois Madore,4 Norman Muirhead,5 Navdeep Tangri,6 Mila Tang,7 Ogjenka Djurdjevic,8 Univ of Manitoba; 3Univ of British Columbia; 4McMaster Univ; 5Univ de Montréal; 6Memorial Univ of Newfoundland; 7London Health Science Center; 8St. Paul’s Hospital; 9British Columbia Renal Provincial Agency.*

**Background:** Proteinuria is an important prognostic variable in patients with chronic kidney disease (CKD). Both albumin-to-creatinine ratio (ACR) and protein-to-creatinine ratio (PCR) are widely used to estimate proteinuria. No study has directly compared the ability of these measures to predict progression to end-stage renal disease (ESRD).

**Methods:** We examined the ability of baseline measures of ACR and PCR to predict progression to ESRD over one year in 2,544 patients participating in CanPREDICT, a prospective cohort study of adult patients with advanced CKD from multiple causes. ACR and PCR were log transformed for analysis. We created a base Cox multivariable model (BCM) for prediction of RRT using standard clinical variables, and then compared differences in the performance (discrimination [c statistic, IDI] and reclassification [NRI]) of enriched Cox models (ECM) created by addition of either logACR or logPCR.

**Results:** Both ACR and PCR independently predicted need for RRT at one year, and each remained highly significant after adjustment for the BCM variables. Both log ACR and log PCR improved BCM performance significantly and to the same degree.

**Conclusion:** Sensitivity analyses using alternate choices for BCM variables did not change these results.

**Funding:** NIDDK Support, Other NIH Support - USPHS GCRC grant #M01-RR06633 from NIH/NCRR-CR. Supported in part by grant UL1TR000451 from the National Center for Advancing Translational Sciences, National Institutes of Health., Veterans Affairs Support, Private Foundation Support

---

**TH-PO227**

**Microalbuminuria and CKD Modify the Association of Arterial Stiffness with Death**

*Javier A. Neyra,1 Ian McCoy,1 Nishank Jain,1 Robert D. Toto,1 Susan Hedayati,1,2 Univ of Texas Southwestern, Dallas; 2Veterans Affairs North Texas.*

**Background:** Pulse pressure (PP), a marker of arterial stiffness, is associated with mortality and is increased in advanced CKD. Few studies investigated the effect modification of CKD on this association of PP with death. We hypothesized that the independent association between higher PP and death would be greater among patients with CKD and microalbuminuria compared to those without.

**Methods:** Logistic regression was used to explore the association of PP with mortality among 2,859 participants of the probability-sampled, population-based, multi-ethnic Dallas Heart Study followed for a median of 8 years. Odds ratios were expressed for each 5-unit increase in PP. Models were adjusted for age, race, gender, eGFR and urinary albumin-to-creatinine ratio (ACR). Interactions between PP X eGFR and PP X ACR were tested. Analyses were stratified by PP x creatinine, defined as an eGFR of <60 mL/min/1.73 m² or presence of microalbuminuria (≥ 17 mg/g creatinine in men and ≥25 in women).

**Results:** Mean (SD) age was 45 (10) years, eGFR 100 (24), and ACR 19 (138). 50% were African American, 31% Caucasian, 17% Hispanic, and 2% of other races. Eight percent (242/2859) had CKD. Those with CKD had a higher PP at 55.9 mmHg, 95% CI (53.0, 57.0) vs. those without, 48.0 (47.6, 48.4) mmHg, p<.0001. There were 155 total deaths with a higher number in the CKD group (48 deaths or 20% vs. 107 deaths or 4% in non-CKD, p<.0001). Every 5-unit increase in PP was associated with a 23% increase in death, OR 1.23, 95% CI (1.18, 1.32), which remained significant after adjustment, OR 1.08 (1.01, 1.16). There was a significant interaction between PP and both eGFR and ACR, p = .02 and 0.46. In stratified adjusted models, PP was associated with death in CKD, OR 1.11 (1.003, 1.23) but not in non-CKD participants, OR 1.04 (0.96, 1.13). This difference was highly significant, p<.0001.

**Conclusions:** Among a multi-ethnic community-dwelling sample, arterial stiffness, estimated by PP, was independently associated with death more so in CKD compared to non-CKD participants. This difference was greater in CKD participants that are stratified by estimated increased by PP may be a way to risk-stratify patients with early CKD.

**Funding:** NIDDK Support, Other NIH Support - USPHS GCRC grant #M01-RR06633 from NIH/NCRR-CR. Supported in part by grant UL1TR000451 from the National Center for Advancing Translational Sciences, National Institutes of Health., Veterans Affairs Support, Private Foundation Support

---

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

**Underline** represents presenting author/disclosure.
TH-PO228
Chronic Kidney Injury and Hypertension Associate with Increased Urinary Succinate Levels
Peter M. T. Deen,1 Joris Huberust Robben,2 Juliette Hadchouel,1 Gerjan Navis,1 Ewout J. Hoon,4 Jack F. Wetzel5

Background: The renal succinate receptor SUCNR1 senses the Krebs cycle intermediate succinate secreted from cells in response to oxidative stress. As it is recently emerged as an activator of RAAS and pro-fibrotic events in DM1 and hypertension, we measured urinary succinate excretion in renal diseases to identify disorders in which SUCNR1 may play a role.

Methods: Urinary succinate was measured with an optimized low-volume enzymatic assay. Measured succinate concentrations were corrected for urinary creatinine levels. P-values <0.05 were considered significant.

Results: Urinary succinate levels were: 2.7 fold higher in CKD stage 2-4 patients than of healthy controls; 4.2 fold higher in hypertensive CKD patients versus controls; 1.4 fold higher in primary aldosteronism patients versus controls; 1.7 fold higher in a mouse model of Familial Hyperkalemic Hypertension (FHH) with βK1 mutations vs. wild-type littermates. In hypertensive CKD patients treated with ACE inhibitors, urinary succinate decreased 3.1 fold following use of Angiotensin receptor blockers (ARBs) and 2.7 fold when subjected to a low-sodium diet. In contrast, subjecting healthy individuals that had normal BP and urinary protein excretion to use ARBs decreased urinary succinate 3.1 fold following use of ARBs and 2.7 fold when subjected to a low-sodium diet. In contrast, subjecting healthy individuals that had normal BP and urinary protein excretion to use ARBs decreased urinary succinate 3.1 fold following use of ARBs and 2.7 fold when subjected to a low-sodium diet.

Conclusions: Renal succinate release is increased in all animal models and patients with affected renal function associated with chronic oxidative stress. With hypertensive CKD patients, urinary succinate levels correlated with the extent of sodium intake, hypertension and proteinuria. As urinary succinate activates SUCNR1, these data indicate to a role for SUCNR1 in activation of the intrarenal RAAS system and renal fibrosis as are commonly observed in these chronic renal disorders.

Funding: Government Support - Non-U.S.

TH-PO229
Microalbuminuria and Risk of Cancer
Ali Abbasi,1,2 Ron T. Gansevoort,2 Rudolf A. De Boer,1 Eva Corpeleijn,1 Rijk O.B. Gans,1 Hans L. Hillege,1 Pim Van der Harst,1 Ronald P. Stolk,2 Gerjan Navis,2 Stephan J.L. Bakker,2 Epidemiology, Univ Medical Center Groningen, Groningen, Groningen, Netherlands; Internal Medicine, Univ Medical Center Groningen, Groningen, Groningen, Netherlands; 3Epidemiology, Med. Centre Rotterdam, Rotterdam, Rotterdam, Netherlands; 4Internal Medicine, Univ Medical Center Groningen, Groningen, Groningen, Netherlands; 5Cardiology, Univ Medical Center Groningen, Groningen, Groningen, Netherlands.

Background: Information on the potential association of microalbuminuria (MA) with cancer risk is sparse. We aimed to investigate whether MA is associated with overall and specific cancer risk in the general population.

Methods: We acquired data of 40,584 participants (aged 28-75 years) from the PREVEND study, an observational cohort study (Groningen, the Netherlands), that started in 1996-97. All incident cancers requiring hospitalisation were ascertained via the Dutch national hospital registry up to 2009.

Results: During a median follow-up of 12.7 years, 4156 (10.2%) subjects developed cancer. The most common cancer sites were respiratory (4.0%), oropharynx (2.4%), genitourinary (2.3%) and digestive system (2.2%). In an age-and sex-adjusted Cox regression model, the HR (95%CI) for all cancer was 1.26 (1.14-1.40) in subjects with MA (urine albumin concentration (UAC)>20mg/L) as compared to normoalbuminuria (UAC<20mg/L)."P<0.001). In a multivariable model adjusted for age, sex, smoking and diabetes, the significant association of MA remained, corresponding with a 23% increased risk of cancer. HRs for MA versus normoalbuminuria for specific cancers were for respiratory 0.93 (0.78-1.12), oropharynx 1.29 (1.04-1.61), genitourinary 1.66 (1.36-2.02) digestive system 0.98 (0.84-1.14), breast 1.17 (0.88-1.56) and prostate 1.29 (0.93-1.80).

In a subcohort of 8,592 subjects, who were screened in detail at baseline, the association of MA (>30mg/24hr) with cancer was corroborated adjusted for the aforementioned variables, even when additionally adjusted for history of cancer, inSCRP, leukocyturia and erythrocyturia (HR 1.29 (1.05-1.53)). No significant independent association was found with eGFR (or impaired eGFR).

Conclusions: MA is independently associated with an increased risk of incident cancer in the general population, particularly genitourinary cancers.

TH-PO230
Overall Prevalence of Proteinuria Is Low but the Relative Prevalence of Non-Albumin Proteinuria Is High in a Community Cohort of Patients with Chronic Kidney Disease: Results from the Triple A Kidney Project
Shona Methven1, Alan G. Jardine,2 Mark S. MacGregor,1 1School of Clinical Sciences, University of Bristol, United Kingdom; 2Institute of Cardiovascular Science and Medical Sciences, Univ of Glasgow, United Kingdom; 3Renal Unit, Univ Hospital, Crosshouse, Kilmarnock, United Kingdom.

Background: Measurement of proteinuria with albumin:creatinine ratio (ACR) alone does not take account of non-albumin proteinuria (NAP). We describe the prevalence of NAP in a community cohort of patients with chronic kidney disease (CKD).

Methods: Participants with a diagnosis of CKD Stage ≥3 were recruited from 7 primary care facilities across Ayrshire, Scotland in the Triple A Kidney Project. Detailed baseline clinical and laboratory assessment was undertaken, including measurement of early morning ACR and protein:creatinine ratio (PCR) in all participants. Albumin:protein ratio (APR) was calculated and compared with that of a nephrology clinic population (n=1874).

Results: Four hundred and eleven participants were recruited, mean age 70±6.9 years, 55% female, 99.5% white, 20% diabetic and median eGFR 54 (IQR 44 – 61) mL/min/1.73m2. Only 2.7% of the cohort had documented glomerular disease and 69% were taking renin-angiotensin blocking drugs. Twenty six per cent (n=107) had detectable proteinuria measured by PCR (≥15mg/mmol, ≥133mg/g equivalent), 17% by ACR (≥25mg/mmol, ≥2.65mg/g equivalent) and 14% had elevated PCR and ACR. Of those with PCR 15-50mg/mmol (133-442mg/g) (n=91), only 50% had detectable albuminuria and 70% had an APR<0.4 (ie predominantly NAP). Of those with PCR>50mg/mmol (>442mg/g), 44% had APR<0.4. In the nephrology clinic population, 55% of those with PCR 15-50mg/mmol had an APR <0.4 and 23% of those with PCR>50mg/mmol had an APR <0.4.

Conclusions: Overall prevalence of proteinuria was low in this community cohort but the relative prevalence of NAP was high, and notably higher than a nephrology clinic population, especially in those with <0.5g/day equivalent total proteinuria. This would not have been detected using ACR alone. The presence of albuminuria and NAP may reflect different underlying disease processes and the outcomes of this discordant group will be assessed.

Funding: Pharmaceutical Company Support - unrestricted educational grant from Bristol-Myers Squibb

TH-PO231
Urinary Albumin/Creainine Ratio (ACR) and Cumulative Systolic Blood Pressure (CumSBP) in the Coronary Artery Disease in Young Adults (CARDIA) Study
Holly J. Kramer,1 David R. Jacobs,2 Cora E. Lewis,5 Kirsten Bibbins-Domingo,1 Alex Chang,4 Carmen A. Peralta,3 Paul Muntner,5 David Siscovick,4 Mark J. Pletcher,3 Kiang Liu.2 Loyola Univ Chicago; 3Univ of Minnesota; 4Univ of California San Francisco; 5Johns Hopkins Univ; 6Univ of Alabama; 7Northwestern Feinberg School of Medicine.

Background: We hypothesized that an association exists between CumSBP exposure from age 30 through 45 years and ACR at age 45 among black and white adults without diabetes at age 30 (n=1895).

Methods: SBP values were averaged between consecutive visits (years 0, 2.5, 7, 10, 15, 20 and 25) and then multiplied by number of years between visits and summed to determine CumSBP (mmHg x years) during ages 30-45 years. Log ACR at age 45 vs. cumulative SBP after adjustment for race, sex, smoking, waist circumference, education, incident diabetes and blood pressure medication use. Multinomial logistic regression models were used to examine the association between CumSBP exposure and presence of high normal ACR (sex and race adjusted ACR 13-24.9 mg/g) at age 45 or albuminuria (sex and race adjusted ACR ≥ 25 mg/g) at age 45 vs. normal ACR (sex and race adjusted ACR < 13 mg/g) at age 45 after adjustment for covariates.

Results: After adjustment for covariates including use of anti-hypertensive medications during age 30-45 years, each 75 mmHg x year increase (5 mmHg per year from age 30-45 years) of CumSBP was associated with a 1% (95% CI 1.02, 1.21) higher odds of high normal ACR at age 45 and a 24% higher odds of albuminuria at age 45 vs. normal ACR at age 45 (95% CI 1.13, 1.36).

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

Funding: Other NIH Support - NHLBI
Obsessive, Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD) among Individuals in the REGARDS Study

Holly J. Kramer,1 Suzanne E. Judd,2 David A. Shoham,3 Paul Muntner,2 David G. Warnock,7 Orlando M. Gutierrez,2 Rikki M. Tanner,2 William M. McClellan.3

1Loyola Univ Chicago; 2Univ of Alabama; 3Emory Univ.

Background: The association between obesity and chronic kidney disease (CKD) is poorly understood. This study examines the independent associations between BMI and waist circumference (WC) with prevalent albuminuria, reduced estimated glomerular filtration rate (eGFR) and incident end stage renal disease (ESRD).

Methods: Participants in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study (n=27,085) with BMI, WC, spot urine albumin-to-creatinine ratio (ACR), and estimated glomerular filtration rate (eGFR) measured at baseline were linked to United States Renal Data System to identify incident cases of ESRD.

Results: Prevalence of albuminuria (ACR ≥30 mg/g) and CKD (eGFR < 60 ml/min/1.73m2), increased across World Health Organization defined obesity categories for BMI and gender-specific WC. After multivariable adjustment there was a significant trend toward lower prevalence for albuminuria and CKD in the BMI groups ≥25 kg/m2 vs. BMI < 25 kg/m2 but higher prevalence in the WC groups ≥80 and ≥94 cm compared to WC referent group (<80 and <94 cm in men and women, respectively). A total of 160 individuals developed ESRD (0.6%); increased BMI was associated with a reduced risk of incident ESRD but no WC. Both BMI and WC were associated with higher risk of ESRD after adjustment for WC and all covariates while higher WC was associated with heightened risk of ESRD. Individuals in the highest WC category (≥108 and ≥122 cm in women and men respectively) had a 5.05-fold (95% CI 2.23, 11.2) higher hazard ratio for ESRD compared to WC referent group after adjustment for BMI. This association was no longer significant after adjustment for all covariates (HR 2.03; 95% CI 0.90, 4.55).

Conclusions: Higher WC is associated with an increased risk of ESRD after adjustment for BMI while higher BMI is associated with decreased ESRD risk after adjustment for WC. The association between higher WC and ESRD risk support the possibility that increased abdominal adiposity may influence kidney disease progression.

Funding: Other NIH Support - U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Services, Pharmaceutical Company Support - Additional funding was provided by an investigator-initiated grant-in-aid from Amgen Corporation

A Cross Sectional Study on the Relationship of Retinal Vascular Diameter, Hypertension and Albuminuria

Wen Huang,1 Ning Ding,1 Leping Jiao,1 Guijuan Zhang,1 Ningli Wang,2 Yuan Bo Liang.2

1Nephrology, TongRen Hospital, Beijing, China; 2Eye Center, TongRen Hospital, Beijing, China.

Background: Microvascular abnormalities are common findings in patients with chronic kidney disease. Recent studies have reported an association between retinal vascular diameter and chronic kidney disease. But there are still some controversies and researches based on Chinese population are scarce. Hence we did a cross-sectional study to test the hypothesis that the retinal vascular diameter may correlate with renal microvascular abnormalities.

Methods: This was a population-based cross-sectional study based on the data of Handan eye study (HES). HES recruited 7577 participants, of whom 5541 had complete information on retinal vascular diameter, albuminuria and blood pressure. Retinal arterial and venular diameters were measured and summarized as central retinal arterial equivalent (CRAE) and central venular equivalent (CRVE). The presence of microalbuminuria was defined as urinary albumin:creatinine ratio ≥17 μg/ml for men and ≥25 μg/ml for women. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication.

Results: Among the 5541 participants, male:female 45.9%, age (51.83±11.63), hypertension (48.2%), DM (6.1%). After adjustment for age, gender and other confounders, the narrowest retinal arterial diameter correlated with an increased risk of albuminuria (multivariable OR: 1.24, 95% CI 1.02-1.51) compared with the widest. Retinal venular diameter had no correlation with albuminuria. Hypertension correlated with an increased risk of albuminuria (multivariable OR: 1.41, 95% CI 1.21-1.64) compared with absence of hypertension. Exposure to both hypertension and retinal arterial narrowing obviously increased the risk of albuminuria (multivariable OR: 1.69, 95% CI 1.31-2.19).

Conclusions: We concluded that retinal arterial diameter was independently correlated with albuminuria, while no such association was found in retinal venular diameter. In hypertensive patients, retinal arterial narrowing was significantly correlated with albuminuria.

Risk Factors for Proteinuria in a National Cohort of HIV-Infected Veterans

Tanushree Banerjee,1 Deidra C. Crews,2 Donald E. Wesson,3 Anca Tilea,4 Rajiv Saran,4 Desmond Williams,5 Nilka Rios Burrows,2 Neil R. Powe.1 UCSC; 2JHU; 3Texas A&M College of Medicine; 4UM; 5CDC.

Background: Previous research in adults with CKD has shown an improvement in kidney injury and slowed GFR decline due to the reduction in dietary acid. We sought to examine the association between high dietary acid load, quantified by dietary net acid excretion (NAE), and progression to ESRD, in a nationally representative sample of US adults.

Methods: Among 1,486 CKD (15% <eGFR ≤60) adults aged ≥20 years who participated in the National Health and Nutrition Examination Survey (NHANES) between 1988 till 1994, NAE was determined by the dietary recall questionnaire (24 hrs) using a model by Remer and Manz. The development of ESRD was ascertained over an average of 13.2 years of follow-up via linkage with the Medicare ESRD Registry. We used the Fine-Grey competing risks model (accounting for competing risk of mortality) to estimate the hazard ratio (HR) for ESRD associated with versus higher low dietary acid load after adjusting for demographics, socio-economic position, diabetes and hypertension, eGFR and urinary albumin:creatinine, and daily caloric intake.

Results: The median value of NAE was 47.24 mEq/d. Persons with higher NAE were younger (p<0.0001). Persons with higher dietary acid load were more likely to be males (58.9%), non-Hispanic black (31.6%), have diabetes (36.9%), or lower eGFR (30.2%) compared to their counterparts (all p<0.05). Poverty, level of education, and hypertension, did not differ across tertiles of NAE. Adults in the highest and middle versus lowest tertile of dietary acid were more likely to develop ESRD (HR [95% CI]: 6.16 [6.12-6.20] and 3.48 [3.46–3.50], respectively) after adjustment even when the competing risk of death before developing ESRD was accounted for. On studying the association of early ESRD events (within 6 years) with dietary acid, the HRs [95% CI] of the highest and middle tertile were 9.93 [9.35-10.54] and 3.79 [3.66-3.92] respectively, compared with the lowest tertile.

Conclusions: Dietary acid load in persons with CKD is independently and strongly associated with increased risk of ESRD over time in a graded fashion.

Funding: Other U.S. Government Support
**TH-PO236**

The Nephropathy in the Patients in the African American Study of Kidney Disease and Hypertension Manifests Low Albumin/Protein Ratios Typical of a Tubulo-Interstitial Nephropathy: Clinical and Pathophysiological Implications  
Udayan V. Bhatt, Robert D. Toto, Shona Methven, Stephen J.L. Bakker, Ron T. Gansevoort, Mahboob Rahman, Daniel J. Birmingham, Cynthia A. Kendrick, Jennifer J. Gassman, Christopher J. Deighan, Tom Greenwald, Brad H. Rowan, Lee A. Hebert, Internal Medicine, Ohio State Univ Wexner Med Ctr, Columbus, OH; Univ of Texas Southwestern; Univ of Bristol, United Kingdom; Univ Medical Center Groningen, Netherlands; Case Western Univ; Cleveland Clinic; Western Infirmary Glasgow, United Kingdom; Univ of Utah.

**Background:** The pathogenesis of the nephropathy (N) studied in African American Study of Kidney Disease and Hypertension (AASK) is unclear. AASK-N is believed to be from hypertension, but in the AASK trial better BP control did not slow GFR decline. Also, biopsy in AASK-N shows pervasive global glomerulosclerosis, suggesting a glomerulopathy, but AASK-N progresses at proteinuria levels far below that of traditional glomerulopathies. Another paradox is that AASK-N albumin/protein ratios (APR) are low, typical of tubulo-interstitial (T-I) N-not glomerulopathy. The present work addresses this paradox.

**Methods:** We analyzed APR and PCR (protein/creatinine ratio) from published works of AASK cohort (691), Glasgow glomerular disease and T-I N (5,586), Groningen Univ transplant-N (606), Ohio SLE Study lupus N (127).

**Results:** The mean age was 49 years, 46% were male, mean eGFR was 84 ± 15 ml/min/1.73m2 and the median 24 h U/AE was 7.2 mg/day (interquartile range 5.4-11). The average of the two 24-hour urine albumin excretion (UAE) measurements served as a proxy for urinary protein excretion, and UAE was also used to calculate a CCR (as a proxy of muscle mass). The overall mean UAE was 5.1 mg/day, with a median of 3.9 mg/day and an interquartile range of 2.7-7.7 mg/day. The mean UAE was significantly lower in the AASK-N cohort compared to the overall AASK cohort (p<0.001).

**Conclusions:** AASK-N manifests as a tubulopathy. So, in AASK-N non-albumin proteinuria may predict progression better than albuminuria.

**Funding:** NIDDK Support

---

**TH-PO237**

The Effect of Normalizing Spot Albumin to Creatinine Ratio Normalized for Creatinine Excretion Rate on Accuracy of Albuminuria Estimation: The Prevention of REnal and Vascular End-Stage Disease (PREVEND) Study  
Joseph A. Abdelmalek, Ron T. Gansevoort, Hiddo Jan Lambers Heerspink, Joseph L. Bakker, Daniel J. Birmingham, Univ Wexner Med Ctr, Columbus, OH; Univ of Texas Southwestern; Univ of Manchester, Manchester, United Kingdom.

**Background:** The urine albumin-to-creatinine ratio (ACR) is recommended instead of proteinuria for estimating albuminuria. In those with extremes of muscle mass, however, variations in the spot urine creatinine value may lead to false under- or over-estimation of albuminuria. Creative variables included sex, age, BMI, mean BP, HbA1c, TG, HDL-C, UA, eGFR, smoking, previous cardiac or stroke or kidney diseases.

**Methods:** In whole subjects, ES significantly ameliorated the incidence of proteinuria (ES 0.9 | 0.86 - 0.94 | P<0.001; ES 0.85 [0.81 - 0.89] | P<0.001; ES 0.77 [0.73 - 0.81] | HR0.9, P<0.001 ). There was significant interaction between ES and BMI in male. After the male subjects were divided into quintile as following BMI, in more than third groups (22.9-BMI<24.1), there was no significant ES effect upon incidence of proteinuria. In female, ES improves incidence of proteinuria, regardless of BMI. Reporting bias might cause this phenomenon in male.

**Conclusions:** Exercise habitant might ameliorate the incidence of proteinuria.

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

---

**TH-PO238**

Exercise Ameliorates Incidence of Proteinuria in a Large Japanese General Population Sample  

**Department of Internal Medicine, Div of Kidney and Dialysis, Hyogo Medical College, Nishinomiya, Hyogo, Japan; Div of Nephrology and Geriatric Medicine, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; Steering Committee for the “Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan”, Tokyo, Japan.

**Background:** Exercise habitant is well known to have favorable effect upon metabolic syndrome. And metabolic syndrome might cause proteinuria and CKD. But it remains unknown that exercise habitant have favorable effect upon proteinuria. Aim of this study is to reveal the effect of exercise habitant upon proteinuria.

**Methods:** This study is cross-sectional cohort study. Subjects were 290213 persons who received the Specific Health Check and Guidance in Japan in Okinawa, Ibaraki, Miyagi, Niigata, Tokyo, Osaka, Fukushima, Fukuoka prefectures, without missing-data. The exercise score (ES) was defined as total of three exercise habitats; more than once a week half hour or over exercise with slight sweat, more than one hour daily walk or physical activity, faster walking than average of same generation. Outcome was defined as proteinuria. Exploratory variables included sex, age, BMI, mean BP, HbA1c, TG, HDL-C, UA, eGFR, smoking, previous cardiac or stroke or kidney diseases.

**Results:** In whole subjects, ES significantly ameliorated the incidence of proteinuria (ES 0.9 | 0.86 - 0.94 | P<0.001; ES 0.85 [0.81 - 0.89] | P<0.001; ES 0.77 [0.73 - 0.81] | HR0.9, P<0.001 ). There was significant interaction between ES and BMI in male. After the male subjects were divided into quintile as following BMI, in more than third groups (22.9-BMI<24.1), there was no significant ES effect upon incidence of proteinuria. In female, ES improves incidence of proteinuria, regardless of BMI. Reporting bias might cause this phenomenon in male.

**Conclusions:** Exercise habitant might ameliorate the incidence of proteinuria.

**Funding:** NIDDK Support

---

**TH-PO239**

Hyperuricemia Is Associated with Cardiovascular Mortality in Chronic Kidney Disease  
Diana Chiu, James Ritchie, Darren Green, Smeeta Sinha, Philip A. Kalra. Salford Vascular Research Group, Univ of Manchester, MAHSIC, Manchester, United Kingdom.

**Background:** Hyperuricemia is a common finding in patients with Chronic Kidney Disease (CKD). There are few long-term outcomes studies examining the association of hyperuricemia with cardiovascular deaths in CKD.

**Methods:** Baseline bloods were analyzed from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS), a prospective observational study of outcome in patients with all-cause CKD stages 3-5, managed in secondary care. Hyperuricemia was defined as serum uric acid >0.43mmol/l. Predictors of cardiovascular deaths, data from NIDDK Statistical Services, were selected using forward stepwise cox regression (included variables with p<0.05 on univariate analysis). As Allopurinol affects uric acid levels, only patients not on this medication were included in this particular analysis.

**Results:** From 883 patients, with available baseline uric acid results and not taking allopurinol, mean eGFR was 35±16.2 ml/min/1.73m2, 542 (61.4%) were males, 293 (33.2%) were diabetics, 171 (19.4%) had history of ischemic heart disease (IHD) and 595 (67.8%) were current/ex-smokers. Median follow-up was 41 months (interquartile range 25-57months), and there were 225 (25.5%) deaths with 60 (6.8%) cardiovascular deaths. In the final Cox regression model hyperuricemia was an independent predictor of cardiovascular death.

**Funding:** National Institutes of Health, National Heart, Lung, and Blood Institute, National Institute of Diabetes and Digestive and Kidney Diseases.
TH-PO240

The Association between Serum Uric Acid and Change of Renal Function in a Community-Based Population: A Longitudinal Survey of a Nationwide Cohort in Japan

Keita Kamei,1 Kazuko Suzuki,1 Kazunobu Ichikawa,1 Tsuneo Konta,1 Shouichi Fujimoto,2 Kunitoshi Iseki,2 Toshiki Moriyama,2 Kunihiro Yamagata,2 Kazuhiko Tsuruya,2 Kenjiro Kimura,2 Ichiro Narita,2 Koichi Asahi,2 Tsuyoshi Watanabe.2 1Dept of Cardiology, University of Medicine, Yamagata, Japan; 2Steering Committee of Research on Design of the Comprehensive Health Care System for Chronic Kidney Disease (CKD) Based on the Individual Risk Assessment by Specific Health Checkup.

Background: Hyperuricemia is a risk for adverse renal outcomes in chronic kidney disease. This study investigated the effect of uric acid on renal function in a large community-based population.

Methods: We used a nationwide database of 110,616 subjects (aged 29-74, male 39%). We participated in an annual health check, “The Specific Health Check and Guidance in Japan” between 2008-2010, and examined the relationship between serum uric acid level at baseline and 2-year change of estimated GFR obtained by the Japanese equation.

Results: The analysis of variance (ANOVA) showed the decline of eGFR was faster in subjects with low uric acid. However, after the adjustment with gender, age, baseline eGFR, and other possible confounders, the eGFR change was inversely correlated with uric acid and the mean value of the 2-year change of eGFR (mL/min/1.73m²) was +0.43, +0.24, -0.09, -0.20 and -0.72 in subjects with baseline uric acid <4.0, 4.0-4.9, 5.0-5.9, 6.0-6.9, and >7.0 mg/dL, respectively (P < 0.001). Multiple linear regression analysis showed that baseline uric acid was independently associated with eGFR change and the regression coefficient of per 1 mg/dL increase of uric acid was -0.24 (95% confidence interval [-0.30, -0.18], P < 0.001) in total population. In sensitivity analysis, the effect of serum uric acid on eGFR change was significant especially in elderly, female, and subjects without obesity, hypertension, diabetes, and alcohol consumption.

Conclusions: This study showed that an increase of serum uric acid is independently associated with faster renal decline in the Japanese general population, especially elderly, female and subjects without comorbidities.

Funding: National Institute of Health - US.

TH-PO241

Association of Serum Uric Acid Genetic Risk Score with Chronic Kidney Disease in Mexican American, American Indian and Alaska Native Populations

V. Saroja Voruganti,1 Sandra L. Laston,1 Karin Haack,1 Shelley L. Cole,2 Jack W. Kent,1 Sven O.E. Ebbesson,2 Jean W. Maccluer,2 John Blangero,2 P. Zager,2 Jason G. Umans,1 Anthony Comuzzie,1 Genetics, Texas Biomedical Research Institute, San Antonio, TX; 3Norton Sound Health Corporation, Nome, AK; 4Univ of New Mexico, Albuquerque, NM; 5Medstar Health Research Institute, Hyattsville, MD.

Background: Serum uric acid (SUA) levels. The solute carrier family 22, member 12 (SLC22A12) gene encodes a urate/anion exchanger localized primarily to the apical membrane of renal proximal tubular epithelial cells. In a previous genome-wide linkage scan of SUA in American Indian participants of the Strong Heart Family Study, we identified a locus on chromosome 11 which has a 1:1 recurrence interval containing the candidate gene SLC22A12.

Methods: We conducted a follow-up fine mapping by genotyping 20 single nucleotide polymorphisms (SNPs) in SLC22A12 to identify potential functional variants that might affect SUA. We used measured genotype analysis, implemented in SOLAR, to investigate the association between SLC22A12 and SUA and CKD phenotypes.

Results: We found significant association of rs17146104 (p = 0.0006) and nominal association with rs12221796 (p = 0.005) with lower SUA levels (minor allele frequency (MAF)= 1-41%). As a replication step we genotyped these same SNPs in Western Alaska Natives from the Genetics of Coronary Artery Disease in Alaska Natives study. While these two SNPs were not associated with SUA; seven other SNPs (rs2360872, rs538737, rs5525307, rs11602930, rs12806249, rs10897518 and rs12786214) from SLC22A12 (MAF~41%) were significantly (p = 0.004) associated with lower SUA, possibly reflecting differences in linkage disequilibrium patterns and/or functional alleles between these populations. Interestingly, these seven SNPs were associated with increased estimated glomerular filtration rate (p < 0.002) in American Indians but not in Western Alaska Natives. In contrast, albumin-creatinine ratio was not associated with this gene in either population.

Conclusions: Our results highlight the value of studies in unique non-European populations to define physiologically-relevant variants contributing to renal phenotypes and outcomes.

Funding: Other NIH Support - C06 RR013556 and C06 RR017515 - Research Facilities Improvement Program; MH59480-NIMH; U01 HL082490 - NHLBI; U01-HL65520, U01-HL41642, U01-HL14652, U01-HL14654 and U01-HL65521 - NHLBI.
Methods: The study population consisted of 1,104 National Health and Nutrition Examination Survey (NHANES) III participants aged 20 yrs or older with eGFR>60 ml/min/1.73 m² and non-missing data for VP, AP, and mortality. VP and AP intake was estimated from 24h dietary recalls. Mortality was based upon the results from a probitstic linkage with vital statistics records through 12/31/2006. Cox regression models were used to relate each 10g in VP or AP with all-cause mortality (ACM).

Results: The clinical characteristics of the study population by VP groups (defined by median VP intake) are summarized in Table 1.

During the follow-up period, 591 deaths (43.0%) occurred. The association of VP and AP with ACM is displayed in Figure 1.

Conclusions: We conclude that VP intake might be associated with lower ACM in CKD population. Interventional trials are needed to establish whether increasing VP will decrease mortality in CKD population.

Funding: NIDDK Support

TH-PO245

Prevalence and Correlates of Sleep Disorders in Hispanics with Chronic Kidney Disease in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

Background: Hispanics/Latinos are disproportionally affected by chronic kidney disease (CKD). In non-Hispanics, sleep disorders are more common in individuals with CKD than in those without CKD. However, few data exist on measures of sleep in Hispanics with CKD. In non-Hispanics, sleep disorders are more common in individuals with CKD population. Interventional trials are needed to establish whether increasing VP will decrease mortality in CKD population.

Funding: NIDDK Support

TH-PO246

The Sleep and Nephropathy Outcomes Research (SNORE) Study: Design and Preliminary Findings

Methods: During the follow-up period, 591 deaths (43.0%) occurred. The association of VP and AP with ACM is displayed in Figure 1.

Conclusions: In a large sample of Hispanic/Latinos, prevalence of sleep apnea and self-reported sleep disorders was higher in persons with CKD compared with those without CKD. In addition, albuminuria was independently associated with a higher risk of sleep apnea.

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

TH-PO247

Low Serum Magnesium Is Associated with the Development of End-Stage Renal Disease (ESRD) in the Atherosclerosis Risk in Communities (ARIC) Study

Methods: In a large sample of middle-aged adults, low serum Mg levels have been associated with incident hypertension and diabetes; both are important risk factors of ESRD. Whether serum Mg levels might independently associate with incident ESRD is unknown.

Funding: Veterans Affairs Support
TH-PO248

Serum Phosphorus and Outcomes in an African-American CKD Population Shailesh Basani,1 Praveen Kandula,2 Ranjani N. Moorhi,1 Deming Mi,2 He Xiu,1 Marc Rosenman,1 Sharon M. Moe,1 Jonathan W. Bazeley,1 1Indiana Univ, Indianapolis, IN; 2Massachusetts General Hospital, Boston, MA.

Background: Serum phosphorus (PO4) levels, even within the normal range, have been positively associated with adverse outcomes in chronic kidney disease (CKD) populations. However, subjects in the previous studies were mainly white and racial differences have not been previously examined despite differences in vitamin D and PTH homeostasis in African-Americans (AA). We tested the hypothesis that race alters the relationship between PO4 level and mortality or time to dialysis initiation.

Methods: A retrospective cohort of adult patients with CKD (eGFR < 60 ml/min at baseline) visiting the nephrology clinic at a large urban county hospital from 2007-10 was studied. Excluding subjects with no PO4 measurement at index date (first clinic visit in 2007-2010a total of 996 subjects were identified and were followed until death or May 2012. A Cox proportional hazard model adjusted for baseline demographics, comorbidities, medications, and laboratory values was used to study the association of PO4, and race on the composite end point of time to death or dialysis initiation (days to event from index date).

Results: Of 996 patients, 53% were female, 60% were AA and 56% had diabetes mellitus. The mean age was 58.5 ± 13.8 years (mean ± SD), mean eGFR was 33.4 ± 13.3 ml/min/1.73m2. The median PO4 level was (3.8 mg/dl; interquartile range 3.3-4.4). During a median follow up of 1125 days, 331 (33.2%) participants either died or initiated on dialysis. In univariate analysis higher PO4 was associated with increased mortality, time to dialysis or both in the whole cohort and in AA only. However, in the multivariable model PO4 was not a significant factor in predicting time to death or dialysis initiation. The adjusted hazard ratio was 1.13 (CI0.98, 1.29) for every 1mg/dl increase in serum phosphorus in the whole cohort and it was similar 1.07 (CI 0.89, 1.3) in the AA cohort.

Conclusions: Phosphorus was not associated with mortality or dialysis initiation in an urban population of CKD patients that was predominantly AA, raising questions on the generalizability of previous research studies to the clinic setting.

TH-PO249

Association of Serum Calcium Concentration with Mortality in a Nationally Representative Cohort of U.S. Veterans with Non-Dialysis Dependent Chronic Kidney Disease Barry M. Wall,1 2Kamyar Kalantar-Zadeh,1 Leigh Darryl Quarles,1 Jun Ling Lu,1 Csaba P. Kovessy,1 1Univ of Tennessee Health Science Center, Memphis, TN; 2VA Medical Center, Memphis, TN; 2Univ of California, Irvine, CA.

Background: Epidemiologic studies have shown an association between higher serum calcium concentration and increased mortality in both dialysis dependent and non-dialysis dependent CKD patients. Data concerning the association of lower calcium with mortality have been conflicting.

Methods: We evaluated the association of serum calcium concentration with all-cause mortality in a national cohort of 528,388 US veterans with stable non-dialysis dependent CKD stages 1-5. The association of calcium concentration with all-cause mortality was examined in time-dependent Cox models. The analyses were adjusted for age, gender, race, comorbidities (DM, CVD, CHF and Charlson index), estimated GFR, serum albumin and bicarbonate concentration, and administration of antihypertensive medications. Uncorrected calcium concentration was used for all analyses.

Results: The mean age of the cohort was 74.9 ± 9.8 and 98% were male. Over a median follow-up of 4.6 years, 177,502 patients died (mortality rate: 78.3/1000 patient-years). Of 5,780 patients with CKD-4, 868 had no follow-up eGFR and 56 died within 30 days. The remaining population of 4,566 was 59% male and 30% AA with mean age 72.8 years. 23% had a subsequent eGFR < 15, confirmed in 512 (10.5%) with a second eGFR < 15.2-year mortality was 4.1%. 40.7% had a nephrology visit during follow-up but only 7.9% had it in CKD-4. Further analysis was limited to the 512 with confirmed CKD-5. Progression was associated with male gender (12.9% vs 9.0%, p<0.001), AA race (12.3% vs 9.8%, p<0.01), younger age (66.6 vs 73.5 years, p<0.001) and diabetes (DM, 13.8% vs 8.8%, p<0.001). In a multivariable logistic regression model, DM, male gender and younger age were still risk factors for progression but the effect of race disappeared. During follow-up, patients with CKD-5 utilized more hospital stays (mean 1.3 ± 0.8, p<0.001), inpatient days (mean 8.7 ± 8.5, p<0.001) and ER visits (mean 23 ± 49, p<0.001).

Conclusions: The risk of progression from CKD-4 to CKD-5 over two years was significant. Progression was associated with greater health care utilization. The infrequency of early nephrology evaluation, which may reduce risk of progression to ESRD, is alarming. There is a need to further clarify the relationship between CKD progression, which did not appear to be affected by race, and the widely disparate rates of incident and prevalent ESRD.

TH-PO250

Serum Calcium and Renal Outcomes in Patients with Chronic Kidney Disease Lee-Moy Lim,1 Hung-Chun Chen.1,2 1Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; 2Faculty of Renal Care, College of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

Background: Mineral disorders especially hyperparathyroidism are associated with adverse renal outcome in chronic kidney disease (CKD) patients. Hypercalcemia and hypocalcemia have been associated with mortality in some studies but the association with renal outcome is not well characterized. Whether adding calcium besides phosphorus or in the form of calcium x phosphorus into the predictive model could improve discrimination of renal outcome is not known.

Methods: We examined whether serum calcium is associated with renal outcomes in a prospective cohort study of 3303 CKD stage 3-5 outpatients. Cox proportional hazard models and logistic regression were performed by quartiles of calcium.

Results: The mean age of our cohort was 63.3 ± 13.5 years, mean eGFR 24.7 ± 15.1 ml/min per 1.73m2 and mean calcium level 9.1 ± 0.8 mg/dL. In the baseline data, cardiovascular disease, hyperparathyroidism, high PTH and hypalbuminemia were associated with hypocalcemia but eGFR did not show the association. Low serum calcium (<7.7 mg/dL) was associated with increased risk for renal replacement therapy (RRT) [adjusted hazard ratio (HR) 1.34 (1.11-1.61), P<0.01] and rapid renal function progression (eGFR slope < -4ml/min/1.73m2) [adjusted odd ratio (OR) 1.28(1.01-1.63), P<0.01] compared those with normal serum calcium (9.1-9.6mg/dL). The result remained significant after stratification for serum phosphors and iPTH. When combination of serum calcium and phosphorus were modeled, high serum phosphorus (≥4.2 mg/dL) in conjunction with low serum calcium (<9.1 mg/dL) had highest risk for RRT and rapid renal function progression [HR 1.69 (1.32-2.18), P<0.01].

Conclusions: In advanced CKD patients, low serum calcium was associated with increased risk of RRT and rapid renal function progression. Integration of serum calcium besides phosphorus should be considered in predicting renal outcomes.

TH-PO251

Multivariable Risk Factors for Progression of CKD from Stage 4 to Stage 5 Mark D. Fafah, Hassan Fehmi, Naima Ogletree, Denise White Perkins, Div of Nephrology, Deps of Int Med, Fam Med & Public Health Sciences, Henry Ford Hospital, Detroit, MI.

Background: The incidence of ESRD in African-Americans (AA) far exceeds that of non-AA patients. There is much less data or agreement about the effect of race and other variables on rates of progression from stage 4 CKD (CKD-4, the likely “last chance” to prevent or delay ESRD) to stage 5 (CKD-5).

Methods: Administrative databases within Henry Ford Health System identified persons with CKD-4 (6 variable MDRD eGFR 15-29 ml/min/1.73 m2) during 2010. The first eGFR defined the index date. Subsequent eGFRs and health care services were assessed for a 2 year follow-up period. Patients dying within 30 days or not returning for eGFR were excluded. Progression to CKD-5 was defined as 2 or more eGFRs <15 ml/min/1.73 m2 at least 30 days apart. Analyses were conducted using SPSS v19.0.

Results: Of 5,780 patients with CKD-4, 868 had no follow-up eGFR and 56 died within 30 days. The remaining population of 4,566 was 59% male and 30% AA with mean age 72.8 years. 23% had a subsequent eGFR < 15, confirmed in 512 (10.5%) with a second eGFR < 15.2-year mortality was 4.1%. 40.7% had a nephrology visit during follow-up but only 7.9% had it in CKD-4. Further analysis was limited to the 512 with confirmed CKD-5. Progression was associated with male gender (12.9% vs 9.0%, p<0.001), AA race (12.3% vs 9.8%, p<0.01), younger age (66.6 vs 73.5 years, p<0.001) and diabetes (DM, 13.8% vs 8.8%, p<0.001). In a multivariable logistic regression model, DM, male gender and younger age were still risk factors for progression but the effect of race disappeared. During follow-up, patients with CKD-5 utilized more hospital stays (mean 1.3 ± 0.8, p<0.001), inpatient days (mean 8.7 ± 8.5, p<0.001) and ER visits (mean 23 ± 49, p<0.001).

Conclusions: The risk of progression from CKD-4 to CKD-5 over two years was significant. Progression was associated with greater health care utilization. The infrequency of early nephrology evaluation, which may reduce risk of progression to ESRD, is alarming. There is a need to further clarify the relationship between CKD progression, which did not appear to be affected by race, and the widely disparate rates of incident and prevalent ESRD.
TH-PO252
Impact of Febuxostat on Renal Function in Gout Subjects with Moderate-to-Severe Renal Impairment. K. Song,1 A. Whelton,2 M. Becker,3 P. MacDonald,4 Y. Zhou,1 L. Gunawardhana.1 1Birmingham VA Medical Center, AL; 2UCRC Inc and Johns Hopkins Univ, MD; 3Univ of Chicago Pritzker School of Medicine, IL; 4Takeda, IL.

Background: Up to 20% of patients with hyperuricemia (serum urate [sUA] >6.8 mg/dL) and gout have moderate-to-severe renal impairment. Higher sUA (>8.5 mg/dL) further increases this risk. This 12-m pilot study evaluated the efficacy of urate-lowering with febuxostat (FEB) on the progression of renal impairment in gout subjects.

Methods: In this randomized controlled trial, subjects received 1:1:1 FEB 30mg BID, FEB 40/80mg QD (40mg to 80mg to achieve sUA <6.0 mg/dL) or placebo (PLB) daily. Eligible subjects fulfilled ARA criteria for gout, were not on uric acid-lowering therapy, had an sUA >7.0 mg/dL and an estimated glomerular filtration rate (eGFR; MDRD) >15 to ≤50 mL/min (severe, 15 to <30 mL/min; moderate, 30 to ≤50 mL/min). Assessments included change from baseline (CFB) in sCr and eGFR, and percentage of subjects with sUA <6.0 mg/dL.

Results: Of 96 subjects enrolled, 80% were men with baseline mean (SD) sUA 10.5 (1.70) mg/dL, 95 qualified for the primary efficacy analysis. Titration from FEB 40mg QD to 80mg QD occurred for 20/32 subjects. CFB in sCr and eGFR was small (Table). At m12, 69%, 45%, and 0% of subjects in the FEB 30mg BID, 40/80mg QD and PLB groups, respectively, achieved target sUA <6.0 mg/dL. (p<0.001). Overall, ≥1 adverse event was reported by 76%, 88% and 78% of subjects in the FEB 30mg BID, FEB 40/80mg QD and PLB groups, respectively. One PLB subject had treatment-related renal impairment.

Conclusions: Our data show a small favorable trend in renal function in subjects receiving FEB compared to PLB. Differences in sCr and eGFR were not statistically different. In this prospective study, reduction of sUA to target level was safe and effective in this selected study population with renal impairment.

TH-PO254
The Association between Change in Weight and Change in GFR: Does Body Surface Area Adjustment Matter? Alex Chang,1 Xuexi Wang,2 Cynthia A. Kendrick,3 Lawrence J. Appel,4 Holly J. Kramer,5 Jackson T. Wright,6 Brad C. Astor,7 Tom Greene.2 1Nephrology, Johns Hopkins Univ; 2Epidemiology, Univ of Utah; 3Nephrology, Loyola Univ Medical Center; 4Nephrology, Case Western Reserve Univ; 5Nephrology, Univ of Wisconsin; 6Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Univ; 7Cleveland Clinic.

Background: Controversy exists over whether glomerular filtration rate (GFR) should be indexed to body surface area (BSA). Higher body mass index is associated with higher absolute GFR but not GFR indexed to BSA in cross-sectional studies. Previous longitudinal studies have indexed GFR to baseline rather than concurrently measured BSA. Little is known about whether longitudinal changes in weight track with changes in GFR, and whether this relationship exists after adjusting for concurrently-measured BSA.

Methods: Participants in the African-American Study of Kidney Disease and Hypertension underwent measurements of weight and GFR at baseline, 3, 6, and every 6 months during the trial. Using linear mixed effects models adjusted for treatment assignment, we examined the association between change in weight from baseline and change in iothalamate-measured GFR indexed to baseline BSA and then indexed to concurrently-measured BSA.

Results: Every 3kg increase in weight was associated with a 1.04ml/min/1.73m2 (95% CI: 0.82 to 1.27; p<0.001) increase in GFR indexed to baseline BSA, but not when adjusted for current BSA (0.14ml/min/1.73m2; 95% CI: -0.80 to 0.37; p=0.2).

Conclusions: Weight change is directly associated with changes in measured GFR; this association essentially disappeared after adjusting for concurrently-measured BSA. Future studies need to be done to understand how weight-related changes in GFR may affect long-term kidney outcomes.

Funding: NIDDK Support

TH-PO255
Combined Effect of Age and Race on Mortality Predictability of Serum Albumin Level in Hemodialysis Patients Alla Victoroff,1 Vanessa A. Ravel,1 Elani Streja,1 Jongha Park,2 Csaba P. Kovcsdy,3 Kamyar Kalantar-Zadeh,4 1Harold Simmons Center, UCI, Orange, CA; 2Univ of Ulsan College of Medicine, Ulsan, Korea; 3Memphis VA Medical Center, Memphis, VA.

Background: Serum albumin level is a well-known marker for morbidity and mortality in end stage renal disease patients and is one of several markers of nutritional status. Although serum albumin is positively associated with better survival overall, the association could be modified by race/ethnicity as well as age.

Methods: Over a 5-year period (7/2001-6/2006), we identified 105,523 maintenance hemodialysis (MHD) patients who had a baseline serum albumin. We used Cox proportional hazard model to compare the mortality among non-Hispanic Whites, Hispanics, and African Americans in 4 different age groups.

Results: After full adjustment, Whites and Hispanics in the younger age group (<65 y) maintained a slight survival advantage over Black MHD patients across the lowest albumin levels (<3.0-3.4 g/dL). In patients aged 65-<70 years, Whites and Hispanics with serum albumin <3.6 g/dL reported increased mortality, but Blacks with serum albumin as low as 3.0-3.4 g/dL failed to show significant mortality increase. In patients aged over 75 years, associations between lower serum albumin levels (<3.6 g/dL) and increased mortality are seen similarly across racial/ethnic groups. However, higher serum albumin levels (>4.0 g/dL) were less frequently observed in this age group compared to patients >65 years old, and did not demonstrate a significant association with greater survival.

Funding: Other NIH Support - NHLBI (1R15HL096097-01)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
of the malnutrition-in-energy wasting. Erythropoiesis-stimulating agent (ESA) and appetite stimulants, including rituximab, were used in about 10% of patients. However, elderly MHD patients seemed to be more vulnerable to protein-energy wasting.

Conclusions: Although baseline serum albumin levels were associated with survival over all, the association could be modified by race/ethnicity as well as age. Younger Black MHD patients may be more tolerant of lower serum albumin levels compared to their counterparts. However, elderly MHD patients seemed to be more vulnerable to protein-energy wasting.

Funding: NIDDK Support, Private Foundation Support

TH-PO256

Association of Race-Ethnicity with Transplant Rates in Incident Peritoneal Dialysis Patients

Elani Streja,1 Chunyang Li,2 Miklos Zsolt Molnar,1 Wei Ling Lau,1 Connie Rhee,2 Csaba P. Kovacs,2 Kamyar Kalantar-Zadeh,1 Rajnish Mehrotra,3 Harold Simmons Center, UCI, Orange, CA; 2Harborview Medical Center, Univ of Washington, Seattle, WA; 3Memphis Veterans Affairs Medical Center, Memphis, VA.

Background: Racial disparities in dialysis patients receiving kidney transplants have been previously reported, particularly for African Americans receiving hemodialysis.

Methods: We compared all-cause mortality of deciles of weight and height in 117,644 MD patients who were followed for up to 6 years (2001 through 2007), using the fifth decile as reference. Mortality risks were estimated with Cox proportional hazards models adjusted for case-mix and MICS markers. Weight analyses were adjusted for height and vice-versa.

Results: Patients were 62 ± SD15 years old and included 45% women and 57% diabetics. For a given weight decile, there was an inverse relationship between height and BMI, which is the reverse of what has been reported in the general population (A Kemkes-Grottenthaler Am J Phys Anthropol 2005;128:340). Whereas both weight and height exhibited incremental and strictly linear associations with death risk, weight deciles showed a wider range of HRs (0.76 to 1.49), whereas the height decile HR range was 0.90 to 1.21, suggesting a stronger association of weight than height with mortality in these patients.

Conclusions: In contrast to the general population, body height is inversely related to HR in MD patients and contributes importantly to the inverse relation between HR/M and BMI in these individuals. Nonetheless, the dramatically altered HR vs. BMI in MD patients vs. normals is driven more by body weight than height. The cause of the altered relationship between HR and height in ESRD needs investigation.

Funding: NIDDK Support

TH-PO258

A Target Organ Damage Based Scoring System (ABCK) Combined with a Cardiovascular Risk Score Improves Prediction of Overall Mortality and Events in a Low Risk Population Cohort

E. N. De Bock,1 Naik G. J. Goodrow,1 A. Van Herck,2 J. D. Miners,2 J. A. Steegers-Theunissen,3 M. J. Farmsen,3 N. D. Melchior,2 A. Staessen,2 Carlo A. Gaillard.4

Background: Current cardiovascular (CV) prediction models rely on risk factors, but not on target organ damage (TOD) in an individual. The current study tested whether a newly developed multi-organ TOD classification improved prediction of death and CV events.

Methods: A population-based prospective cohort (n=1970) was evaluated for traditional CV risk factors. In addition, TOD was staged in arteries, brain, cardiac and kidneys (ABCK classification). Using baseline SCORE, Framingham and ABCK scores, cox proportional hazard models were developed to assess independent effects of each system in predicting 10 year mortality and CV events.

Results: Over 10 years, 163 subjects died, 49 (2%) had an AMI, 45 (2%) had a stroke, 46 (2%) developed end-stage renal disease and 14 (0.7%) developed severe peripheral artery disease. Using patients with a very low TOD burden as reference, increasing ABCK scores were associated with increased 10 year risk of overall mortality and CV events: low TOD group hazard ratio (HR) 2.10 (95%CI 1.05-2.88); medium TOD group risk HR 5.97 (95%CI 4.15-8.58), high TOD group risk HR 27.7 (95%CI 14.7-52.6). When related to the SCORE and Framingham scores, the ABCK score was still independently associated with death and CV events in medium and high-risk individuals. Moreover, when combined with Framingham or SCORE, ABCK substantially increased the HR for mortality (HR ranged from 2 in low risk and TOD groups to 60 in highest risk and TOD groups).

Conclusions: Addition of a relatively simple-to-use TOD score can improve the prediction of CV events in a population cohort.

Funding: NIDDK Support

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

Underline represents presenting author/disclosure.

162A
Arterial Stiffness Is Associated with Vascular Calcification in Chronic Kidney Disease

Jing Chen, Raymond R. Townsend, Matthew Jay Budoff, Faheemuddin A. Ahmed, Chung-Shiuwan Chen, Yanxi Liu, Maria Wright, Heather LaGuardia, Damodor R. Kumbala, Fred E. Hussert, Eric E. Simon, L. Lee Hamm, Jiang He, Tulane Univ, New Orleans, LA; Univ of Pennsylvania School of Medicine, Philadelphia, PA; Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center in Torrance, Los Angeles, CA; Ochsner Health System, New Orleans, LA

Background: Arterial stiffness is very common and associated with increased risk of cardiovascular disease in patients with chronic kidney disease (CKD). The underlying etiology for increased arterial stiffness is not fully understood.

Methods: We investigated the association of vascular calcification with risk of arterial stiffness in 235 patients with chronic kidney disease (CKD). Arterial stiffness was measured by aortic pulse wave velocity (PWV) and defined as PWV greater or equal to 12 m/sec. Vascular calcification was assessed using electron-beam computed tomography (EBCT) and coronary artery calcification (CAC) Agatston score was calculated.

Results: The prevalence of arterial stiffness was 37% in this study population. In the linear regression model, log-transformed coronary arterial calcification (CAC) was significantly and positively associated with log-transformed pulse wave velocity. For example, one standard deviation higher log-transformed CAC Agatston score (2.8) was associated with a 0.03 m/sec (95% confidence interval: 0.02, 0.05; p<0.0001) higher log-transformed pulse wave velocity after adjustment for age, gender, race, high-school education, physical activity, current cigarette smoking, weekly alcohol drinking, body mass index, LDL-cholesterol, plasma glucose, mean arterial pressure, estimated glomerular filtration rate (eGFR), and history of cardiovascular disease.

Conclusions: These data indicate that CAC may be associated with increased arterial stiffness in patients with CKD independent of the risk factors for arteriosclerosis.

Funding: Other NIH Support - the National Center for Research Resources, National Institutes of Health, Bethesda, MD.

TH-PO260

Varied Relationships between Urinary Symptoms and CKD in the U.S. Population

Paul L. Kimmel,1 Chyng-Wen Fwu,2 Kevin C. Abbott,3 Ziya Kirakili,1 Tamara G. Bavendam,4 Paul W. Eggers,5 Div of Kidney, Urologic and Hematologic Diseases, NIDDK, NIH, Bethesda, MD; Social & Scientific Systems, Inc., Silver Spring, MD; Walter Reed National Military Medical Center, Bethesda, MD.

Background: The relationship between urinary symptoms, genitourinary disease and CKD has been unclear. Conventional wisdom suggests nocturia is an early sign of CKD, without supporting evidence.

Methods: We used the US National Health and Nutrition Examination Survey (NHANES) 2005-2010 to assess the subjective report of nocturia ≥ 2 times per night and NHANES 2001-2010 to identify self-reported cases of urinary incontinence (UI) with markers of CKD (defined as urinary albumin-creatinine ratio ≥ 30 mg/g or eGFR < 60, by CKD-EPI equation). We limited our study sample to participants ≥ 40 years old because CKD and nocturia are most prevalent among older populations. Longitudinal odds ratios (OR) were calculated for nocturia and UI associated with CKD after adjusting for age, race or ethnicity, diabetes mellitus, hypertension, BMI, parity (for models in women), diuretics and renin-angiotensin inhibitors. Because of gender differences in occurrence of nocturia and UI, separate analyses were conducted in men and women.

Results: 8,960 participants were included in nocturia analyses and 14,187 participants were included in UI analyses. The multivariate-adjusted OR of nocturia in CKD compared to non-CKD was 1.44 (95% confidence interval, 1.19-1.74), significant, among men, and 1.26 (1.07-1.47), significant, among women. The adjusted OR of UI was 1.19 (0.98-1.44) and 1.14 (0.97-1.33) among men and women, respectively.

Conclusions: Although the association of CKD and UI could not be detected after adjustment for known risk factors, a robust relationship between UI and CKD are marked by other factors, but nocturia is a potential diagnostic symptom independently associated with CKD. Absence of nocturia makes a diagnosis of CKD less likely.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO261

 Persistent Asthma Increases the Risk of Chronic Kidney Disease: A Retrospective Cohort Study in China

Zhanguo Liu,1,2 'Nephrology, The First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China; 'Key-Disciplines Laboratory Clinical-Medicine Henan, Zhengzhou, Henan, China.

Background: Chronic kidney disease (CKD) is a growing public health problem with well-established risk factors. Other contributing factors, however, remain to be identified. Systemic inflammation in asthma plays a significant role in the development of other diseases. We therefore initiated a study to assess whether the growing prevalence of asthma is associated with an increase in the risk of CKD.

Methods: This retrospective study used data from 3015 patients with asthma at the Department of Respiratory Medicine from 2005 to 2011. History, asthma control test (ACT), and asthma stage were used to assess the traits of asthma. CKD was defined as estimated glomerular filtration rate (eGFR)<60 ml/min/1.73 m² in two consecutive follow-up surveys. Odds ratios (OR) were obtained by logistic regression.

Results: A total of 2354 subjects with complete data were recruited for this study. After 8 years of follow-up, 72 (1.1%) participants developed CKD. Persistent asthma was associated with a significantly increased risk for CKD (OR: 2.37; 95% CI, 1.41-5.03) in unadjusted analyses. After adjustment for demographic factors and additional adjustment for hypertension, diabetes, BMI, and personal smoking habits, the increased risk for CKD (OR: 2.07; 95% CI, 1.34-4.42) remained significant. Compared to patients with no asthma traits, there was a significant risk for those who met all three criteria (OR: 5.39; 95% CI, 3.68-7.37) after adjusting for potential confounding factors.

Conclusions: We found that persistent asthma was associated with an increased risk of CKD in a study group from China.

Funding: Government Support - Non-U.S.

TH-PO262

Oral Disease in People with Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Cohort Studies

Giovanni F.M. Strippoli,1,2 Suetonia Petruzzi,3 Faheemuddin A. Ahmed,1 Chung-Shiuan Chen,1 Yanxi Liu,1 Maria Waight,1 David W. Johnson,1 Pauline J. Ford,1 Marcello Tonelli,2 Michele De Benedictis,1 Massimo Petruzzi,1 D. Diaverum;2 Mario Negri Sud Consortium;1 Univ of Bari;1 Univ of Sydney;1 Univ of Otago;1 Univ of Perugia;1 Univ of Queensland;1 Univ of Alberta.

Background: Oral disease includes a wide spectrum of clinical abnormalities affecting the mouth including mucosa, teeth, periodontal tissue and salivary function. While observational data for these diseases are available in people with chronic kidney disease (CKD), existing published information has not yet been systematically evaluated. We aimed to summarize the overall prevalence of oral diseases in people with CKD and explore associations between oral disease and mortality.

Methods: We conducted a systematic review and meta-analysis of observational studies regarding prevalence or clinical outcomes of oral disease in people with CKD. English-language studies were identified from systematic searching MEDLINE through April 2010. Multiple reviewers extracted participant characteristics. Estimates of prevalence, mean score, or risk of mortality were summarized using random-effects meta-analysis and expressed as rates or means and 95% confidence intervals (CI). Effects of severity of CKD on estimates were analyzed using subgroup analysis.

Results: 112 studies (150 cohorts) including 18 339 people with CKD and 16 310 controls were analyzed. 103 cohorts were in people on dialysis, 22 cohorts were in earlier stages of CKD and 25 cohorts were in kidney transplant recipients (15.6%). The mean decay/missing/filled teeth (DMFT) index in people with CKD was 13.7 and number of teeth was 19.4. Nearly 40% of people with CKD had enamel hypoplasia and over half had periodontitis. Overall, the mean plaque index was 1.62 and periodontal pocket depth (PD) of 4 mm. Approximately 25% of people with CKD never brushed their teeth. Conclusions: Data evaluating the prevalence and severity of oral disease in people with CKD are sparse and incomplete. Large longitudinal studies of the prevalence and clinical associations with oral disease in CKD are now needed.

Funding: Other NIH Support - the National Center for Research Resources, National Institutes of Health, Bethesda, MD.

TH-PO263

Reasons Patients Might Not Pursue Kidney Transplant: A Survey of Nephrologists’ Perceptions

Jeffrey P. Yourshaw, Ankita Tandon, Kevin C. Roe, Nasrollah Ghahramani. Internal Medicine, Penn State College of Medicine, Hershey, PA.

Background: Unfavorable views about kidney transplant (KT) have been cited as potential reasons for reluctance by some patients to actively pursue KT. We examined nephrologists’ perceptions of the reasons for patients to not pursue KT and analyzed the association between these perceptions and respondent demographics, practice characteristics, and previous training.

Methods: Invitations were sent to 3180 nephrologists in the eastern US. 822 expressed interest, and 250 were randomly invited to complete a questionnaire about demographics, practice characteristics, and their perceptions of reasons why patients might not choose KT. A total of 216 surveys with complete responses were analyzed. Chi-square and stepwise logistic regression were performed.

Results: The 3 most common factors perceived by nephrologists as important reasons their patients might not choose KT included “inadequate understanding of the process” (84% of respondents), “inadequate financial resources” (76%), and “cumbersome pre-transplant testing” (70%). In multivariate analysis, nephrologists who were the first to have a transplant program had were more likely to consider inadequate understanding (OR: 4.0; p=0.001) and inadequate financial resources (OR: 5.01; p=0.002) as important reasons patients might not pursue KT. Nephrologists who attended at least one transplant-related CME per year considered inadequate financial resources as important reasons patients might not pursue KT (OR: 2.61; p=0.001). In practices where less than half of the respondent’s patients completed high school, cumbersome testing was considered an important reason patients would not pursue KT (OR: 2.75; p=0.01).

Conclusions: Nephrologists believe that inadequate understanding, insufficient financial resources and cumbersome testing are regarded by patients as the most important reasons they might not pursue KT. Nephrologists’ perceptions are influenced by their training and ongoing medical education, as well as the characteristics of their patient population. It is possible that nephrologists’ perceptions of the reasons for patient reluctance might, in turn, impact their encouragement of pursuing KT.

Funding: NIDDK Support

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

Underline represents presenting author/disclosure.

163A
TH-PO264

MDRD versus CKD-EPI Equation to Estimate Glomerular Filtration Rate in Obese Patients


Methods: We studied in a large modern cohort of patients with higher, and black race with lower CrCl/GFR ratio, as suggested by prior literature. The ratio does not vary with degree of proteinuria or race/ethnicity. The ratio is also closer to blacks was -0.03 [95% CI-0.09 - 0.03] compared with whites, p=0.38).

Results: The population included 366 patients (185 women) from two different areas. Mean age was 55 ± 14 years and mean BMI was 36 ± 7 kg/m². Mean mGFR was 56 ± 26 mL/min/1.73 m² (71 ± 35 mL/min without induction). In the total population, mean bias was +1.0 than reported by several frequently cited reports in the literature.

Conclusions: The CKD-EPI equation did not outperform the MDRD study equation in patients with a mGFR above 60 mL/min/1.73 m² questions the physiological relevance of BSA indexation which may lead to underestimated renal function in obese patients.

TH-PO265

Determants of the Creatinine Clearance to Glomerular Filtration Rate Ratio in Patients with Chronic Kidney Disease

Yeun Chang Liu, Nisha Bansal, Eric Vittinghoff, Alan S. Go, Chi-Yuan Hsu.

Results: Mean iGFR was 48.0 ± 19.9 mL/min/1.73 m², median albuminuria was 84 mg per day, and 36.8% of the study participants were black. Mean Cr/CrGFR ratio was 1.19 ± 0.48. There was no association between the Cr/CrGFR ratio and urine albuminuria (coefficient 0.11 [95% CI -0.01 - 0.22] for highest versus lowest levels of albuminuric, p = 0.07). There was also no association between race and Cr/CrGFR ratio (coefficient for blacks was -0.03 [95% CI-0.09 - 0.03] compared with whites, p=0.38).

Conclusions: Contrary to what had been suggested by prior smaller studies, Cr/CrGFR ratio does not vary with degree of proteinuria or race/ethnicity. The ratio is also closer to blacks was -0.03 [95% CI-0.09 - 0.03] compared with whites, p=0.38).

TH-PO266

Assessment of Cystatin C Glomerular Filtration Rate in Patients with Liver Cirrhosis

Kriengsak Vareesangthip, Sukit Raksasuk, Supot Nimanong, Wimolphan Artsom, Sunanta Chiewvit, Kanit Reesukumal.

Results: Mean iGFR was 48.0 ± 19.9 mL/min/1.73 m², median albuminuria was 84 mg per day, and 36.8% of the study participants were black. Mean Cr/CrGFR ratio was 1.19 ± 0.48. There was no association between the Cr/CrGFR ratio and urine albuminuria (coefficient 0.11 [95% CI -0.01 - 0.22] for highest versus lowest levels of albuminuric, p = 0.07). There was also no association between race and Cr/CrGFR ratio (coefficient for blacks was -0.03 [95% CI-0.09 - 0.03] compared with whites, p=0.38).

Conclusions: Contrary to what had been suggested by prior smaller studies, Cr/CrGFR ratio does not vary with degree of proteinuria or race/ethnicity. The ratio is also closer to blacks was -0.03 [95% CI-0.09 - 0.03] compared with whites, p=0.38).

TH-PO267

Comparing Cystatin C and Creatinine for Estimating Measured GFR and CKD Prevalence in a Community-Based Sample of the Elderly


Results: eGFRcr-cys had a higher rate of false positive diagnosis of CKD Stage 3-5 [29% [24-33]] compared with eGFRcr or eGFRcys, and determined prevalence of CKD Stage 3-5 (GFR>60 ml/min/1.73m²). Cystatin C and cystatin C assays are traceable to reference materials.

Conclusions: eGFRcr-cys have a higher rate of false positive diagnosis of CKD Stage 3-5 [29% [24-33]] compared with eGFRcr or eGFRcys, and determined prevalence of CKD Stage 3-5 (GFR>60 ml/min/1.73m²). Cystatin C and cystatin C assays are traceable to reference materials.
3.50 0.80 72 0.87 29 86
10.5 0.70 49 0.71 38 62

Background: Performing iohexol clearance in people with considerably reduced kidney function is a logistic challenge as it requires a 24h measurement. As an additional project of the Berlin Initiative Study (BIS) we measured iohexol clearance including a 24h-measurement in 61 individuals with chronic kidney disease and compared measured GFR (mGFR) including the 24h measurement to mGFR results without the 24h measurement.

Methods: In a sample of 61 subjects mGFR was determined by using iohexol measurements at 120 min, 180 min, 240 min, 300 min (=5h), and 1440 min (=24h). mGFR was determined using measurements until 300 min (mGFR300) and measurements until 1440 min (mGFR1440). For both approaches the slow component according to the method of Schwartz was determined and the body surface area was adjusted for by the Dubois formula. Absolute and percentage differences were calculated.

Results: Patients were 79.4 years old (mean, range 70 to 94 yrs), 23% were female. mGFR300 and mGFR1440 were highly correlated (R² = 0.90) but mGFR1440 (25.0 ± 7.44 mL/min/m²) was significantly smaller than mGFR300 (31.0 ± 8.26 mL/min/m²). The raw difference mGFR1440 - mGFR300 was 6.0 ± 2.65 mL/min/m² and the percentage difference was 19.8 ± 8.2%. Moreover, in 60 of 61 subjects (98%) mGFR1440 was smaller than mGFR300 (R² < 0.01). Applying the correction formula mGFR1440 = 1.486 + 0.854×mGFR1440 led to an error of ±4.76 mL/min/m² (two-fold standard error of estimation). Inclusion of a quadratic term did not improve the prediction of mGFR300.

Conclusions: The reason for the decline of mGFR300 compared to mGFR1440 was the fact that the actual iohexol measurement values at 24h were considerably larger as predicted by extrapolation of the slow component from measurements at 5h. We conclude that the exponential decay does not fit the longterm filtration of iohexol. A linear correction formula for mGFR1440 leads to an R² of 0.90 which should be sufficient for applications.

Funding: Private Foundation Support

TH-PO270
GFR Estimating Equations in HIV-Infected Patients: One Patient, One GFR Estimating Equation Amandine Gagneux-Brunon, Pierre Delanaye, Christopher R. Marrat, Olivier Moranne, Université Hospital of Saint-Etienne, Saint-Etienne, France, 4CHU de Liege, Belgium, 5CHU de Nice, France.

Background: An accurate Glomerular Filtration Rate estimation is needed in HIV-infected (HIV+) patients. CKD-EPI equations based on serum creatinine only or with serum cystatin C were described as accurate in this population. Yet, they are biased; Our aim was to validate GFR estimating Cockcroft and Gault (CG), MDRD, CKD-EPI equations, and to identify factors affecting performance of eGFR in HIV+ European patients with measured GFR. 1,2,3 Comparisons of measured Glomerular Filtration Rate (GFR) against estimated GFR (eGFR) as measured by glomerular filtration rate (GFR) estimated by the Cockroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, and cystatin C (CysC) were performed.

Methods: Patients tested for HIV between February 2011 and June 2012 were included; 79% had a mean age of 49 ± 10 years, were 63% male, and 53% were infected with hepatitis C virus. 4,5,6 About 60% were on highly active antiretroviral therapy, with a mean estimated glomerular filtration rate (eGFR) of 68 ± 21 mL/min/1.73m². Mean eGFR was significantly lower than measured GFR (mGFR; 83 ± 35 mL/min/1.73m²). Linear regression was used to determine the capacity of demographic markers, gender, age, body weight, height and BSA, and the biochemical markers, including HIV-viral load, ethnicity and measured GFR. Accurate-30% for CG, MDRD, CKD-EPI Scr, CKD-EPI CysC, CKD-EPI combined 1.1 (± 24.6), -3.3 (± 23.5), -10.4 (± 30.6), -10.4 (± 30.6), -3.3 (± 23.5). Results: vGFR versus mGFR300 leads to an R² of 0.90 which should be sufficient for applications.

Conclusions: GFR estimating equations in HIV+ patients. Clinicians should be aware that factors as GFR level, diabetes mellitus, HIV-viral load were not associated with bias of measured GFR while bias of CKD-EPI Scys was associated with diabetes mellitus, HIV-infected (HIV+), patients. CKD-EPI equations based on serum creatinine only or with serum Cystatin C provide a better correlation with measured GFR.

Funding: Government Support - Non-U.S.
with the exogenous-marker clearance method and the enzymatic creatinine, for the Chinese population.

**Methods:** We combined variables for the estimation of eGFR (cGFR) with a reduced set of measurements of the marker iohexol (mGFR). In a population based sample of 570 subjects (70+ ys), we investigated 3 types of GFR equations: (1) the BIS1 and BIS2 equations based on age, gender, serum creatinine, and cystatin C; (2) the BI-PETIA Cystatin C equation, and (3) the BI-PETIA Cystatin C equation when the model included BI parameters. Correlations and SEE with mGFR were compared.

**Conclusions:** The accuracy of GFR estimation can be improved by use of a BI model which considers muscular mass, fluid volume and degree of hydration, regardless of the filtration marker used and more markers is better than using either alone. This model could be helpful to improve GFR estimation.

Table 1

<table>
<thead>
<tr>
<th>Comparison</th>
<th>All Subjects</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic model</td>
<td>0.68</td>
<td>0.63</td>
<td>0.15</td>
<td>0.72</td>
<td>0.70</td>
</tr>
<tr>
<td>Basic + Cys</td>
<td>0.72</td>
<td>0.68</td>
<td>0.49</td>
<td>0.77</td>
<td>0.70</td>
</tr>
<tr>
<td>Basic + Cys + SCR</td>
<td>0.73</td>
<td>0.75</td>
<td>0.60</td>
<td>0.80</td>
<td>0.71</td>
</tr>
<tr>
<td>ST (in mln/min, T1/2)</td>
<td>All subjects</td>
<td>100</td>
<td>100</td>
<td>112</td>
<td>100</td>
</tr>
<tr>
<td>Pred-XV</td>
<td>18.5</td>
<td>18.5</td>
<td>11.3</td>
<td>10.9</td>
<td>10.9</td>
</tr>
<tr>
<td>Pred-XV</td>
<td>18.5</td>
<td>18.5</td>
<td>11.3</td>
<td>10.9</td>
<td>10.9</td>
</tr>
<tr>
<td>Pred-XV + Cys</td>
<td>18.5</td>
<td>18.5</td>
<td>11.3</td>
<td>10.9</td>
<td>10.9</td>
</tr>
</tbody>
</table>

**TH-PO275**

**Association of Traumatic Amputation with Concentrations of Serum Creatinine and Cystatin C in Male Soldiers with Pre- and Post-Operative Data:**

**Methods:** We prospectively compared cystatin C (human PETIA and mouse ELISA), creatinine (Jaffe and enzymatic assays) and urea to GFR (inulin clearance: mGFR) in male or female C67Bl6 mice, aged between 14 and 20 weeks, healthy or subjected to chronic renal failure (partial nephrectomy or following acute kidney injury).

**Results:** In a first group (n = 80), urea, enzymatic creatinine and ELISA cystatin C were significantly correlated to mGFR. Neither PETIA Cystatin C, nor Jaffe creatininemia were correlated with mGFR. We therefore focused on ELISA cystatin C, enzymatic creatinine and urea using complementary groups. Urea was significantly but weakly correlated to mGFR (r Spearman -0.28, p = 0.05). ELISA Cystatin C and creatinine were significantly correlated although cystatin C correlation was tighter (r Spearman -0.76 and -0.62, respectively). When applied to a population split by mGFR level (<120, 120 to 240, >240 mL/min, n = 15 in each group), ELISA cystatin C was the only marker able to significantly distinguish groups from each other (Kruskall-Wallis test, p < 0.001). Finally, a Cystatin C-based equation to estimate GFR in mice was developed and validated using Bland & Altman approach.

**Conclusions:** Our results indicate that mELISA cystatin C, but not iPETIA, is better correlated to GFR in mice than enzymatic creatininemia and could be an interesting and highly discriminative GFR marker. Conversely, the use of Jaffe creatinine and urea to estimate GFR is not relevant.

Funding: Government Support - Non-U.S.

**TH-PO276**

**Plasma Cystatin C Is a Valid Marker of Glomerular Filtration Rate in Mice:**

**Background:** Whether concentrations of serum creatinine, or Cystatin C, are correlated to GFR in human but its relevance, in mice, is unknown.

**Methods:** We prospectively compared cystatin C (human PETIA and mouse ELISA), creatinine (Jaffe and enzymatic assays) and urea to GFR (inulin clearance: mGFR) in male or female C67Bl6 mice, aged between 14 and 20 weeks, healthy or subjected to chronic renal failure (partial nephrectomy or following acute kidney injury).

**Results:** In a first group (n = 80), urea, enzymatic creatinine and ELISA cystatin C were significantly correlated to mGFR. Neither PETIA Cystatin C, nor Jaffe creatininemia were correlated with mGFR. We therefore focused on ELISA cystatin C, enzymatic creatinine and urea using complementary groups. Urea was significantly but weakly correlated to mGFR (r Spearman -0.28, p = 0.05). ELISA Cystatin C and creatinine were significantly correlated although cystatin C correlation was tighter (r Spearman -0.76 and -0.62, respectively). When applied to a population split by mGFR level (<120, 120 to 240, >240 mL/min, n = 15 in each group), ELISA cystatin C was the only marker able to significantly distinguish groups from each other (Kruskall-Wallis test, p < 0.001). Finally, a Cystatin C-based equation to estimate GFR in mice was developed and validated using Bland & Altman approach.

**Conclusions:** Our results indicate that mELISA cystatin C, but not iPETIA, is better correlated to GFR in mice than enzymatic creatininemia and could be an interesting and highly discriminative GFR marker. Conversely, the use of Jaffe creatinine and urea to estimate GFR is not relevant.

Funding: Government Support - Non-U.S.
no significant difference of diagnostic accuracy between CKD-EPI creatinine & cystatin formula and simple \( S_c \) formula was found \((P=0.455)\). Bland and Altman analysis for the same cut-offs showed that CKD-EPI creatinine & cystatin formula underestimated (bias: 10.1 ml/min/1.73m\(^2\)) and simple \( S_c \) formula (bias: 11.8 ml/min/1.73m\(^2\)) overestimated measured GFR. Both equations lacked precision. Analysis of ability to correctly predict patient’s GFR below or above 45 ml/min/1.73m\(^2\) showed similar ability for simple \( S_c \) formula \((96.2\%)\) and CKD-EPI creatinine & cystatin formula \((66.9\%)\).

**Conclusions:** Our results indicate that simple \( S_c \) formula is a reliable marker of GFR in stage 3 CKD patients and is comparable to CKD-EPI creatinine & cystatin formula.

**TH-PO280**

**The Correlation and Comparison among Three Methods for GFR Measurement: Renal Inulin Clearance, Systemic Inulin Clearance, and 51Cr-EDTA Plasma Clearance**

**Background:** Renal inulin clearance with continuous infusion method has been recognized as the gold standard for the measurement of glomerular filtration rate (GFR). However, inconvenience and complications associated with the method led to the development of alternative methods. We aimed to explore the relationships among three different methods for GFR measurement.

**Methods:** Three different tests including renal inulin clearance with continuous infusion method (gold standard), systemic inulin clearance with a single injection method (standard protocol for 4 hours and extended protocol for 24 hours), and plasma \(^{51}\)Cr-EDTA clearance over 5 hours were performed in each subject to measure GFR. Total of 114 participants had all of three tests.

**Results:** There was a strong correlation between systemic inulin clearance and renal inulin clearance with a single injection method \((r=0.89, P<0.001)\), but renal inulin clearance overestimated systemic inulin clearance in overall. There was a very strong correlation between systemic inulin clearance measured by standard protocol and extended protocol \((r=0.98, P<0.001)\), and the difference between them was very small. The strong correlation between gold standard method and systemic inulin clearance with single injection method (standard protocol) was observed \((r=0.89, P<0.001)\). The systemic inulin clearance (standard protocol) underestimated renal inulin clearance, in general \((correlation coefficient:0.89)\); however, systemic inulin clearance also had a very strong correlation with gold standard method \((r=0.92, P<0.001)\), and overestimated the renal inulin clearance on the whole \((correlation coefficient:0.92; slope:0.81)\).

**Conclusions:** Renal inulin clearance overestimated systemic inulin clearance using a single injection method in overall. Alternative methods for GFR measurement such as systemic inulin clearance with a single injection method and plasma \(^{51}\)Cr-EDTA clearance correlated well with gold standard, even though those alternatives somewhat underestimated and overestimated gold standard, respectively.
TH-P0282
Performance of Japanese and CKD-EPI GFR Equations in Japanese Subjects

Background: Japanese GFR equations based on serum creatinine (Scr) (EqScr), serum cystatin C (Scys) and average value of eGFRc and eGFRys (Eqave) were developed in 413 Japanese and validated in 350 Japanese patients, however they have not been well evaluated in another validation set. Thus, their performances were analyzed in comparison with CKD-EPI equations based on Scr (CKD-EPIscr), Scys (CKD-EPIscys) and EqScr in combination with Scr (CKD-EPI-EqScr) in this study.

Methods: Study subjects were 291 consecutive Japanese patients examined GFR by inulin renal clearance in Nagoya University Hospital. Standardized Scr was measured by enzymatic method, standardized Scys was measured by colloidal gold immunoassay. Performance of Japanese equations (EqScr, EqScr, Eqave) were compared with CKD-EPI equations (CKD-EPIscr, CKD-EPIscys and CKD-EPI-Eqscr, respectively).

Results: Age (mean ± SD, years old) and gender distributions (male %) were 59.7 ± 13.5, 67% in 183 CKD, 64.0 ± 13.5, 80% in 86 malignancy before uni-nephrectomy and 61.0 ± 7.9, 40% in 22 renal transplant donor. GFR (mean ± SD, mL/min/1.73 m²) were 47.6 ± 24.7 in CKD, 61.3 ± 25.1 in malignancy and 74.2 ± 18.1 in donor. 15% and 30% accuracy, correlation and root mean square error (RMSE) were shown in Table.

Table: Performance of CKD-EPI and CKD-EPI-EqScr equations overestimated GFR.

<table>
<thead>
<tr>
<th>Equation</th>
<th>N</th>
<th>15% accuracy</th>
<th>30% accuracy</th>
<th>Correlation</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EqScr</td>
<td>183</td>
<td>47.6 ± 24.7</td>
<td>61.3 ± 25.1</td>
<td>74.2 ± 18.1</td>
<td>1.82</td>
</tr>
<tr>
<td>EqScr</td>
<td>61.3 ± 25.1</td>
<td>74.2 ± 18.1</td>
<td>1.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eqave</td>
<td>61.3 ± 25.1</td>
<td>74.2 ± 18.1</td>
<td>1.82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Japanese and CKD-EPIscr GFR equations performed well among Japanese patients.

Funding: Government Support - Non-U.S.

TH-P0283
Regional Differences in Chronic Kidney Disease Prevalence in Japan: A Japanese Nationwide Health-Check Study

Background: Regional variations in the increasing rate of End Stage Kidney Diseases (ESKD) was reported in Japan, however, factors associating these regional differences have not been fully elucidated. In this study, prevalence of Chronic Kidney Disease (CKD) and its risk factors were analyzed in a Japanese nationwide database with a focus on the regional differences.

Methods: Study subjects were 386,517 (163,454 male) participants in a Japanese nationwide health-check including 13 prefectures. Prevalence of CKD and risk factors, including hypertension (HTN), diabetes mellitus (DM), dyslipidemia (DL) and obesity (OB), were analyzed in 4 regions divided by the increasing rate of ESKD as follows; the highest area (H area), followed by M1 area, M2 area and L area.

Results: CKD prevalence in H, M1, M2 and L areas were 21.4%, 25.5%, 20.9% and 16.8%, respectively. Prevalence of HTN, DM and OB were 16.8%, 3.7% and 19.0%, respectively.

Conclusions: Association between regional variations in CKD prevalence and those regional variations were demonstrated. Although HTN, DM and OB were risk factors for CKD, the rate of under treatment and good blood pressure control rate were significantly high in L area.

Funding: Government Support - Non-U.S.

TH-P0284
Validation of Korean Coefficient for GFR Estimation by the Modification of Diet in Renal Disease (MDRD) Equations
Yun Jung Oh, Ran-Hoo Cha, Chung Kook Lee, Hajeong Lee, Dong Ki Kim, Yo Su Kim. Internal Medicine, Cheju Halla General Hospital, Jeju, Korea; Internal Medicine, National Medical Center, Seoul, Korea; Internal Medicine, Seoul Nat'l Univ College of Medicine, Seoul, Korea.

Background: Race and ethnicity are important determinants of estimating glomerular filtration rate(GFR). Korean coefficients for the isotope dilution mass spectrometry(IDMS) Modification of Diet in Renal Disease(MDRD) equations were developed in 2010, however, these coefficients were not well validated thoroughly. We validated our previous study.

Methods: Equation development and validation were performed in separate groups(development group; N=147 from 2008 to 2009, validation group; N=125 from 2010 to 2011). We compared the performance of original IDMS MDRD equations and modified equations with Korean coefficients. And the performance was assessed by correlation coefficient, bias, and accuracy between estimated GFR(GFR) and reference GFR(GFR).

Results: We found strong correlation between GFR calculated by modified equations with Korean coefficients and GFR(GFR)=0.890 and 0.890 for modified 1 and 6 variable IDMS MDRD equation, respectively. However, this correlation coefficient was not different from the correlation coefficients between GFR calculated by IDMS MDRD equations and GFR. Based on modified equations, performed with less bias than original IDMS MDRD equations, overall performance was not significantly different from each other showing a similar accuracy. New Korean coefficients for 4 and 6 variable IDMS MDRD equations were 1.020 and 0.973, respectively. The overall performance of new Korean IDMS MDRD equations was better than those from previous studies.

Conclusions: Korean coefficients for IDMS MDRD equations developed before showed good performance in the validation study group. However, there was no significant difference between original and modified IDMS MDRD equation with new Korean coefficient in terms of performance of GFR estimation after all.

Funding: Government Support - Non-U.S.

TH-P0285
Prevalence of Chronic Kidney Disease in Europe
Katharina Breuck, Vianda S. Stel, Christoph Wanner, Wim Van Beise, Charles Tomison, Giovanni Tripepi, Carmine Zoccali, Kitty J. Jager. ERA-EDTA Registry, Netherlands; Univ Hospital Würzburg, Germany; Ghent Univ Hospital, Belgium; Southmead Hospital, United Kingdom; CNR-IBIM, Italy; On behalf of the European CKD Burden Consortium.

Background: The wide variation in definitions for prevalence of chronic kidney disease (CKD) complicates attempts to compare the burden of CKD between countries. The aim of our study was to examine the prevalence of CKD in all stages in subjects not on replacement therapy across Europe, using standardised definitions.

Methods: A literature review was performed to identify all European studies that could provide data on CKD prevalence. The representatives of eligible studies received a questionnaire on the availability of data and health care system characteristics. Based on available data and the new KDIGO practice guideline, standardised definitions for CKD prevalence were defined as presence of albuminuria >= 30mg/g and/or eGFR by CKD-EPI formula <60mL/min/1.73m² without the chronicity criterion (as only 4 studies had these data). These definitions were used to extract the prevalence of CKD for various subgroups (e.g. age group, gender and diabetic status). All prevalence data were age and sex standardized to the EU27 population.

Results: Out of 71 studies, we so far received data on prevalence from 16 studies from 11 countries. The age and sex standardized prevalence of CKD stage 3-5 in the age group 20-74 years ranged from 1% in central Italy to 5.4% in Portugal. In this age group, the CKD stage 3-5 prevalence ranged from 1.3-6.4% in females and 0.8-4.2% in males. In the age group 65-74 years, this prevalence was 4.8% in central Italy, 11.4% in Finland, 13.3% in Poland, 19.7-21.5% in Germany, 22.3% in the Netherlands and 24.3% in Portugal.

Conclusions: This is the first study on international differences in the prevalence of CKD using standardized definitions. The prevalence of CKD varied hugely across European countries. Data on co-morbidities and health care system characteristics will be used to explain the international differences in CKD prevalence. Together they will provide a complete overview of the burden of CKD in Europe.

TH-P0286
Estimated Glomerular Filtration Rate and Urine Albumin Creatinine Ratio Category-Specific Prevalence and Descriptions of People with Type 2 Diabetes in the U.S. Robert A. Bailey, Yiting Wang, Vivienne J. Zhu, Marcia Rupnow, Janssen Scientific Affairs, LLC, Parsippany, NJ; Janssen Research and Development, LLC, Titusville, NJ.

Background: Kidney Disease: Improving Global Outcomes (KDIGO) updated classification of chronic kidney disease (CKD) in 2013, using both estimated glomerular filtration rate (eGFR) and urine albumin creatinine ratio (ACR). However, little is known about eGFR and/or ACR category-specific prevalence among people with type 2 diabetes (T2D) using this new classification.

Methods: We used the continuous National Health and Nutrition Examination Surveys (NHANES), 1999-2010, and identified participants with T2D using a definition similar to previous studies. eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation. eGFR and ACR categories were defined according to KDIGO, and prevalence was age-adjusted to the 2010 diabetes population according to the National Health Interview Survey (NHIS). We used SAS® (v9.2) survey procedures to account for the strata (year, state) in the NHIS survey sample.

Results: The final analysis included 2,413 participants with T2D; mean age was 61.4; diabetes duration was 9.8 years. Mean (standard error) of eGFR (ml/min/1.73m²) and ACR (mg/g) were 79.6 (0.7) and 107.8 (1.9), respectively. The weighted eGFR and ACR category-specific prevalence is shown in Table.

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

Underline represents presenting author/disclosure.

168A
Conclusion: Our study is the first to provide estimates of eGFR and ACR category-specific prevalence for T2D based on the KDIGO classification in a nationally representative sample.  

Funding: Pharmaceutical Company Support - Janssen Scientific Affairs, LLC

TH-PO287  
Detection of Subclinical Chronic Kidney Disease (CKD), in Relatives of Dialysis Patients and Cardiovascular Disease Patients in Chile  
Alvino A. Castillo, 1 Mauricio J. Castillo, 2 Domingo Lancellotti, 2 Alejandra Lagos, 2  
1 Dialysis Unit, Hosp. La Serena, La Serena, Chile; 2 Salud Publica, Faculty Medicine, U. Catolica Norte, Coquimbo, Chile.

Background: CKD is a serious public health problem. It can be prevented with early detection and treatment. Our objective is to determine the prevalence of sub-clinical CKD in different risk groups in Chile.

Methods: Performed in 3 regions of Chile (Coquimbo, Santiago, Valdivia). Groups analyzed: 1) Primary Health Care (PHC) consults without cardiovascular risk factors (CON), 2) Patients from Cardiovascular (CV) program of PHC (PHC-CV) 3) Family ≥18 y. (parent-brother-children) of dialysis patients (non genetic etiology) (FAM). Approved by Ethical Committee. 1,143 subjects signed informed consent, from 12 health centers. Survey applied based on: Chilen CKD Guidelines. Hypertension, blood pressure measurement, height, lab tests: Creatinine, Microalbuminuria/Creatininuria Ratio (ACR), Urine dipstick. eGFR using MDRD-4 equation. Classification of CKD and ACR according to KKF-KDQI.

<table>
<thead>
<tr>
<th>Weighted N (unweighted N)</th>
<th>eGFR (ml/m²/1.73m²) Categories</th>
<th>ACR</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 (60-89)</td>
<td>2.5% (637)</td>
<td>3% (81)</td>
<td>1.2% (182)</td>
</tr>
<tr>
<td>28 (45-59)</td>
<td>2.5% (637)</td>
<td>5% (81)</td>
<td>2.8% (182)</td>
</tr>
<tr>
<td>18 (35-49)</td>
<td>2.5% (637)</td>
<td>5% (81)</td>
<td>3.1% (182)</td>
</tr>
<tr>
<td>14 (15-29)</td>
<td>2.5% (637)</td>
<td>5% (81)</td>
<td>3.1% (182)</td>
</tr>
</tbody>
</table>

Table 1: Prevalence of CKD stages in Chilean Population

Conclusions: PHC-CV and FAM showed high prevalence of CKD and abnormal ACR, significantly higher than CON. Early detection of CKD should focus on these groups. FAM is easy to access through the relative on dialysis. In Chile 18,000 patients are on dialysis, data allows estimating that 8,000 FAM would suffer CKD, currently undetected. FAM presents high prevalence of hypertension, ACR and CKD, despite being significantly younger than PHCV.

Funded by FONIS-CONICYT (SA1020040).

Funding: Government Support - Non-U.S.

TH-PO288
Prevalence of Chronic Kidney Disease and Metabolic Syndrome in an Adult Korean: Result from the Korean National Health Screening Yong Un Kang, Joon Seok Choi, Chang Seong Kim, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim. Dept of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea.

Background: Chronic kidney disease (CKD) and metabolic syndrome (MS) are increasing public health problems. However, there has been limited data on CKD and MS prevalence, and its relationship in large based population. This study was aimed to examine the prevalence of CKD and MS, and the association between MS and its components with CKD in Korea.

Methods: We performed a cross-sectional study in non-institutionalized civilians using the general health screening data of 10,549,230 (47.2±13.9 years, men 56.3%) participants aged more than 20 years from the Korean National Health Screening 2011. CKD was defined as dipstick proteinuria or an estimated GFR (eGFR) of <60 ml/min per 1.73 m².

Results: The prevalence of CKD (n=688,182) was 6.52% (5.75% in men, 7.52 in women). The prevalence estimates of CKD stage, respectively, were 0.86% for stage 1; 0.95% for stage 2; 3.74% for stage 3; 0.1% for stage 4; 0.86% for stage 5. 23.5% of the study population (n=2,477,247) had MS (12.1% for central obesity; 12.5% for high triglyceride; 5.9% for low HDL cholesterol; 15.5% for high blood pressure; 5.9% for high fasting glucose). 41.1% of the study population with CKD (n=282,551) had MS (11.4% for central obesity; 8.2% for high triglyceride; 5.1% for low HDL cholesterol; 17.3% for high blood pressure; 4.4% for high fasting glucose). In multivariate-adjusted analysis, presence of MS was associated with an increased risk for CKD (odds ratio=1.45, 95% confidence interval 1.450–1.467, P < 0.0001). Also, the individual components were associated with increased risk for CKD.

Conclusions: MS and the individual components predict the risk of prevalent CKD.

TH-PO289
Gangadarsnhi Chandramohan, 1 Kamary Kalantar-Zadeh, 2 Magda Shaheen, 1  
1Pediatrics, Harbor-UCLA Medical Center, Torrance, CA; 2Internal Medicine, Charles Drew Univ Research Center, Los Angeles, CA; 3Internal Medicau & Pediatrics, Univ of California: Irvine, Irvine, CA.

Background: Prevalence of type II diabetes (DM), is high among minority children. In type II DM, the early sigh of renal injury is increase in eGFR due to hyperfiltration. 

Methods: A retrospective cross-sectional analysis of children between the ages of 13-17 years from the National Health and Nutrition Survey (NHANES) obtained from 2004-2005, was performed. Abnormal fasting blood sugar (FBS) was defined using the standard guidelines. High eGFR was defined as the 4th quartile of eGFR of the study population. Statistical analysis were done using SUDAAN and SAS software program.

Results: There were 1149 children, high FBS 10%. Among Whites, AA and Hispanics, high eGFR noted in 25%, 18% and 13% (p=0.009), respectively. High FBS found in 10, 11, 10% in White, AA and Hispanics respectively. The mean eGFR differed significantly between the ethnic groups. Odds ratio to have high eGFR was high among Whites and Blacks with high FBS. Table 1: The odds ratio for having 4th quartile of eGFR Based on FBS among the Total population and by Ethnicity.

Conclusions: Prevalence of high eGFR was significantly high among Hispanic than other ethnic groups. Mean eGFR was significantly higher among Hispanic than AA and Whites. Analyzing FBS independently in each ethnic groups revealed an interesting finding among adolescent children, exciting an association with high eGFR. Therefore, in determining eGFR in children with abnormal FBS may shed light on future management in regards to the aggressiveness of the intervention, with a potential role for ACE inhibition, even before the development of microalbuminuria.

Funding: Other NIH Support - National Institutes of Health: NIMHID grants P20MD00182 and US4MD007598 (formerly US4R26138)

TH-PO290
Epidemiology of Autosomal Dominant Polycystic Kidney Disease in the United States Cynthia J. Willey, 1 Frank S. Czerwiec, 2 Holly Krasa, 1 Robert D. Mehigan, 2 Herbert W. Turner 3, Mary S. Brough, 3, 4Pract, Pharmacy Practice, Univ of RI, Kingston, RI; 1Otsuka Pharmaceutical, Rockville, MD; 3Univ of Colorado, Aurora, CO; 4Mayo Clinic, Rochester, MN.

Background: Most studies of PKD in the U.S. focus upon small cohorts of patients and have limited generalizability. Only one population-based study examined US incidence of ADPKD using data from Olmsted County, Minnesota from 1935 to 1980. Our study reviewed current literature and analyzed national data to estimate total and diagnosed prevalence of ADPKD in the U.S.

Methods: Diagnosed and total prevalence were derived using incidence rates from Iglesias et al based on symptomatic or screened cases compared with the addition of cases diagnosed at autopsy. Diagnosis rates were then increased by 25% to reflect recent improvements in diagnostic imaging technology. Data from the U.S. Renal Data System (USRDS) were used to estimate average survival time. Validation analyses were performed using the National Ambulatory Medical Care Survey (NAMCS) to examine consistency between expected patients in the U.S. with ADPKD and the annual number of ambulatory visits patients with ADPKD.

Results: USRDS data suggest an average duration of disease of approximately 61.8 years for adult patients with ADPKD. Taken with incidence rates from the Rochester Epidemiology Project, a total prevalence rate of 0.46 per 1,000 was calculated with an estimate that 95% of those are currently diagnosed. Validation analysis using data from the NAMCS focused on probable ADPKD and included patients with autosomal dominant or unspecified polycystic kidney disease (ICD9 CM: 753.12-753.13). Results were consistent with 97,667 diagnosed cases estimated from the NAMCS and 116,288 estimated using data from the Rochester Epidemiology Project.

Conclusions: Although total prevalence (including undiagnosed cases) will be slightly higher, these data support a diagnosed prevalence of approximately 1/2000 and yield an estimate of less than 200,000 diagnosed ADPKD cases in the U.S.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical

TH-PO291
Switching from Modification of Diet in Renal Disease to Chronic Kidney Disease Epidemiology Collaboration Formula Has Negligible Impact on Staging in an Established Chronic Kidney Disease Population  
Eduard A. Iliescu, 1, 2 Sandra Belanger, 2 M. Khaled Shamseddin, 1, 2 Sarah Aloudat, 1, 2 Christine A. White, 1, 2 Queen’s Univ, Kingston General Hospital, Kingston, Canada.

Background: The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Guidelines recommend the CKD-EPI formula to calculate eGFR from serum creatinine (1B). The aim of this study is to examine the practical impact of switching from MDRD
Prevalence of CKD and Associated Risk Factors in Italy: The CARHES Study. Luca De Nicola,1 Chiara Donfrancesco,2 Roberto Minutolo,1 Cinzia Lo Noce,2 Luigi Palmieri,2 Amalia De Curtis,3 Licia Iacoviello,3 Giuseppe di Blasio. Methods: The cardiovascular risk in Renal patients of the 2008-12 national Health Examination Survey (CARHES) examined random samples of Italian general population in a nationally representative survey in Europe. Background: Identification of CKD and associated cardiovascular (CV) comorbidities is a key priority for public health worldwide. No study however has addressed this issue in a nationally representative survey in Europe. Prevalence of CKD was 14.5%. Micro- and macroalbuminuria prevalence was 5.9% and 3.4%, respectively. The average decline in eGFR during the follow-up was 1 ml/min/year. Genetic risk score, old age, female gender, and hyperuricemia were independently correlated with all the outcomes. Diabetes and abnormal kidney length were associated with CKD; hypertension was correlated to fast eGFR decline. Diabetes, hypertension, and high baseline eGFR were significantly predictive of future decline of eGFR. Conclusions: CKD prevalence was similar to observations in China, higher than in Norway, and lower than in the USA. Genetic risk score contributes independently of traditional CKD risk factors. Along with differences in health practice and in traditional risk factors, it may provide an entrée to further exploration of differential CKD prevalence worldwide.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
evidence of severe RI (eGFR <30), 51% received IVBP therapy. By deriving age and gender specific CKD prevalence, age and gender distribution for each HB was obtained and expected rates were used to adjust CKD rates for deprivation. There is considerable unexplained variation in CKD rates amongst HBs. The cohort included 15,623 pts (mean age 67.1 ± 12 years, weight 76.5 ± 18 kg; female 56%; breast, prostate or lung cancer 83%), of whom, 49.2% had RI during a mean 23.7 months of follow-up after bone mets dx (9.7% with eGFR <30).

**Results:**

- Among pts with RI and at least one eGFR after 90 days, 80.7% (4,686/5,810) had CKD and 62% received an IVBP within 12 months from eGFR<60. Similarly, among pts with evidence of severe RI (eGFR<30), 51% received IVBP therapy.

- **Conclusions:** These data from pts treated in community oncology clinics across the US demonstrate that nearly half of pts with bone mets had evidence of RI during the course of their disease. Despite RI, a large proportion of pts were treated with an IVBP. Careful consideration of treatment options and close monitoring of renal function in this population is imperative to achieve optimal therapeutic outcomes.

**Funding:** Pharmaceutical Company Support - Amgen, Inc

**TH-PO296**

Understanding Variation in CKD Prevalence amongst Scottish Health Boards Beng Hock So,1,2 Mario D. Hair,1 Shona Methven,1 Alan G. Jardine,1 Mark S. MacGregor,1 Western University, University Hospital Crosshouse, Scotland; 2Univ of Glasgow, Scotland, 3Univ of Bristol, England.

**Background:** Almost all people in Scotland are registered with primary care practices, which maintain registers of chronic kidney disease (CKD) stages 3-5. Registry CKD prevalence is 4.1% nationally. However, there is marked variation between the 14 Health Boards (HB) from 3.1 to 5.4%. We explored the reasons for this variation.

**Methods:** CKD prevalence, age and gender distribution for each HB was obtained from NHS Scotland. We derived age and gender standardised CKD (AGCKD) rates; all CKD stages 3-5 were identified from NHS Ayrshire & Arran’s (A&A) laboratory database (218 population 313,503) with two or more eGFRs <60 mL/min/1.73m2 ≥90 days apart. We applied AGCKD to the population structures of the other HBs to derive expected rates. Based on A&A data we derived a regression co-efficient to adjust CKD rates for deprivation.

**Results:**

- In A&A, 18,291 adults had CKD (5.83% total, 7.34% women, 4.24% men).

- The reported prevalence is 5.4%; the gap represents failure of ascertainment. Applying AGCKD to the population structure of each HB reduced variation. The gap between observed and expected prevalence varied from 0.6% to 3.1% and was significant (p<0.01). At primary care practice level, AGCKD was associated with deprivation (r=0.66, p<0.001). After adjusting HB prevalence for deprivation the gap between observed and expected rates varied from 0.2% to 3.4%.

**Conclusions:** There is considerable unexplained variation in CKD rates amongst HBs. By deriving age and gender specific rates of CKD relevant to our population then adjusting for deprivation, we derived expected CKD rates for each HB, allowing benchmarking the gap between observed and expected CKD rates may represent failure of ascertainment, or true prevalence differences due to unexplained factors in those populations and requires further exploration.

**TH-PO297**

**TH-PO298**

**Short Term Risk versus Lifetime Risk in Stage 3 Chronic Kidney Disease**

Candace D. Grant, Shayan Shirzadian, Pardeep Kumar, Milind K. Bhagat, Joseph Mattana, Dept. of Medicine, Winthrop Univ Hospital, Mineola, NY.

**Background:** While there are proven therapies that slow CKD progression, these therapies can at times be harmful and costly. The ability to accurately predict the risk of CKD progression and overall lifetime risk would be extremely valuable. The short term risk of CKD progression should be taken into account when making clinical decisions based on risk assessments. In a representative CKD practice, we compared the short term and lifetime risk assessment in our stage 3 CKD patients to determine whether decisions based on short term risk assessment would underestimate the lifetime risk of CKD progression.

**Methods:** The electronic charts of 120 CKD stage 3 patients seen in our nephrology practice were reviewed. Eligible patients had at least one documented eGFR within the past year. Additional variables collected for risk assessment were urine albumin to creatinine ratio (UACR), total cholesterol, history of coronary artery disease and history of stroke. Risk factors independently associated with CKD were older age, hypertension, diabetes, history of stroke, raised systolic BP, raised fasting glucose and raised triglycerides. About 51% CKD patients with hypertension were on anti-hypertensive medications and only 6.7% had their BP controlled to <130/80 mm Hg.

**Conclusions:** CKD is common among adults in Pakistan, especially among older individuals with co-morbidities. Blood Pressure control and use of anti-hypertensive medications among CKD patients is sub-optimal. Efforts to prevent CKD in Pakistan must target high risk populations and be integrated with major non-communicable diseases care in Pakistan and neighboring South Asian countries.

**Funding:** Private Foundation Support

**TH-PO299**

**Renoprotective Effect of Pentoxifylline in Childhood Chronic Kidney Disease**

Yo Han Ahn, Jiwon M. Lee, Hee Gyung Kang, Hae II Cheong, IL Soo Ha, Dept of Pediatrics, Seoul National Univ Children’s Hospital.

**Background:** Pentoxifylline (PTX) attenuated renal fibrosis in animal studies. It was also reported to offer beneficial effects on renal function and proteinuria in diabetic kidney disease and membranous nephropathy in adults. Previously our group presented a preliminary data of PTX in pediatric chronic CKD patients, and here we report our updated result.

**Methods:** From 2004 to 2013, 52 children with stage 2 to 4 CKD (estimated glomerular filtration rates (eGFR) 15~90 mL/min/1.73m2) were treated with PTX of 700 mg/m2/day
for 25.128 months. All of them were also on either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to attenuate progression of CKD. Among them, 29 patients (16.3%) had MN, 36 patients (22.4%) had FSGS, 31 patients (17.2%) had AGGS, and 12 patients (7.2%) had MN + FSGS. At the beginning of PTX, 2.3±1.8% had a baseline eGFR < 30 mL/min/1.73 m2. However, after administration of PTX, there was no significant decline of eGFR during the next 12 months (38.0±17.2 mL/m2 at 12 months after PTX treatment (+12mo, P=0.863). When analyzed the change of eGFR (DGFR) before and after PTX treatment, PTX showed renal protection in each patient in lower grade CKD, stage 2/3a, -4.2±11.1 before vs. 1.5±0.5 after treatment, P=0.019) while those with CKD stage 3b/d showed no significant difference (0.4±4.2 vs. 1.5±0.5, P=0.710). Compare to patients with underlying glomerulopathy (GN) against those with non-GN, PTX was more beneficial for those with non-GN (P = 0.037).

On the other hand, significant number of patients (n=23, 42%) experienced side effects of PTX, such as nausea or vomiting and drug fever, and had to discontinue PTX.

Conclusions: PTX showed renoprotective effect in childhood CKD, especially in early stage CKD and in those with non-GN cause of CKD. However, significant side effect was observed at the same time, thus randomized controlled trial is necessary to validate the benefit of this anti-fibrotic medication.

TH-PO300

Is Glomerular Filtration Rate Related to Vascular Lesions in HIV Patients? 
Corinne Insard-Bagnis,1 Philippe Rouvié,2 Sophie Tezenas du Montcel,2 Paulo Francisco Fernandes,3 Macroui Sonikian,3 Jerome Tourret,4 Rachid Agher,5 Gilbert Deray,1 Marc Antoine Valantin,6 Roland Tubiana,7 Christine Katlama,4 Nephrology, Assistance Publique Hôpitaux de Paris, Paris, France; 5Pathology Department, 1Dept, Assistance Publique Hôpitaux de Paris, Paris, France; 2Pathology Dept, Assistance Publique Hôpitaux de Paris, Paris, France; 3Clinical Research Unit, Assistance Publique Hôpitaux de Paris, Paris, France; 4Infectious Disease Department, Assistance Publique Hôpitaux de Paris, Paris, France; 5Nephrology, 6A Fleming General Medical Hospital, Athens, Greece; 7Nephrology, Hospital Santa Maria, Lisbon, Portugal.

Background: Renal diseases in HIV patients are secondary to the viruses (HIV or HIV-HCV co-infection), their treatments or to metabolic complications. As the causes of chronic kidney disease evolve in HIV population, it is critical to describe what histopathological lesions correlate with glomerular filtration rate (GFR).

Methods: 196 biopsies performed in a single center over 10 years in HIV patients were retrospectively analyzed. For 82 biopsies, corresponding clinical and biological data were available both at the time of biopsy. GFR was estimated using MDRD formula.

Results: Among the 196 biopsies, the main renal histopathological diagnosis included: Acute tubular necrosis (n=34, 17.4%), FSGS (n=29, 14.8%), diabetic glomerulosclerosis (NAS) (n=28, 14.3%), FSGS (n=25, 12.8%), interstitial fibrosis, tubular atrophy (IFTA) (n=11, 5.6%), and diabetic glomerulosclerosis (n=10, 5.1%). IFTA was present in 25% of HIV-related diagnosis (FSGS/HIVAN) and 36% in non HIV-related (all others) diagnosis (P=0.11). NAS was present in 25% of HIV-related diagnosis (FSGS/HIVAN) and 44% in non-related diagnosis (all others) diagnosis (P=0.058). IFTA did not influence GFR in any diagnosis. When NAS lesions were present in HIV-related diagnosis, GFR was significantly lower (P<0.032).

Conclusions: Nephroangiosclerosis lesions are more frequent in non HIV-related histopathological diagnosis (patients with metabolic complications) and significantly influence glomerular filtration rate in HIV patients. Accelerated ageing and endothelial vascular lesions secondary to HIV infection and HAART may explain this correlation.

Funding: Private Foundation Support

TH-PO301

Chronic Kidney Disease in Patients with Sickle Cell Anemia 
Elvira Gosmanova1, Sahar Zaidi,2 Jim Y . Wan,3 Patricia Adams-Graves. 1Esho Georges, Harshia C. Gondi, Rafath Ullah, Mana Dissadee, Andre Serraino. Nephrology Div, Mount Sinai Hospital Medical Center, Chicago, IL.

Background: The purpose of our study is to review all renal pathologies done at our institution between 2006-2012, to identify the renal diseases that affect our population which composed mainly of Hispanics and African-Americans.

Methods: We reviewed medical records of our (100) cases retrospectively looking for renal pathology, gender, ethnicity, age group, labs and other data done at time of diagnosis.

Results: The mean age of the group was 45.7 yr with 55% females and 45% males. Hispanics account for 52% and African-Americans for 44%. At the time of biopsy, 67% of patients have hypertension and 34% have diabetes mellitus. The mean serum creatinine is 2.8 mg/dl and mean urine protein/creatinine is 5.1 gm/mg.

Diabetic nephropathy (DN) and focal segmental glomerulosclerosis (FSGS) are the most common pathology (each accounts for 19%), followed by advanced global glomerulosclerosis (AGGS) (17%), IgA nephropathy (IgAN) (12%) and membranous nephropathy (MN) (12%). Interestingly, almost close to one fifth of the patients have end-stage renal disease, which likely indicates lack of medical evaluation in this group of patients.

Among Hispanics, FSGS was the most common diagnosis (23%), followed by IgAN (21.1%), DN (19.7%), AGGS (19.2%) and MN (9.6%). Among African-Americans, the most common diagnosis was DN (20.4%), followed by MN (15.9%), AGGS (13.6%), and FSGS (11.3%). It is interesting that MN was more frequent among African-Americans than FSGS, which traditionally has been described to be more prevalent in this population, and that FSGS was the most common diagnosis among the Hispanics. Among diabetics, DN was the most common diagnosis (55.8%). However, (44.2%) of the diabetic patients have a different diagnosis.

Conclusions: In conclusion, DN and FSGS are the most common cause of renal disease at our institute. However, almost close to one fifth of cases have AGGS, which likely indicates lack of medical evaluation and unawareness of their renal disease. Among African-Americans, DM and MN were more frequent than FSGS. Finally, more than 40% of patient with diabetes mellitus, have a diagnosis that was not DN.

TH-PO303

A Panel of Novel Biomarkers of Kidney Injury Improves Prediction of Glomerular Filtration Rate Decline in Chronic Kidney Disease 
Boon Wee Teo1, Peh Hoo J0,2 Qi Chun Toh,1 Hwee Min Loh,3 Martin B. Lee,1 Evan J.C. Lee. 1Medicine, Yong Loo Lin School of Medicine, National Univ of Singapore, Singapore; 2Statistics and Applied Probability, Faculty of Science, National Univ of Singapore, Singapore; 3Medicine, National Univ Hospital, Singapore.

Background: The association of a panel of novel kidney injury or disease biomarkers in spot urine (KIM1, kidney injury molecule 1; LFAFB, liver-type fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; oGST and cGST, gluthathione s-transferase; collagen IV) with progression of chronic kidney disease (CKD) in stable patients is unknown. We hypothesize that a panel of these markers can provide additional predictive value in estimated glomerular filtration rate (eGFR) decline beyond traditional predictors including proteinuria. We assess a panel of biomarkers with eGFR decline in a multi-ethnic Asian population of CKD.

Methods: We retrieved stored urine samples from the Asian Kidney Disease Study patients with CKD (n=81, 49.4% male). We examined traditional and novel biomarkers against eGFR decline using uni- and multivariate analysis. Variables of interest were natural log-transformed where appropriate. We used exhaustive stepwise selection of variables in multiple linear models to determine the best predictive models and Akaike Information Criterion (AIC) to select the best. We used cross-validation to validate and rank the models by prediction error.

Results: Population means: age 58.7±12.4 years, 53.1% diabetes history, serum creatinine 1.7±0.5 mg/dL, serum total protein 70.6±7.5 g/L, urine creatinine 6.9±4.6 mmol/L baseline eGFR 45.2±26.8 mL/min/1.73m2, Kim-1 1.07±0.6 ug/mL, LFAFB 42.2±50.0 ug/L, NGAL 29.8±52.1 ug/L, oGST 6.5±23.8 ug/L, cGST 6.9±11.1 ug/L. Collagen IV 5.7±6.0 ug/L. Urine albumin to creatinine ratio (UACR) is rendered insignificant in a model including diabetes history, serum protein, oGST, NGAL, and L-FABP but is the best model with the smallest AIC value (20.26) and smallest prediction error.

Conclusions: A panel of novel biomarkers of kidney injury offers additional prediction of CKD progression in a model including albuminuria.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author/disclosure.

172A
TH-PO304

Uric Acid Transporter ATP-Binding Cassette Transporter G2 (ABCG2) Is Increased in the Intestine of the Rat 5/6 Nephrectomy Model of Chronic Kidney Disease
Hitomi Yano, Yoshifuru Tamura, Kana Kobayashi, Shunya Uchida.
Nephrology, Teikyo Univ School of Medicine, Tokyo, Japan.

Background: Uric acid (UA) remains to be a risk factor of chronic kidney disease (CKD). Therefore, it is important to clarify the mechanism of UA excretion in CKD. The specific mechanisms of intestinal excretion in extrarenal urea are unknown. We evaluated the expression of UA transporter, ABCG2, in the ileum, duodenum, jejunum, ileum, and transverse colon tissues. We measured actin activity in the liver. Expression of ABCG2 in intestinal mucosa was measured with a real time PCR.

Results: NX group showed significantly decreased uric acid excretion/body weight and UA clearance compared to the control group at 4 and 8 weeks after nephrectomy. In contrast, serum UA and uricase activity were not significant. In NX group, the expression of ABCG2 in the ileum showed significant increase upregulation. While other intestines revealed no changes.

Conclusions: Urate excretion of uric acid and the over-expression of ABCG2 in ileum. The fact that serum UA did not increase despite the decrease in UA excretion suggests that other excretory pathway, probably intestine, beside kidney may operate as a complementary role that corroboration the increase in ABCG2 expression in the ileum.

TH-PO305

Visceral Fat Area (VFA) Assessed by Bioelectric Impedance Analysis (BIA) Is Associated with Renal Function in Healthy Subjects
Soo Bong Lee, Il Young Chung, Dong Won Lee, Byeong Yun Yang, Eun Young Seong, Ihm Soo Kwak. Dept of Internal Medicine, Pusan National Univ School of Medicine, Yangsan, Republic of Korea.

Background: Bioelectric impedance analysis (BIA) can be used in many clinical settings and easily give us information about body composition of each person including muscle mass, percentage of total body fat and visceral fat area (VFA). Though some studies have been reported regarding the adverse effect of abdominal obesity on renal function in chronic kidney disease (CKD) patients, that effect in healthy population is less well known. Therefore, we evaluated the effects of VFA on glomerular filtration rate (GFR) in healthy subjects.

Methods: We searched healthy subjects over 18 years old who underwent BIA and routine laboratory tests through health screening and promotion center in our university hospital in 2012. All of them have no underlying illness and subjects with proteinuria or hematuria were excluded. GFR was estimated by the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology (CKD-EPI) equations. Multiple linear regression analysis between eGFR and body composition measured by BIA was done. Because the eGFR was affected by body mass, subjects were divided two groups according to BMI and compared their eGFR.

Results: Total 500 healthy subjects were included. Percentage of total body fat, obesity index and waist hip ratio did not show meaningful relationship with eGFR. Age, body weight, skeletal muscle, VFA were statistically significant predicting factors of eGFR by multiple linear regression analysis (p<0.001). Interestingly, the association of increased VFA with decreased renal function is more prominent in non obese group with low BMI below 25 than others (p<0.001 vs. p=0.295, respectively).

Conclusions: VFA is a significant determinant of eGFR in company with Age, body weight, skeletal muscle especially in non obese group in healthy subjects. Although many studies focused on association of general obesity and renal function, visceral fat reflecting abdominal obesity seems to have important role on renal function and should not be ignored even in healthy subjects.

TH-PO306

Lower Albumin Level Is Associated with Higher Fractional Excretion of Creatinine
Masaru Horio,1 Enyu Imai,2 Yoshinari Yasuda,3 Tsuyoshi Watanabe,4 Seiichi Matsuo.3 Functional Diagnostic Science, Osaka Univ Graduate School of Medicine, Osaka, Japan; 2Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan; 3Third Dept of Medicine, Fukushina Medical Univ, Fukushina, Japan.

Background: Creatinine clearance (Ccr) overestimates glomerular filtration rate (GFR) due to the tubular secretion of creatinine. Fractional excretion of creatinine (FE-Cr) ratio of Ccr to GFR increases with decreasing GFR. Association of serum albumin level with the tubular secretion of creatinine was also reported previously. Alteration of FE-Cr may affect the performance of GFR estimating equations based on serum creatinine. We analyzed the factors influencing FE-Cr and compared the performance of GFR equations in subjects stratified by albumin levels.

Methods: 757 Japanese subjects were included. GFR was measured by inulin renal clearance. GFR and Ccr were measured simultaneously. Multivariate analysis was used to evaluate the factors influencing FE-Cr. Age, gender, GFR, body mass index (BMI), body height, weight and serum albumin level were analyzed. Estimated GFR was calculated by Japanese GFR equations based on serum creatinine (Eq-cr), serum cystatin C (Eq-cys) and 5 variables including serum albumin (Eq-5var). Results: FE-Cr in subjects with serum albumin <3.0, 3.0-3.9 and >4.0 g/dl were 1.63±0.48, 1.53±0.55, and 1.40±0.36, respectively. Multivariate analysis showed that GFR (p<0.0001) and serum albumin level (p=0.004) were independent parameters affecting FE-Cr. Biases of Eq-cr, Eq-cys and Eq-5var in subjects with serum albumin <3.0 g/dl were 0.1±2.17, -0.71±1.7, and 0.61±1.8 mL/min/1.73m², respectively. Eq-cr significantly overestimated GFR compared with Eq-cys or Eq-5var. Biases in subjects with serum albumin >4.0 g/dl were 6.4±18.8, 2.0±18.1 and 3.0±18.3 mL/min/1.73m², respectively. Eq-cr significantly underestimated GFR compared with Eq-cys or Eq-5var.

Conclusions: GFR and serum albumin level were independent parameters affecting FE-Cr. Alteration of FE-Cr according to the serum albumin levels may be one of the reasons of the bias of GFR equation based on serum creatinine.

Funding: Government Support - Non-U.S.

TH-PO307

Effects of C-Reactive Protein (CRP) on the Risk of Developing Chronic Kidney Disease in Rheumatoid Arthritis
Masako Kouchi,1 Kentaro Kohagura,1 Kunitoshi Iseki,2 Yusuke Ohyu.1 Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyus, Nishihara-Cho, Japan; 2Diadysis Unit, Univ of the Ryukyus, Nishihara-Cho, Japan.

Background: Chronic inflammation is common in Rheumatoid arthritis (RA) and related to the risk of cardiovascular, liver and pulmonary disease in RA patients. However, the effects of inflammation on chronic kidney disease (CKD) progression are unknown in RA.

Methods: We retrospectively investigated the effects of baseline C-reactive protein (CRP) on the incidence of CKD defined as positive dipstick testing for proteinuria and/or an eGFR (estimated glomerular filtration rate) of ≤60 mL/min/1.73 m². We studied 361 outpatients, 61 men and 300 women, and the mean age and eGFR were 59.9 years and 92.9 mL/min/1.73 m², respectively.

Results: Among the RA patients, C-reactive protein (CRP) was measured in 244 patients (61.7%) and eGFR was measured in 204 patients (56.0%). Among them, 173A patients (39.2%) were positive for CRP test. In those patients, the expression of C-reactive protein and the kidney function were measured every 4 weeks after nephrectomy. In contrast, serum UA and uricase activity were not significant. In Nx group, the expression of ABCG2 in the ileum showed significant increase upregulation. While other intestines revealed no changes.

Conclusions: C-reactive protein and kidney function were measured every 4 weeks after nephrectomy. In contrast, serum UA and uricase activity were not significant. In Nx group, the expression of ABCG2 in the ileum showed significant increase upregulation. While other intestines revealed no changes.

TH-PO308

Markers of Inflammation and Oxidative Stress in Patients with Predialysis Chronic Kidney Disease
Luís H B C Sette,1 Edmundo Pessoa Lopes,1 João Geraldo Carvalho Fernandes,1 André Martins Galvão,2 Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil; 2Laboratório de Imunobiologia Keizo Asami LIKA, Recife, Pernambuco, Brazil.

Background: Nontraditional cardiovascular risk factors such as inflammation, malnutrition and oxidative stress (OS) promote and accelerate atherosclerosis in CKD patients and can be assessed by measuring the inflammation markers: serum ferritin, C-reactive protein (CRP) and albumin and the OS markers: gamma glutamyl transferase(GGT), TBARS, thiol, carbonyl and catalase.

Methods: Between September 2011 and December 2012 we evaluated patients in the clinic of Nephrology at the Hospital of Clinicals of the Federal University of Pernambuco (HC-UFPE) Glomerular filtration rate (GFR) was estimated by the Cockcroft-Gault formula and the patients were classified into five stages of CKD. Were measured in serum: markers of inflammation: ferritin, CRP, albumin, GGT and markers of EO: TBARS, thiol, carbonyl and catalase.

Results: Were included 140 patients with a mean age of 64.4 years and 51.4% male. Mean GFR was 28.8 mL/min/1.73m² and patients showed the following distribution according to the stages of CKD: 16 (11.4%) stage 5 patients, 69 (49.2%) stage 4, 55 stage 3 patients (39.2%). Among the markers of inflammation assessed it was observed an increase in serum ferritin and reduction of albumin in accordance to the GFR and the progression of CKD. There was no association between serum GGT, CRP and markers of EO with the GFR or the stages of CKD.

Biomarkers  GLomerular Filtration Rate

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>GFR 1</th>
<th>GFR 2</th>
<th>GFR 3</th>
<th>GFR 4</th>
<th>GFR 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ferritin</td>
<td>0.256</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>CRP</td>
<td>0.541</td>
<td>0.541</td>
<td>0.541</td>
<td>0.541</td>
<td>0.541</td>
</tr>
<tr>
<td>TBARS</td>
<td>0.066</td>
<td>0.066</td>
<td>0.066</td>
<td>0.066</td>
<td>0.066</td>
</tr>
<tr>
<td>thiol</td>
<td>0.146</td>
<td>0.146</td>
<td>0.146</td>
<td>0.146</td>
<td>0.146</td>
</tr>
<tr>
<td>catalase</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: Among the markers of inflammation and oxidative stress evaluated, there was an increase in serum ferritin and reduction of albumin as the fall in GFR and progression of CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
The The Time Is Now to Implement Novel Urinary Biomarkers to Identify Cardiorenal Syndrome in Children with Dilated Cardiomyopathy

Background: Type II cardiac-renal syndrome (CRS) describes renal dysfunction in the presence of chronic heart disease. Traditionally, elevated serum creatinine (Cr) and proteinuria have been used as markers for renal dysfunction. The role of the novel urinary biomarkers (NUB) has not been investigated in children with dilated cardiomyopathy (DCM). We aim to evaluate the changes in traditional kidney function markers in DCM children, and determine the diagnostic value of NUB in DCM children.

Methods: This is a cross-sectional study in children with DCM and left ventricular dysfunction defined as ejection fraction < 55%, urine and blood samples were collected to run measure serum Cr, urinary protein/ Cr ratio, and four NUB: KIM-1, NGAL, IL-18, and L-FABP. eGFR was calculated using modified Schwartz formula. The NUB concentrations were adjusted for each mg of urinary Cr. NUB concentrations were compared to 22 control urine samples taken from 22 healthy children.

Results: 40 subjects between 2 and 21 year-old have been enrolled. The mean (SD) eGFR was 116 (62.1) ml/min/m². The median urinary protein / Cr ratios was 0.15 (0.09-0.24) mg/mg (normal is < 0.2). Both NGAL and IL-18 concentrations were significantly higher in DCM children than controls. Similarly, FABP concentration was higher in DCM children but the difference was not statistically significant. KIM-1 concentration showed no difference between the two groups.

Conclusions: Our data suggests that the majority of children with DCM have normal eGFR and urinary Protein/Cr ratio; however, both NGAL and IL-18 were significantly higher in DCM children than in controls indicating subclinical ongoing kidney injury that cannot be detected by currently available renal function markers. Our data demonstrates the importance of using more sensitive markers to diagnose CRS in children with DCM.

TH-PO310

Estimated GFR Differs from Measured GFR in Its Associations with Retinal Vasculopathy in the General Population

Background: Estimated GFR (eGFR) from creatinine and/or cystatin C is used extensively in epidemiological research. Validation of eGFR against measured GFR (mGFR) has demonstrated reasonably good performance. However, both creatinine and cystatin C depend on non-GFR factors which can confound associations with pathological examination of non-neoplastic tissue from the resected kidney to determine chronic kidney disease (CKD). Since a solitary kidney has been considered an absolute contraindication to percutaneous biopsy, histologic diagnoses in the patients received nephrectomy would be an obstacle. In this study, we investigated the clinical value of pathologic examination of non-neoplastic tissue from the resected kidney to determine unrecognized kidney disease.

Methods: In the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6), we measured GFR as iohexol clearance and performed retinal photography in a representative sample of middle-aged persons from the general population without cardiovascular disease. Results: Of the 34 cases, 10 (29.4%) showed vascular diseases (7 hypertensive nephrosclerosis, 2 glomerulonephritis). During the median follow-up period of 9 months, 14 patients (46.7%) had died. None of the clinical variables was associated with the pathologic abnormality. 

Conclusions: The association of GFR estimated at dialysis initiation with mortality varies significantly and substantially according to measured concentrations of urea and creatinine. Late dialysis initiation is associated with elevated mortality risks in selected patient subgroups.

Funding: Private Foundation Support

TH-PO313

Clinical Value of Pathologic Examination of Non-Neoplastic Kidney in Patients with Upper Urinary Tract Malformations

Background: Despite surgical resection remains the standard care in the treatment of upper urinary tract malformations, nephrectomy is a recognized a risk factor for developing chronic kidney disease (CKD). Since a solitary kidney has been considered an absolute contraindication to percutaneous biopsy, histologic diagnoses in the patients received nephrectomy would be an obstacle. In this study, we investigated the clinical value of pathologic examination of non-neoplastic tissue from the resected kidney to determine unrecognized kidney disease.

Methods: Between January 2010 and July 2012, 32 patients with renal cell carcinoma and 2 patients with transitional cell carcinoma received nephrectomy or uninephrectorectomy. The routine pathologic evaluation of non-neoplastic tissue was performed.

Results: Out of 31 patients, only 9 patients (29%) had normal kidney. Thirty-four cases of pathologic diagnoses were obtained because 3 patients had dual diagnoses. Of the 34 cases, 10 (29.4%) showed vascular diseases (7 hypertensive nephrosclerosis, 3 ischemic nephropathy), 8 (23.5%) showed diabetic nephropathy, 6 (17.6%) showed glomerulonephritis (2 Iga nephropathy, 4 C1q nephropathy), and 1 case (3%) showed reflux nephropathy. During the median follow-up period of 9 months, 14 patients (46.7%) experienced post-operative acute kidney injury (AKI) and 10 patients (32.3%) progressed to CKD. Patients who experienced AKI had higher rates of developing CKD (p = 0.002, odds ratio 16.3). None of the clinical variables was associated with the pathologic abnormality.

Conclusions: Our study indicates that a routine pathologic examination of nephrectomized, non-neoplastic tissue will provide valuable information on the remnant kidney. Further studies based on a larger patient population will be needed to determine the influence of pathologic diagnoses on the long-term renal outcome.

TH-PO314

Early Detection of Kidney Disease in Children and Adolescents in Mexico: A Pilot Study

Background: Early detection of chronic kidney disease (CKD) is important to treat patients and prevent the progression to end stage kidney disease. The etiology of CKD is different in children and adolescents than in adult population, congenital anomalies (A/ Hypo dysplastic kidney, obstructive uropathy and reflux uropathy) and glomerulonephritis are the leading cause in pediatric patients, in contrast to adults where diabetes and hypertension are the main causes.

Methods: A pilot study was performed in Mexico City. Children and adolescents with any of the following risk factors were invited to participate: history of prematurity, history of urinary tract infection, history of acute renal injury, hypertension, obesity, weight or
height below 10th percentile for age and gender, ≥5 years with diabetes, familiar history of CKD (first grade). Patients with previous diagnosis of chronic kidney disease were excluded. Informed consent was obtained in all cases. A questionnaire was applied. Blood pressure, weight, height, abdominal circumference were measured. A urine sample was obtained for urinalysis and microalbumin/creatinine ratio. Blood sample was obtained for serum creatinine, blood gasometry, glucose, sodium, potassium, chloride, calcium, BUN, hemoglobin, hematocrit. Glomerular filtration rate was estimated with Schwartz formula.

Results: Eighty-eight participants were included, median age 10 years (range 1 month-18 years), 45 (52%) were female. The most common risk factors were family history of CKD in 33 (37.5%), prematurity in 18 (20.4%), obesity 14 (15.9%). Twenty-nine participants (33%) had an abnormal renal evaluation including one or more of the following: 12 (13.6%) had microalbuminuria, 8 had anemia (9%), 7 had hematuria (7.9%), 10 had hypertension (11.3%), 3 leukocyturia (3.4%), 1 renal glycosuria (1.1%), only two patients (2.2%) had eGFR<60ml/min/1.73m² (CKD stage 3). None had metabolic acidosis.

Conclusions: The prevalence of kidney disease was 33% in children with known risk factors. Early detection programs are useful to diagnose and prevent CKD progression in this population.

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

TH-PO314
Implementing Surveillance/Education Programs to Facilitate Timely Renal Referral in Chronic Kidney Disease
Nicole Pierro,1 Loretta Simbartl,1 Charuhas V. Thakar.1 Nephrology, VA Medical Center, Cincinnati, OH; 1Nephrology, Univ of Cincinnati, Cincinnati, OH.

Background: Referral to a renal subspecialty in patients with Stage IV chronic kidney disease (CKD4)glomerular filtration rate (GFR) < 30 ml/min/1.73m²) allows optimal management of conditions including end stage renal disease (ESRD) and permits timely renal referral in patients with Stage IV CKD.

We examined the impact of development and implementation of a surveillance/education program to facilitate timely renal referral followed by a shared care approach to manage CKD complications.

Methods: Within our Veterans Affairs healthcare system, starting Nov 2012, a customized informatics program compiles a monthly report of patients who have had 1 outpatient lab revealing a GFR < 30; we also identify demographics, comorbidities [e.g. hypertension, including home blood pressure (BP) monitoring], and renal evaluation in the prior 24 months. Concurrently, an educational program, led by nephrology and pharmacy is offered to primary care providers to raise awareness of CKD evaluation, and management of its complications. We compared (Chi-square) a historical cohort (2006 – 2010) with the 6-month implementation period (11/2012-04/2013) to evaluate improvement in renal referral in those with Stage IV CKD.

Results: In the historical cohort (42,942 veterans within our system) 79% patients were without CKD 19% with CKD Stage III, and 2% had CKD Stage IV. Compared to those without CKD, proportion of patients with renal referral in Stage III and Stage IV CKD was 35.7% and 47.6% respectively (p < 0.0001). Since the beginning of the surveillance program in Nov 2012 there were 348 patients with Stage IV CKD seeking care in our system, with 63% completing renal referrals. 97.4% of them had a diagnosis of hypertension, and 8% were enrolled in the program for home BP monitoring. After accounting for differences in demographics and comorbid conditions, renal referral during the implementation period was higher than historical period (63% vs 47.6%, p < 0.0001).

Conclusions: A combination of system-wide surveillance and education facilitates timely renal referral in patients with Stage IV CKD. This allows for increased opportunities for co-morbidity management and proper ESRD planning.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO315
The Cost Effectiveness of Primary Screening for Chronic Kidney Disease: A Systematic Review
Thomas W. Ferguson,1 Paul Komenda,2 Kerry Mcdonald,4 Claudio Rigatto,1 Manish M. Sood,5 Navdeep Tangri.1 1Community Health Sciences, Univ of Manitoba, Winnipeg, Canada; 2Nephrology, Seven Oaks General Hospital, Winnipeg, Canada; 3St. Boniface General Hospital, Winnipeg, Canada; 4Library Services, Univ of Manitoba, Winnipeg, Canada.

Background: Chronic Kidney Disease (CKD) is a major health problem with a rising incidence and prevalence worldwide. Data on the cost-effectiveness of CKD screening in the general population is lacking.

We conducted a comprehensive systematic review using the Cochrane Database of Systematic Reviews and 12 electronic databases. Data were extracted using standardised abstraction tools. Risk of bias was assessed using the Cochrane handbook. Heterogeneity was assessed using the I² statistic.

Results: Our systematic review included 20 RCTs, 5 cohort studies, 1 cross sectional study, and 1 expert opinion. The settings varied from healthy general population, primary care, dialysis population, to chronic diseases. The degree of improvement varied, from 13% to 100%.

Conclusions: The cost-effectiveness of CKD screening is variable, depending on the setting and the degree of improvement. Further research is needed to determine the most effective screening strategy for the general population.

Funding: None.
National Health Insurance System and it enabled physicians to use ESAs in non-dialytic CKD patients at half the previous cost. In this study, we investigated the prescription rate of ESAs and the status of anemia control before and after reimbursement.

Methods: Medical records of patients with non-dialytic CKD stage 4, 5 (eGFR <30ml/min/1.73m²) were reviewed in one tertiary medical center. The prescription of ESAs, Hb, estimated GFR, history of transfusion, and iron supplementation at 6 months before, 6 months and 12 months after the change of reimbursement criteria. 

Results: A total of 607 medical records were analyzed. The mean age of patients was 59.2 ± 14.5, and mean eGFR was 19.10 ± 6.80 ml/min/1.73m². The proportion of patients received ESAs was 20.6% before reimbursement while the proportion was increased to 37.5% at 6 months and 40.4% at 12 months after reimbursement (p <0.001). Especially, 36.9% of patients with Hb <10g/dl were prescribed ESAs before reimbursement, whereas 57.7%, and 64.0% of those patients at 6 months and 12 months after reimbursement (p <0.001). However, neither mean Hb nor the proportion of patients with Hb <10g/dl was changed. Mean Hb was 9.60 ± 1.97 g/dl before reimbursement, 9.34 ± 1.83 g/dl, and 9.71 ± 1.78 g/dl and at 6 months and 12 months after reimbursement (p=0.195). The proportion of patients with Hb <10 g/dl was 51.0% before reimbursement, 59.9%, and 56.8% at 6 months and 12 months after reimbursement (p=0.458). The requirement of red blood cell transfusion was 0.46 pint/person-year before reimbursement, 0.32 pint/person-year, and 0.15 pint/person-year at 6 months and at 12 months after reimbursement (p=0.001).

Conclusions: With reimbursement of ESAs in patients with non-dialytic CKD, the prescription rate of ESAs in the population was increased. Although mean hemoglobin levels did not change in the population, the requirement of red cell blood transfusion was significantly decreased.

TH-PO319
End-of-Life Cost Trajectories among Medicare Beneficiaries with End-Stage Renal Disease Ann M. O’Hare,1 William Kreuter,2 Paul Louis Hebert,3 Kenn B. Daratha.4 1Depts of Medicine and Health Services, VAPSHCS and Univ of Washington, Seattle, WA; 2School of Nursing, Washington State Univ, Spokane, WA.

Background: Little is known about trajectories of healthcare intensity before death among patients with ESRD.

Methods: We used group based trajectory modeling to describe cost trajectories during the year before death among adults who entered the USRDS registry between January 1, 1995 and December 31, 2007, had Medicare as primary payer for ESRD during the year before death and died before January 1, 2009 (n=199,120).

Results: We identified three groups of patients with distinct cost trajectories: those with late cost escalation, those with early cost escalation and those with persistently high costs (Figure).

Across these respective groups, median costs during the last year of life ranged from $57,513 to $187,476, median hospital days ranged from 7 to 44, median ICU days ranged from $57,513 to $157,476, median hospital days ranged from 7 to 44, median ICU days ranged from 7 to 44.

Conclusions: With reimbursement of ESAs in patients with non-dialytic CKD, the prescription rate of ESAs in the population was increased. Although mean hemoglobin levels did not change in the population, the requirement of red cell blood transfusion was significantly decreased.

TH-PO320
Trends in Timing and Indications for Chronic Dialysis within a Large U.S. Health System (2000-2009) Ann M. O’Hare,1,2 Bruce Wyman,3 Mark Perkins,1 Chun-fen Liu,1 1Jaclyn Lemon,2 Paul Louis Hebert,1 1,2Dept of Veterans Affairs, VA Health Services Research & Development Center of Excellence, Seattle, WA; 2Dept of Medicine, Univ of Washington, Seattle, WA; 3Dept of Health Services, Univ of Washington, Seattle, WA; 4Group Health Research Institute, Seattle, WA.

Background: Reasons for an upward trend in estimated glomerular filtration rate (eGFR) at the time of dialysis initiation are not known. Prior studies have been limited by an absence of information on clinical indications for dialysis.

Methods: To evaluate whether trends in eGFR at dialysis initiation reflect changes in indications for dialysis and/or timing of initiation, we reviewed the electronic medical records of a national random sample of patients who initiated chronic dialysis in the Department of Veterans Affairs (VA) in fiscal years (FY) 2000-09 (n=1,735).

Results: Between FY2000-04 and 2005-09, the percentage of patients with an eGFR<15ml/min/1.73 m² at initiation increased from 13.5 to 17.9% (P=0.012).

In both time periods, types of clinical indications were similar, as was the proportion of patients in which the decision to initiate dialysis was based only on level of renal function (27.6% vs. 29.1%, P=0.48). The adjusted odds ratio for initiation at an eGFR<15ml/min/1.73 m² in FY2005-09 vs. 2000-04 was 1.31 (95% confidence interval (CI) 0.99, 1.71) for the overall cohort, 0.84 (95% CI 0.48, 1.47) for those in whom the decision to initiate dialysis was based only on level of renal function, and 1.49 (95% CI 1.09, 2.05) for those with one or more clinical indications.

Conclusions: Recent trends in eGFR at initiation within the VA were driven by a selective tendency toward earlier initiation of dialysis among patients with clinical signs and symptoms, and did not reflect changing indications for dialysis or earlier initiation in asymptomatic patients.

Funding: Veterans Affairs Support

TH-PO321
Variability in Management of Hemodialysis Patients and Associated Healthcare Utilization Bjoerg Thorsteinssottir,1 Priya Ramar,2 Megan Reinalda,2 Robert C. Albright,1 Amy W. Williams,1 Nilay D. Shah.2 1Medicine, Mayo Clinic, Rochester, MN; 2Health Care Policy and Research, Mayo Clinic, Rochester, MN.

Background: With new efforts to define care models, it is essential to understand the impact of different providers on quality and resource utilization. We studied the role of nephrologists (Neph) and primary care physicians (PCP) in the care of hemodialysis(HD) patients in a health system serving a population of 395,000. Nephrologist presence varies between units, offering a natural experiment in the management of HD patients between PCP and Neph.

Methods: Patients initiating HD from 2001-2010 were linked to United States Renal Database System Medicare claims. Patients with <90 days follow up were followed as were services after a transplant. Outpatient (OP) visits were identified using CPT-4 codes and specialty. Mid-Level providers were grouped with Neph as most worked in HD. The proportion of PCP visits per person-year (ppy) was grouped into quartiles. We estimated the association between the quartile of PCP visits with hospitalizations, emergency department (ED) and other specialty visits.

Results:

<table>
<thead>
<tr>
<th>Groups*</th>
<th>25th percentile(N=399)</th>
<th>75th percentile(N=1,960)</th>
</tr>
</thead>
<tbody>
<tr>
<td>follow-up (ppy)</td>
<td>1.9</td>
<td>3.2**</td>
</tr>
<tr>
<td>Mean age(years)</td>
<td>56.0</td>
<td>61.0**</td>
</tr>
<tr>
<td>Male(%)</td>
<td>64.1</td>
<td>60.0**</td>
</tr>
<tr>
<td>Race(%)</td>
<td>84.1</td>
<td>78.0**</td>
</tr>
<tr>
<td>transplant(%)</td>
<td>3.5</td>
<td>2.5**</td>
</tr>
<tr>
<td>median survival years</td>
<td>4.2</td>
<td>6.0**</td>
</tr>
<tr>
<td>eGFR at start year of HD</td>
<td>3.9</td>
<td>5.9**</td>
</tr>
<tr>
<td>1.5 X upper ppy</td>
<td>0.0**</td>
<td></td>
</tr>
<tr>
<td>2.5 X upper ppy</td>
<td>0.0**</td>
<td></td>
</tr>
<tr>
<td>hospitalization ppy</td>
<td>0.0**</td>
<td></td>
</tr>
<tr>
<td>medical specialty ppy</td>
<td>0.0**</td>
<td></td>
</tr>
</tbody>
</table>

*Groups based on proportion of primary care E&M visits out of total E&M visits to primary care, mid-level/nephrology providers. **Denotes p-value < 0.05 when compared to <25th percentile group.

Funding: Private Foundation Support
Conclusions: Patients who get most of their care from primary care providers are older, sicker, utilize more resources, and have worse outcomes than those managed primarily by nephrologists. Further studies are needed to better understand the differences in these patient groups.

TH-PO322
Role of Meditation in Reducing Sympathetic Hyperactivity and Quality of Life in Lupus Nephritis Patients with Chronic Kidney Disease Sairawit Bantornwan, Nuttasith Larpparisuth, Tanyarat Tecaromanlert, Kriengsak Vareesangthip. Dept of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand.

Background: Lupus nephritis is an important leading cause of chronic kidney disease (CKD) among the young populat. Some physiological studies reveal that meditation may reduce sympathetic hyperactivity which is commonly found in SLE. We hypothesized that meditation could be beneficial in correcting autonomic dysfunction and improving quality of life in lupus nephritis patients with CKD.

Methods: We prospectively enrolled thirty lupus nephritis patients and categorized into two groups. Method of meditation was instructed by a expert in Buddhist studies every month. Participants in the intervention group were advised to meditate every day for 24 weeks. To evaluate the change in sympathetic activity, heart rate variability was measured at beginning and the end of study compared between both groups. Quality of life was determined by SF-36. Heart rate variability was also measured in meditation group at baseline and after practice.

Results: After meditation for 6 months, serum normetanephrine level decreased in both groups, but without statistically significant (p=0.28). In aspect of quality of life, score of physical and mental components improved significantly. In meditation group, physical score increased from 16.9 (4.4-60) to 72.4 (45.1-81.6) points (p=0.01) and mental score increased from 19.4 (10.4-49.2) to 55.4 (36.4-83.4) points (p=0.01) respectively, but quality of life score in meditation group increased more significantly (p=0.01). The parameter of heart rate variability in time and frequency domain also improved in meditation group.

Conclusions: In lupus nephritis patients with CKD, meditation reduced normetanephrine, improved quality of life and heart rate variability. Our results support the important role of meditation as a valuable adjunctive treatment of CKD from lupus nephritis.

Funding: Government Support - Ono-U.S.

TH-PO323

Background: Patient awareness of kidney disease is limited and varies related to clinical outcomes. Different methods to characterize awareness may contribute these inconsistent findings. Furthermore, little is known about the impact of a patient’s understanding of the severity of their chronic kidney disease (CKD).

Methods: In a cross-sectional study from May 2012 to July 2013, adults with CKD (eGFR<60 ml/min) seen in nephrology clinic were asked questions regarding their CKD diagnosis and its severity. Blood pressure (BP) readings were abstracted from the medical record.

Results: Among 252 patients the mean age was 57.9 (12) years, 42% were male, 17.3% were Black, and 13.2% had limited health literacy. Patients answered three awareness questions: “Do you have a problem with your kidneys?” (96% correct), “Do you have chronic kidney disease?” (80 % correct), and “Do you have decreased kidney function?” (84% correct). Thirty-six percent (p=0.01) correctly identified their CKD stage; 12% (n=30) agreed with 24-hr mSBP(70.8%). The 9:30PM was lesser agree(60.7%). By ROC curve, in evaluation of diagnostic values for hypertension, its standard is 135mmHg, 7am had the best(AUC: 0.843) and office mSBP had least(AUC: 0.774).

Conclusions: These data suggest that optimal time to measure BP in CKD patients may be 7AM in the morning, and 9:30PM in the evening. This shows that office mSBP is less useful than our time to measure BP.

Funding: Pharmaceutical Company Support - sanofi-aventis Korea Company

TH-PO324
The Optimal Time to Measure Blood Pressure as a Representative Value of 24-Hour Mean Blood Pressure Jiwon Ryu, Han-Hui Cha, Sunae Yoon, Dong-Ryol Ryu, Jeun Oh, Sejoong Kim, Sang Youb Han, Yon Su Kim. Internal Medicine, Seoul National Univ Bundang Hospital, Republic of Korea; Internal Medicine, National Medical Center; Internal Medicine, Catholic Univ College of Medicine; Internal Medicine, Ewha Womans Univ Adm. of Medicine; Internal Medicine, Hannam Univ College of Medicine; Internal Medicine, Inje Univ College of Medicine; Internal Medicine, Soon Chun Hyang Univ College of Medicine; Internal Medicine, Seogang National Univ College of Medicine; Kidney Research Institute, Seoul National Univ Medical Research Center.

Background: Hypertension is important treatment target in chronic kidney disease(CKD). 24 hours blood pressure(BP) is gold standard to measure high BP, but, which is quite discomfortable. However representative time for BP as a 24-hrs BP in CKD patients is still unknown.

Methods: We evaluated whether there may be proper time to measure BP for predicting the average of 24 hrs BP in CKD patients(stage 2-4) from the multicenter, cross-sectional study (n, 1317; mean age, 57 years; men, 62.9%).

Results: Regression analysis showed that systolic BP(7AM) at the 7AM and 9:30PM are best agreed with the 24-hr mean mSBP(mSBP)=0.677, r=0.656, respectively. The proportion of patients within 30% of 24-hr mSBP was the most at 7AM(95.6%) and then 9:30PM(95.5%). Among corresponding values of BP to 135mmHg by calculation with regression, 7AM was the closest(36.74mmHg), 9:30PM was the next(138.78mmHg), office mSBP was the last(142.61mmHg).

Conclusions: We advise patients should consider 7AM in the morning, and 9:30PM in the evening. This shows that office mSBP is less useful than our time to measure BP.

Funding: Pharmaceutical Company Support - sanofi-aventis Korea Company

TH-PO325
Seroversion Rates following Intradermal and Intramuscular Hepatitis B Vaccine in Hemodialysis Patients Not Responding to Primary Vaccination Protocol – A Review of Prospective Trials Aliva Saeed, Farhanah Yousaf, Barraclough et al, Smith Kline & Beecham

Background: The response to Hepatitis B vaccine in dialysis population is reduced. Alternative route of vaccine administration may elicit a response via a distinct immunologic pathway that may help achieve seroconversion.

Methods: We performed a literature search using Medline with Mesh terms including “hepatitis B”, “hepatitis B vaccines,” and “injections, intradermal.” The inclusion criteria was any prospective trial comparing seroconversion rates defined as antibody titer of > 10 IU/L immediately(1-3 months), 6 months, or at 12 months after the completion of intradermal (ID) and intramuscular (IM) administration of a fixed hepatitis B vaccination protocol in previously non-responding dialysis patients.

Results: Four of 158 studies met inclusion criteria. A total of 204 patients were studied, 120 of whom received ID hepatitis B vaccine while 84 received IM. At 1-3 months, 6 months, and 12 months, the mean seroconversion rate in ID group was 85%, 70%, and 61% versus mean seroconversion rates of 64%, 61%, and 28% in IM group, respectively.

Conclusions: ID vaccination may achieve higher seroconversion rate and the effect may be maintained longer versus IM vaccination. Additional trials are needed to elaborate the role of ID vaccination in previous non-responding hemodialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Volume-Outcome Relationship in Percutaneous Native Renal Biopsy

Background: Hemorrhagic complication remains the major complication of percutaneous renal biopsy. Our aims in this study are to identify individual-level risk factors relating to hemorrhagic complications of the procedure, and to investigate a volume-outcome relationship after adjusting for these risk factors.

Methods: Using a large claim-based data called Diagnosis Procedure Combination (DPC) database in Japan, we identified inpatients with renal disorders who underwent percutaneous biopsy within four days after admission during July to December in years 2007 to 2010 (total 24 months). Patients were classified by age, sex, clinical syndromes (chronic nephritic syndrome, nephrotic syndrome, rapidly progressive nephritic syndrome, recurrent or persistent hematuria, acute nephritic syndrome and other disorders), and quintiles of hospital volume of the biopsy. Generalized estimation equation was used to account for clustering of patients at institutional levels.

Results: A total of 15191 patients from 942 hospitals were enrolled to this study. Overall hemorrhagic complication incidence was 2.1%, including hemorrhagic events on ICD codes (1.6%); red blood cell transfusion (0.5%); required angiography or endovascular procedure (0.1%); surgical interventions (0%). In-hospital deaths with hemorrhagic complications were observed in 0.06% of the patients. Significantly high complication incidence was observed in patients group younger than 30 (adjusted OR 1.97, 95% CI 1.39-2.80), and those aged 60 and over (adjusted OR 1.64, 95% CI 1.15-2.36) with reference to middle-aged patients group. Patients who had rapidly progressive nephritic syndrome (adjusted OR 3.41, 95% CI 2.23-5.25) had significantly higher hemorrhagic complication incidence with reference to patients who had chronic nephritic syndrome. No significant difference was observed across the hospital volume groups after adjustment of patient-level variables.

Conclusions: This study finds no significant volume-outcome relationships in hemorrhagic complication.

Funding: Government Support - Non-U.S.

A Pilot Quality Improvement Program to Minimize Catheter-Related Bloodstream Infection in an Outpatient Hemodialysis Setting

Background: The Technical and adaptive approaches from the Johns Hopkins University Armstrong Institute have reduced catheter-related bloodstream infection (CRBSI) in hospitals.

Methods: To evaluate whether similar approaches could prevent CRBSI in chronic dialysis patients, we conducted a collaborative, multifaceted, quality improvement program in 26 Maryland-area DaVita hemodialysis facilities. We used the Armstrong Comprehensive Unit-based Safety Program (CUSP) to survey elements of culture and practice in patient safety, adapted tools and interventions for the dialysis setting, and monitored CRBSI rates.

Results: The survey was completed by 431/497 teammates (TMs; employees). We found areas for systematic improvement in pre-, intra-, and post-dialysis central venous catheter (CVC) care from the medical literature. We created a procedural kit with checklist, antimicrobial swabs for skin prep, triple-antibiotic ointment for exit site application, alcohol swabs to facilitate hub scrub, and exit site dressing. Another kit/procedural checklist was obtained with this method are comparable to those achieved in randomised controlled trials of antimicrobial interventions.

Conclusions: Safety assessment tools and interventional approaches that reduce CRBSI in hospitals can be successfully applied to reduce CRBSI in chronic dialysis facilities.

Funding: Government Support - Non-U.S.

Reduction in Catheter-Related Bacteremia in a Renal Network Using Quality Improvement Methodology

Background: Haemodialysis catheter related bacteremia remains a significant safety issue in HD care. Despite initiatives to increase definitive access, 30% of patients in the UK still use catheters for haemodialysis. In two of our dialysis units we had 36 catheter-related bacteremias in 12 months at baseline, resulting in 24 admissions, 296 bed days and 3 transfers to level 3 care, despite evidence-based interventions such as antimicrobial line locks to reduce infections.

Methods: We sought to improve our catheter-related bacteremia rate using multifaceted interventions learned from best available evidence and learning from best practice in improvement collaborative over a two year period. We used plan-do-study-act (PDSA) cycles to rapidly introduce small scale changes and implement them fully if successful. This method allowed frontline staff to learn from each other and share their experience of improvement. Successful changes were compiled into a change package for use elsewhere in our network. Data was collected prospectively for a formal evaluation of our work.

Results: Our units tested and implemented multiple changes including: dressing care, exit site and bacteremia database, traffic light system and an algorithm for high-risk HD catheters, nurse-led antimicrobial protocols and patient information leaflets.

The total number of catheter-related bacteremias decreased by 83% (36 to 5). There was a significant reduction in admissions (24 to 5) and bed days (296 to 108). No patient required level 3 care. Our bacteremia rate decreased by 78% from 1.8 to 0.4 per 1000 catheter days (p<0.01) over the 2-year cycle. This has been sustained for 7 months since the end of the project, at 0.57 per 1000 catheter days.

Conclusions: We have demonstrated a significant improvement in our catheter-related bacteremia rate. This was achieved by staff being given the responsibility and power to change practice within an improvement framework. Critically, we have also begun to achieve a change in our culture and attitude to preventable harm from bacteremia. Results obtained with this method are comparable to those achieved in randomised controlled trials of antimicrobial interventions.
Methods: We conducted a prospective cohort study including a total of 720 consecutive chronic kidney disease patients being seen on an outpatient basis at the St. Luke’s International Hospital (Tokyo, Japan) between April 2012 and March 2013. Admitted patients receiving a CT or those undergoing hemodialysis or emergency CT were excluded (n=507). Our CIN prevention program consists of (1) an automatic alerting system when a physician orders enhanced CT for patients with GFR less than 45 mL/min/1.73m2, (2) an automatic nephrologist referral to order prophylactic saline hydration and follow-up, and (3) monthly quality indicator (QI) measurements and feedback to physicians. The percentage of patients with eGFR<60 ml/min/1.73m2 who received appropriate prophylactic saline hydration before and after CT and nephrologists’ follow-up were selected as quality indicators and were reported monthly.

Results: The mean age of the study participants was 73.8±9.6 years and comprised of 65.3% males and an average eGFR of 35.6±10.4 ml/min/1.73m2. Implementation rates of the protocol improved from 0.0% to 40.7%, and the hydration performed rates improved from 20.0% on April 2012 to 74.1% on March 2013. The two patients developed CIN (1.8%). The rate was relatively lower than that of previous studies.

Conclusions: To close the evidence-practice gap of contrast-induced nephropathy, hospital-wide prevention programs and monthly QI measurements and reporting can enhance overall adopted practice, reduce the incidence of CIN, and increase the appropriate use of enhanced CT.

TH-PO331
Chronic Kidney Disease in Primary Care: Assessing the Role for Sub-Specialty Co-Management
John Andrew Updike, George P. Bayliss. Medicine, Rhode Island Hospital, Providence, RI.

Background: This study sought to determine whether nephrology sub-specialty co-management of chronic kidney disease (CKD) positively affects adherence to the Kidney Disease Outcomes and Quality Initiative practice guidelines and whether co-management affects screening and treatment independent of CKD severity or identification of disease by the primary care provider as evidenced by a designated ICD-9 code.

Methods: A retrospective cohort study of 160 patients with at least one provider visit at the Rhode Island Hospital Medical Primary Care Unit resident trainee clinic between Feb, 1, 2012, and Feb, 1, 2013, with an eGFR<60 ml/min/1.73m2 on two lab draws 3 months apart. Independent variables included age; gender; severity of renal impairment; nephrology sub-specialty referral; co-management correspondence; ICD-9 coding; KDOQI recommended annual assessment of anemia, nutrition, bone health, electrolytes, kidney disease progression; treatment with Angiotensin converting enzyme inhibitor or receptor blocker.

Results: 90% of patients had stage III CKD. 26% were co-managed with nephrology sub-specialists. Documented correspondence was present in only 53% of these patients. Only 54% of patients had ICD-9 codes documenting CKD. Serum creatinine level and the presence of Stage IV CKD demonstrated significant logistic fit between nephrology referrals (p<0.001, p<0.0001), co-management (p<0.0001, p<0.0015) and ICD-9 documentation (p<0.0003, p<0.0018). There were significant one-way comparisons between ICD-9 documentation and nephrology referrals (p<0.0001) and co-management (p<0.0001), Multivariate analysis showed nephrology co-management to be an independent predictor of screening for bone health (serum phosphorus, p<0.037; serum PTI, p<0.0088) and anemia (hemoglobin, p<0.012).

Conclusions: There are significant correlations between adherence to screening recommendations and identification, documentation and sub-specialist CKD co-management in the primary care setting. Nephrology co-management independently affects bone health and anemia screening. Further work should be directed at assisting medical residents identify patients with stage III CKD and increase the percentage of successful nephrology referrals.

Funding: Clinical Revenue Support

TH-PO332
Multidisciplinary Intervention Model Is Better Than Conventional Health-Care and Nurse-Coordination Models in the Management of Early CKD in Type 2 Diabetes Mellitus

Background: Multidisciplinary approach could optimize care in early CKD. Aim: to compare the effect of a multiple intervention model (MIM); conventional health-care model (CHCM); nurse-coordinated model (NCM) on lifestyle and renal function of DM2 patients and early CKD.

Methods: MIM was carried out in a Family Medicine Unit with patients receiving an educational intervention, by multidisciplinary team: social worker, dietitian, physical trainer and family physician (FP) for 4 wks, and supported by self-help groups; in other unit, NCM was seen by a nurse, focused on individual’s needs; CHCM were managed by FP. Patients had lifestyle, clinical, biochemical evaluations and follow up by 12 months. Max. score of lifestyle questionnaire is 100. All FP had course in early CKD.

Results: Comparison of delta results

<table>
<thead>
<tr>
<th>Lifestyle Questionnaire</th>
<th>MIM</th>
<th>NCM</th>
<th>CHCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients %</td>
<td>88%</td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td>Adherence to treatment</td>
<td>65 ± 5.4</td>
<td>91 ± 4.7</td>
<td>92 ± 3.7</td>
</tr>
<tr>
<td>Weight management</td>
<td>86 ± 5.5</td>
<td>4.4 ± 4.9</td>
<td>70 ± 3.6</td>
</tr>
<tr>
<td>Tobacco consumption</td>
<td>90 ± 1.5</td>
<td>91 ± 2.9</td>
<td>90 ± 1.9</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>77 ± 2.3</td>
<td>96 ± 2.3</td>
<td>76 ± 2.6</td>
</tr>
<tr>
<td>Total score</td>
<td>12 ± 2.9</td>
<td>2.2 ± 1.9</td>
<td>9 ± 1.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical and Biochemical Variables</th>
<th>MIM</th>
<th>NCM</th>
<th>CHCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb A1c (%)</td>
<td>1.8 ± 2.0</td>
<td>0.3 ± 1.9</td>
<td>0.3 ± 2.0</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>5 ± 13*</td>
<td>0.3 ± 11</td>
<td>3 ± 9*</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>27 ± 1.6*</td>
<td>27 ± 2.5</td>
<td>26 ± 1.6</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>53 ± 15</td>
<td>0.3 ± 22</td>
<td>5.7 ± 16</td>
</tr>
<tr>
<td>Albuminuria (mg/µl)</td>
<td>28 ± 1.98*</td>
<td>2.2 ± 13</td>
<td>19 ± 13</td>
</tr>
</tbody>
</table>

MIM could improve the lifestyle habits of patients with DM2 and early CKD and preserve better renal function than NCM and CHCM.

TH-PO333
PRIMED for Patient Care: Multi-Disciplinary Simulation-Based Team Training Develops Staff Confidence and Skills in Managing Dialysis Emergencies
Laura E.A. Harrison, Katie Fielding, Richard J. Fluck, Lindsay J. Chesterton. Renal Medicine, Royal Derby Hospital, Derby, United Kingdom.

Background: Emergency situations can occur frequently during haemodialysis (HD) treatments and present a number of specific challenges to ensuring best patient outcomes. Realistic relevant simulation training can improve clinical knowledge and technical skills and strengthen communication and team behaviour, with a resulting improvement in patient safety.

Methods: We designed a simulation-based team education programme, PRactical Interdisciplinary Management of Emergencies on Dialysis (PRIMED) training, which has been delivered to over 100 renal staff (53% nurses, 16% doctors, 31% HD support workers).

Clinical emergency scenarios take place in the dialysis unit with a Laerdal SimMan® 3G, standard HD machine and a dummy HD treatment. Session format includes facilitated debrief and feedback, with the opportunity for further guided, hands-on practice. Impact on staff confidence and skills was assessed using Likert-based evaluation forms, coupled with audit of weekly emergency buzzer calls.

Results: More staff felt confident in their management of emergencies during HD after PRIMED training (70% pre, 89% post). 95% of staff felt the training had a beneficial effect on their clinical practice. Composite confidence score was 44/55 pre-session, 48/55 post-session and 50/55 at follow-up, p=0.04. Staff confidence increased collectively in 2-3 specific areas after individual sessions, dependent on clinical and human factors highlighted in the session, including information handover, management of the HD machine, leadership and decision-making. There was a significant decrease in emergency buzzer use from 25% to 0-3/week.

Conclusions: PRIMED is an innovative workplace based simulation programme that aims to equip all renal team members with a structured approach to the recognition, assessment and management of the acutely unwell patient on HD. Implementation has improved confidence across the spectrum of staff involved in dialysis. Frequency of emergency calls has fallen, potentially related to earlier recognition and treatment of unwell patients. Further work is ongoing to assess the impact on patient care and clinical practice.

TH-PO334
Podocalyxin Regulates Pronephric Glomerular Development in Zebrafish
Tomoaki Obara. Cell Biology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background: Vertebrate glomerular podocytes possess a highly sialylated transmembrane glycoprotein, Podocalyxin. In mammals, the sialic acid of Podocalyxin plays a crucial role in the formation of the characteristic podocyte architecture required for glomerular filtration.

Methods: To explore the possibility, we examined the function of Podocalyxin in the developing zebrafish pronephros by disrupting the expression of podocalyxin through the use of morpholino antisense oligonucleotides.

Results: Podocalyxin was localized at the apical membrane of podocytes throughout sh pronephric development. Translational blocking of podocalyxin expression resulted in pericardial edema and a hypoplastic glomerulus. Whereas regular foot processes with a slit diaphragm covered 66.7 ± 7.8% of the urinary surface of glomerular basement membrane, only 14.4 ± 7.5% of this area was covered with regular foot processes in the translationally blocked morphants. Splice blocking of podocalyxin exon 2, which partially encodes the bulky mucin domain containing sequence from podocalyxin mRNA. Approximately 40% of these splice-blocked morphants had mild pericardial edema. Although the pronephric glomeruli in the splice-blocked morphants exhibited almost normal appearance with developed glomerular capillaries and mesangium, they had only 36.3 ± 6.9% of the area covered with regular foot processes.

Conclusions: Podocalyxin is predominantly expressed in the podocytes and plays a distinct role in the formation of the podocyte foot processes with a slit diaphragm during zebrafish pronephric development.
TH-PO335

Zebrafish Pronephros Tubulogenesis Is Reliant on the Protein Complex Prkc Iota and Zeta

Gary F. Gerlach, Rebecca A. Wingert. Dept of Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: The zebrafish pronephros provides an excellent in vivo renal system to study the mechanisms of vertebrate nephrogenesis. When and how renal progenitors undergo tubulogenesis to form nephrons is poorly understood, but is known to involve a mesenchymal to epithelial transition (MET) and the acquisition of polarity. Early studies determined the precise timing of these critical events during pronephros tubulogenesis, and documented that lumen formation is preceded by the apical and basolateral segregation of proteins. As the ternary polarity complex is an essential regulator of epithelial cell polarity across tissues, we performed gene knockdown studies to assess the roles of the related factors protein kinase C iota (prkc.iota) and zeta (prkc.zeta), which exhibited tight localization to the nephron epithelium apical surface prior to lumen formation and maintained this localization within the fully developed nephron.

Results: Nephron epithelial cells in prkc.iota/zeta morphants had disrupted polarity, with aberrant localization of phospho-ERM and Nck, a kinase that regulates MET, at their respective basolateral domains, and the actin cytoskeleton displayed a disordered arrangement. In addition, prkc.iota/zeta morphants had dramatic defects in nephron tubule morphogenesis, with the proximal tubule failing to undergo normal convolutions. prkc.iota/zeta morphants showed several deficiencies in nephron functionality, including aborted renal clearance and proximal tubule dextran uptake, a measure of endocytosis. Surprisingly, tubule cells in prkc.iota/zeta morphants displayed ectopic expression of podocyte-specific genes, including wif1, wtb1, and podc1-like.

Conclusions: These data suggest a model in which the redundant activities of prkc.iota and prkc.zeta are essential to establish polarity and also maintain proper epithelial cell-type identity in the nephron tubule. Our studies provide a useful foundation for further analysis of MET during nephrogenesis, and have implications for understanding the pathways that affect nephron epithelial cells during kidney disease and regeneration.

Funding: NIDDK Support, Other NIH Support - NIH Director’s Innovation Grant

TH-PO336

mecom Is Essential for Proximodistal Segmentation and Epithelial Cell Fate Choice in the Zebrafish Pronephros

Yue Li, Christina N. Cheng, Valerie Verdun, Rebecca A. Wingert. Dept of Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: The zebrafish pronephros provides a conserved developmental model to study nephrogenesis, in particular to delineate the poorly understood processes of proximodistal (PD) patterning and distal segment patterning, and that MCC fate choice is modulated by a complex interplay of MET during nephrogenesis.

Methods: To study the mechanisms of vertebrate nephrogenesis, in particular to delineate the poorly understood processes of proximodistal (PD) patterning and distal segment patterning, and that MCC fate choice is modulated by a complex interplay of MET during nephrogenesis. We incubated rat metanephric mesenchyme with growth factors that elicited expression of the single-minded homologue 1a (sim1a) expression is dynamic during nephrogenesis and ultimately maintained in both the proximal tubule segments (PCT, PST) along with the cluster of CS progenitors.

Results: These findings suggest that sim1a might have roles in nephron segment patterning and CS formation. We performed functional analysis of sim1a using morpholino knockdowns. sim1a deficiency caused an expansion of the PCT and an abrogation of the PST and CS populations. However, the domains of both the DE and DL segments were unchanged. These results suggest that sim1a activity is necessary to pattern the PST and CS, and may negotiate the PCT/PST boundary, possibly by inhibiting PCT fate choice.

Conclusions: Taken together, our study has revealed novel roles for sim1a during nephrogenesis. These findings provide useful insights into the genetic pathways that direct nephron development, and may have implications for understanding the causes of renal birth defects in humans.

Funding: NIDDK Support, Other NIH Support - NIH Director’s Innovation Grant

TH-PO338

Development of Intercalated Cells Requires Transcription Factor CP2l1

Max Werth, Kai M. Schmidt-Ott, Andong Qiu, Jonathan M. Barasch. 1 Medicine, Columbia Univ, New York, NY; 2 Max-Delbrueck Center for Molecular Medicine, Berlin, Germany; 3 Tongji Univ, Shanghai, China.

Background: Kidney epithelia derive from metanephric mesenchyme by a process that includes epithelial conversion followed by specification of different epithelial cell types. Little is known about how multiple cell types come to occupy the collecting ducts. Here we investigated a transcription factor that was induced during tubulogenesis.

Methods: To identify genes that regulate specific cell types, we created an in vitro model of nephrogenesis. We incubated rat metanephric mesenchyme with growth factors that elicit epithelial conversion. We identified transcription factors that were regulated during epithelial conversion. We next over-expressed each of these factors in the metanephric mesenchyme using adenoviral-mediated gene transfer and found that only one transcription factor induced conversion, the Grainyhead family member, Cp2l1. We then generated kidney-specific knockout of Cp2l1.

Results: During development Cp2l1 was expressed in distal parts of s-shaped bodies and in the ureteric bud. In the adult Cp2l1 was observed in the loop of henle, distal convulated tubule and collecting ducts. In the conditional knockout we observed the complete absence of alpha- and beta-Intercalated Cells and their markers and instead we observed a monotonous pattern of principal cell-like epithelia. To further investigate Cp2l1 function we compared ChIP-seq with gene expression data from Cp2l1 knockouts. The comparison yielded 82 genes that were significantly downregulated in the knockouts and contained Cp2l1 binding sites within 10KB of the transcriptional start site. Many of these genes were components of mature intercalated cells, confirming a direct role for Cp2l1 in regulating intercalated cells differentiation. Moreover, both gene expression and ChIP-seq data suggested that Cp2l1 regulates the patterning of Notch signaling throughout the collecting duct.

Conclusions: Taking together, this data implicate that Cp2l1 plays a continuing role in the establishment and maintenance of the kidney intercalated cells.

Funding: NIDDK Support

TH-PO339

Ureteropelvic Junction Obstructions in Mice with Conditional Inactivation of Exocyst Sec10 in Kidney and Upper Urinary Tract Epithelium

Noemi Polgar,1 Vanessa H. Lui,1 Amanda J. Lee,1 Xiaofeng Zuo,2 Joshua H. Lewis,1 Ben Fogelgren,1 Anatomy, Biochemistry, and Physiology, Univ of Hawaii; 2 Medicine, Univ of Pennsylvania.

Background: Congenital obstructive nephropathy, the most common cause of pediatric end-stage kidney disease, is caused by obstruction of the ureteric tract during fetal development. The most common cause of congenital obstructive nephropathy is ureteropelvic junction obstruction (UPJ obstruction), which the stenosis is localized to the upper urinary tract where the renal pelvis transitions into the ureter. Despite the high prevalence and medical burden of UPJ obstructions, we have a poor understanding of its molecular and genetic basis, with a scarcity of non-surgical genetic animal models.

Methods: In previous studies using cell culture models, we have shown the eight-protein exocyst trafficking complex to be critical in maintaining aspects of polarized epithelial cells. To further in vivo studies of polarized exocytosis in renal development and disease, we have generated a novel transgenic mouse model to conditionally knockout Sec10, a central component of the exocyst. This is the first conditional mouse strain for any exocyst subunit, and should be valuable in studying the exocyst’s role in various tissues and diseases.

Results: We crossed this Sec10 conditional knockout mouse strain to induce a knockout in Sec10 specifically in ureteric bud-derived epithelial cells during development. Surprisingly, 90% of the Sec10−/−;Ksp-Cre conditional knockout mice died quickly after birth, displaying severe bilateral hydronephrosis due to congenital obstructions of the upper urinary tract. From histological analysis, these blockages were due to an overgrowth of the surrounding smooth muscle cells at the UPJ, with complete disappearance of the ureter lumen.

Conclusions: This novel transgenic mouse model of UPJ obstruction may be valuable for further studies of the causes and consequences of human congenital obstructive nephropathy.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
TH-PO340
Bmp7 Maintains Undifferentiated Kidney Progenitor Population and Determines Nephron Numbers at Birth
Motoko Yanagita, Mayumi Tomita, Misako Asada, Nariaki Asada, Jin Nakamura, Akiko Oguchi, Atsuko Y. Higashi, Shuichi Endo, Ais N. Economides. 1 2 3

Methods: We utilized conditional-null allele of Bmp7 in combination with systemic inducible Cre deleter mice in order to analyze Bmp7 function at desired time points during kidney development. We also employed kidney explants culture system and colony-forming assays to investigate the inhibitory effect of Bmp7 on epithelialization of the progenitor cells. Results: Systemic knockout of Bmp7 in vivo after the initiation of kidney development resulted in the precocious differentiation of the kidney progenitor cells to nephron (glomeruli and tubules), in addition to the prominent apoptosis and the reduction of progenitor cells. Quantitative assessment also confirmed that knocking out of Bmp7 in kidney explants culture resulted in accelerated differentiation of progenitor population, and the same effect could be imparted by inhibiting Shh signaling in wild-type kidney explants. Finally colony-forming assays demonstrated that Bmp7 inhibited epithelialization of the progenitor cells. Conclusions: During embryonic development, Bmp7 acts on progenitor cells as an anti-apoptosis and anti-differentiation factor, and thereby coordinate maintains the renal progenitor pool in an undifferentiated status, and determines the nephron number at birth. Funding: Government Support - Non-U.S.

TH-PO341
Preterm Birth: Kidney Size and Function in Early Adulthood
Megan B. Sutherland, Catherine Fallaha, Anne-Laure Lapeyraque, Fanny Huizard, Marianne Bertagnolli, Anik Cloutier, ThuY Mai Lua, Anne Monique Nuyt. 1 2

Methods: In early adulthood, both renal size (significantly greater GFR compared to the term-born controls) and the intercalated cell/collecting duct ratio, and decreased expression of the intercalated cell master regulator, Foxi1. Results: Young adult born preterm at ~29 weeks gestation (~9 male, 11 female), between 1987-1993 (Montreal, Quebec), were compared to age-matched controls born at term (~7 = 13 female). Morning blood and urine samples were assessed for creatinine levels and microalbuminuria; GFR was estimated using the MDRD equation. Ultrasonography was performed to measure kidney size, and to determine the resistivity index (RI) of the renal arteries.

Results: Subjects born preterm had a significantly greater GFR compared to the term-born controls, particularly the females (males: control 93.8 ± 8.4, preterm 104.8 ± 5.3 ml/min/1.73 m2; females: control 107.5 ± 4.8, preterm 122.7 ± 12.2 ml/min/1.73 m2). There was no significant difference in the albumin:creatinine ratio between groups (control: 0.70 ± 0.07 mg/mmol; preterm: 0.67 ± 0.09 mg/mmol). Significant reductions in both absolute and relative kidney size were observed in the preterm group compared to the controls, but no difference in the relative volume of the left kidney. There was no difference between the groups in the RI of the renal arteries.

Methods: In early adulthood, both renal size (significantly reduced) and function (possible hyperfiltration) were affected by preterm birth. In the long-term, these changes have the potential to predispose to renal disease. Funding: Government Support - Non-U.S.

TH-PO342
The Super Kidney: Putting the Foundation for the Future
Ashraf El-Meanawy, Sterling E. Udom, Adil Jadoon. 1 2

Background: The molecular mechanisms determining nephron number during embryogenesis have not yet been clarified. Germline knockout of bone morphogenetic protein 7 (Bmp7) results in massive apoptosis of the kidney progenitor cells and defects in early stages of nephrogenesis. This phenotype has precluded analysis of Bmp7 function in the later stage of nephrogenesis.

Methods: Knocking out of Bmp7 in kidney explants culture resulted in accelerated differentiation of progenitor population, and the same effect could be imparted by inhibiting Shh signaling in wild-type kidney explants. Finally colony-forming assays demonstrated that Bmp7 inhibited epithelialization of the progenitor cells. Results: During embryonic development, Bmp7 acts on progenitor cells as an anti-apoptosis and anti-differentiation factor, and thereby coordinate maintains the renal progenitor pool in an undifferentiated status, and determines the nephron number at birth. Funding: Government Support - Non-U.S.

TH-PO343
Modulation of Maternal Light Exposure Affects Circadian Gene Expression in Fetal Kidneys
Krivtznna Meszaros, 1 Linda Pruess, Matthias Gordan, Eberhard Ritz, 2 Franz S. Schaefer, 3 Ashraf El-Meanawy, Sterling E. Udom, Adil Jadoon. 4

Methods: Pregnant SD rats were randomly allocated to different light patterns (12h:12h (LD), constant light (LL) and constant darkness (DD)) with free access to food and water at constant temperature. Mothers (6-10 per group) with their offspring were sacrificed at 4-h intervals one day before the expected delivery. Intrarenal circadian gene expression patterns were profiled by RT-PCR for the canonical clock gene Clock, Per1, Cry1, Cry2 and the clock-controlled genes eNac, NHE3, BSC1, AFR2 and SGK1.

Results: Pups from mothers kept at LD displayed circadian expression of the core clock gene Clock (p<0.01) and the clock-controlled genes eNac (p=0.001) and NHE3 (p<0.001). Kidneys of fetuses from mothers exposed to LL exhibited circadian expression of Clock (p<0.01), Per1 (p<0.05), Cry2 (p<0.03), eNac (p<0.001), SGK1 (p<0.001), NHE3 (p<0.001), BSC1 (p<0.01) and AFR2 (p<0.05). In contrast, fetal kidneys with maternal DD exposure completely lacked circadian variations of intrarenal gene expression.

Conclusions: Circadian expression of clock and clock controlled genes is present even before birth in the developing kidney and differentially affected by modulation of light exposure. Maternal exposure to constant light enhances, whereas constant darkness suppresses the development of circadian gene expression in the fetal kidney.

TH-PO344
Abstract Withdrawn

TH-PO345
The Histone H3K79 Methyltransferase, Dot1l, Regulates the Fate of Ureteric Bud Tip Cells
Fenglin Wang, Xiao Yao, Zibaida R. Saffiedin, Samir S. El-Dahr. 1 2

Background: Ureteric bud tip cells (UB-TCT) act as progenitors during branching morphogenesis by generating daughter tip and trunk cells. Current models suggest that UB epithelial progenitors give rise to plastic cellular lineages, which have the potential to give rise to intercalated cells. This process is restricted epigenetically by the histone H3K79 methyltransferase, Dot1l. The role of Dot1l in UB-TCT fate is unknown.

Methods: 1. Developmental expression of Dot1l and H3K79me2 was determined by QPCR, immunofluorescence and Western blots; 2. The role of Dot1l in the UB lineage was examined by crossing Hoxb7-Cre:GFP and Dot1l(fl/fl) mice and progeny was examined at E12.5-P1; 3. The renal phenotype was analyzed by section IF and IHC.

Results: 1. p63, a master regulator of epithelial cell differentiation in skin and prostate, marks a subset of Ret + UB-TC. p63+ cells display two distinctive features: transient expression of Foxi1, a lower intercalated cell/collecting duct ratio, and decreased expression of the intercalated cell master regulator, Foxi1. This marks a subset of Ret + UB-TC. p63+ cells display two distinctive features: transient expression of Foxi1, a lower intercalated cell/collecting duct ratio, and decreased expression of the intercalated cell master regulator, Foxi1. 3. Loss of H3K79me2 in UB lineage increases the number of p63+ cells; this effect is preceded by premature onset of p63 expression at E12.5, expansion of the Ret + population and increased number of dividing (ph3+) cells in terminal ampulla. UB branch number and overall kidney size are not affected by Dot1l deletion.

4. At P1, elongating collecting ducts lacking H3K79me2 exhibit ectopic presence of p63+ cells, a lower intercalated cell/collection duct ratio, and decreased expression of the intercalated cell master regulator, Foxi1.

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

Underline represents presenting author/disclosure.

181A
Conclusions: 1. Chromatin-based mechanisms mediated via Dott/H3K79 methylation control the terminal differentiation fate of UB-TC. 2. In the absence of Dott1, p63+ UB-TC proliferate and later generate elongating collecting ducts. 3. Dot1i deletion disrupts the balance between p63 vs Fox1, which may determine the fate of collecting duct precursor cell types.  
Funding: NIDDK Support

**TH-PO346**
Ureteric Bud Branching Is Suppressed by the Loss of Trps1 due to the Activation of TGF-β Signaling  
Ting Gui, Yasutera Muragaki, Gengxin Zhou. 
1 Pathology Dept, The Medical School of Shandong Univ, Jinan, Shandong, China; 2 The First Dept of Pathology, Wakayama Medical Univ, Wakayama, Japan.

Background: We previously found that ureteric bud branching is suppressed in the embryos of Trps1-deficient (KO) mice (published in JASN, 2011). However, how Trps1 is involved in UB branching remains unknown.  
Methods: E11.5 ureteric bud and E12.5 whole kidney exposing culture with smad3 and smad4 mutants from E11.5 kidneys of WT and KO embryos, we found abnormal expression of genes associated with the transforming growth factor (TGF)-β/Smad signaling pathway in the KO UBs. Western blot and immunohistochemical analyses showed increased levels of Rb1cc1, Arkadia1, and phosphorlated Smad3 and decreased levels of Smur2, Smad7, and c-ski in the KO embryonic kidneys. In addition, TUNEL staining and immunohistochemical detection of PCNA revealed that the apoptosis of UB cells was upregulated and, conversely, that cell proliferation was suppressed. Finally, we demonstrated that the suppression of UB branching in the KO UBs was restored by the exogenous addition of the Smad3 inhibitor SIS3, whereas the addition of TGF-β1 accelerated the suppression of UB branching in organ cultures of both isolated UBs and whole embryonic kidneys.  
Conclusions: Considering these results, we conclude that UB branching is suppressed through increased activation of the TGF-β/Smad3 signaling pathway when Trps1 is lost.  
Funding: Government Support - Non-U.S.

**TH-PO347**
Unraveling the Molecular Mechanisms Regulating Principal Cell Differentiation  
Kameswaran Sureshran, Justin J. Grassmeyer, Malini Mukherjee. 1 Children’s Health Research Center, Sanford Research/USD, Sioux Falls, SD; 2 Dept of Pediatrics, Sanford School of Medicine, Sioux Falls, SD.

Background: The mammalian collecting ducts are composed of principal and intercalated cell types that arise from a common precursor. Studies in mice identified Minn bomb-1 (Mbnl1), a mediator of Notch and Wnt signaling, to be critical for principal cell differentiation. Mice with Mbnl1 deficient collecting ducts develop symptoms similar to patients with mutations in aquaporin-2 (Aqp2) and arginine-vasopressin receptor 2 (A2br) who suffer from nephrogenic diabetes insipidus (NDI). Considering these results, we hypothesize that Mbnl1 regulates genes that control principal cell differentiation. For this purpose we analyzed mice in which Rbpj and hence Notch signaling is inactivated in developing collecting ducts.  
Methods: We compared the following between wild-type littermates and mice with Rbpj-deficient collecting ducts: number of principal and intercalated cells, mRNA levels for genes involved in principal cell differentiation using immunohistochemistry and quantitative (RT)-PCR, urinary concentrating capacity, gene expression profiles using Illumina mouse bead chips, and expression pattern of Aqp2 using E15 using E15 wild type versus mutant kidneys with p<0.05. One of the down-regulated genes was Aqp2, which we observe is expressed in principal cell lineage prior to Aqp2. Ectopic Notch activation in developing collecting ducts resulted in precocious Aqp2 expression.  
Results: Collecting duct inactivation of Rbpj increased intercalated and, diminished principal cell number, and reduced urine-concentrating capacity. Comparison of gene expression profiles of wild-type developing kidneys and those with Notch signaling deficient collecting ducts revealed a total of 180 differentially expressed genes by at least 1.25-fold in wild type versus mutant kidneys with p<0.05. One of the down-regulated genes was Aqp2, which we observe is expressed in principal cell lineage prior to Aqp2. Ectopic Notch activation in developing collecting ducts results in precocious Aqp2 expression.  
Conclusions: Notch/RBPJ signaling regulates key principal cell fate selection to ensure proper water homeostasis. E15 is an early principal cell lineage marker activated in a Notch signaling dependent manner and is a candidate regulator of principal cell differentiation.  
Funding: Private Foundation Support

**TH-PO348**
Dicer Ureteric Bud Mutant Analysis: New Insights in Mammalian Kidney Development  
Vidya Nagalakshmi Kusma Harinathan, Jing Yu. Dept of Cell Biology, Univ of Virginia, Charlottesville, VA.

Background: In order to understand the ureteric bud (UB)-derived microRNAs (miRNAs) in mammalian kidney development, we have generated a conditional Dicer UB mutant with a HoxB7Cre driver line. Our earlier mutant analyses imply a critical role for miRNAs in UB branching and tubule size control. The present study aims at identifying the target genes up-regulated in Dicer UB mutants and analyzing the UB-expression pattern of up-regulated transcripts during various stages of embryonic kidney development.  
Methods: Our combined approach involved, transcriptional profiling, in situ hybridization, and bioinformatics analyses on some of the potential miRNA target genes up-regulated in Dicer UB mutants.  
Results: We have observed that the potential miRNA target genes up-regulated in Dicer mutants are spatially and temporally restricted during kidney development. We identified, for the first time, temporally regulated genes in the wild-type UB epithelium whose expression is present in the UB epithelia during early stages and absent in later stages of kidney development. Moreover, this temporal regulation is subjected to miRNA regulation, as in Dicer mutants expression of these genes persists into later stages. Further analysis on mechanistic roles of these temporal genes in kidney development is underway and will help us to understand the intricate developmental processes occurring at cellular level in UB epithelial morphogenesis and the importance of miRNAs in their regulation during kidney development.  
Conclusions: In summary, our study demonstrated the requirement of UB-derived, Dicer-dependent miRNAs in mammalian kidney development and revealed the previously unrecognized developmental phenomenon which implicates miRNAs in temporal control of mammalian UB development.  
Funding: Private Foundation Support

**TH-PO349**
A Grainhead-like 2/Ovo-like 2 Pathway Regulates a Transcriptional Network That Controls Collecting Duct Lumen Size  
Janett Ruffert, 1 Annekatrien Aue, 1 Christian Hinze, 1 Katharina Walentin, 2 Max Werth, 2 Jonathan M. Barach, 1 Andong Qiu, 1 Kai M. Schmidt-Ott, 2 Max Delbruck Center for Molecular Medicine, Germany; 3 Dept of Nephrology, Charité-Universitätsmedizin Berlin; 4 Dept of Medicine, Columbia Univ College of Physicians and Surgeons, New York.

Background: The molecular and cellular mechanisms that govern tubular lumen size regulation may provide critical insights into the pathogenesis of kidney diseases. The transcription factor grainhead-like 2 (Grhl2) is expressed in epithelial cells of the ureteric bud and the distal nephron.  
Methods: To investigate the role of Grhl2 in the renal collecting duct (CD) we bred Hoxb7/Cre; Grhl2+/- mice, which exhibit a deletion of functional Grhl2 protein in most cells of the CD. For further analysis of Grhl2 function in CD epithelia, we generated inner medullary collecting duct (IMCD3) cells with a lentiviral knockdown of Grhl2.  
Results: A closer examination of the CD in Grhl2-deficient mice revealed that the papillary CD lumen area was markedly reduced at 4 weeks of age. In three-dimensional culture, IMCD3 cells formed cysts of polarized epithelial cells enclosing a central lumen. However, in Grhl2 knockdown cells lumen formation was perturbed resulting in cysts with a markedly reduced lumen area. Genome-wide screening for Grhl2 targets by microarray analyses of Grhl2-deficient IMCD3 cells and chromatin immunoprecipitation with next generation sequencing in IMCD3 cells and kidneys revealed that Grhl2 regulates multiple genes involved in epithelial junction formation and polarity, as well as other transcription factors including the gene encoding the zinc-finger transcription factor ovo-like 2 (Ovolo2). Ovolo2 expression was markedly reduced in IMCD3 cells following Grhl2 knockdown and in Hoxb7/Cre; Grhl2+/- kidneys. Overexpression of Ovolo2 in Grhl2 knockdown cells rescued cystic lumen formation. Microarray analyses of Grhl2 knockdown cells overexpressing Ovolo2 showed reconstitution of the transcription levels for the majority of Grhl2-dependent genes.  
Conclusions: Our data thus indicate a novel Grhl2/Ovolo2 pathway that controls a transcriptional network governing collecting duct lumen size regulation.  
Funding: NIDDK Support

**TH-PO350**
Tissue Specific Knockout of Dragon in Collecting Duct Leads to Urinary Concentrating Defect  
Wenjie Chen, 1 Richard Bouley, 2 Dennis Brown, 2 Yin Xia, 1 Herbert Y. Lin. 1 Program in Membrane Biology, Div of Nephrology, Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; 2 Program in Reproduction, Development and Endocrinology, The Chinese Univ of Hong Kong, Hong Kong, China.

Background: Dragon, encoded by the RGMB gene, acts as a bone morphogenetic protein (BMP) coreceptor that enhances BMP signaling. The Dragon global knockout mouse dies 2-3 weeks after birth (Ma et al. 2011). In a previous study, we showed that Dragon localized predominantly to the apical surfaces of tubular epithelial cells in the thick ascending limbs, distal convoluted tubules, and collecting ducts of mice, and may play a role in maintaining tight junction integrity in these cells (Xia et al. 2010).  
Methods: To further investigate the role of Dragon in kidney function, we generated the Dragon-Flxoxed mouse and crossed this line with the Hoxb7-Cre mice, to generate the collecting duct conditional knockout mouse Dragon (cd/cd) with a C57BL6/CD-1 mixed genetic background.  
Results: The 6-week old Dragon (cd/cd) mice had increased volume of urine by 54 percent and water intake by 18 percent, and had decreased urine osmolality by 28 percent compared to control mice. Immunofluorescence and real-time PCR analysis showed that Aqp2 mRNA levels were decreased by 20 percent in Dragon (cd/cd) mice. In addition, in some Dragon (cd/cd) mice the papilla was grossly hypomorphic.  
Conclusions: We hypothesize that Dragon regulates the development of the collecting duct and the expression of AQP2 and urine concentration in the kidney.  
Funding: NIDDK Support

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

182A
TH-PO351
The Ureteric Bud Epithelium-Derived Cdc42 Regulates Fzd4/8 Expression and Ureteric Bud Branching Morphogenesis during Mammalian Kidney Development
Qun Ren, Jing Yu. Cell Biology, Univ of Virginia, Charlottesville, VA.

Background: Cdc42 is a ubiquitously expressed small GTPase belonging to the Rho family. Active Cdc42 regulates a wide variety of cellular function and affect multiple cellular processes such as establishing and maintain cell polarity and regulate epithelial morphogenesis. However, its role in the ureteric bud epithelium during kidney development has not been examined.

Methods: To address this issue, we specifically ablated Cdc42 function from the ureteric bud epithelium with Hoxb7cre (referred to as Cdc42 mutants).

Results: This genetic manipulation led to neonatal lethality within 48 hours post-partum. The mutant kidneys were hypoplastic and exhibited cystic dilatation, and were defective in principal and intercalated cell differentiation. Ureteric bud branching morphogenesis was compromised as early as E12.5, and expression of Fzd4 and Fzd8 in the ureteric bud epithelium was greatly reduced. Interestingly, apico-basal polarity of the ureteric bud epithelium was unaffected, nor was the apical localization or phosphorylation of αPKC, indicating that Cdc42 does not regulate apico-basal polarity of the ureteric bud epithelium and does not employ αPKC as its effector in the ureteric bud epithelium. Instead, αPK1 phosphorylation was reduced significantly in the ureteric bud epithelium. Consistent with a role of αPK1 in mediating Cdc42 function in the ureteric bud epithelium, inhibition of the αPK activity disrupted ureteric bud branching morphogenesis.

Conclusions: Our work demonstrates that Cdc42 regulates the expression of Fzd4/8 in the ureteric bud epithelium and is required for kidney branching morphogenesis, most likely through its effector αPK1.

Funding: NIDDK Support

TH-PO352
Ureteric Bud (UB) Prorenin Receptor (PRR) Is Essential for Normal Collecting Duct (CD) Development and Function Renfug Song, Graeme James Preston, Ibor V. Yosypiv. Pediatrics, Tulane Univ School of Medicine, New Orleans, LA.

Background: We tested the hypothesis that inactivation of the PRR in the UB epithelia using Hoxb7cre (PRR^+/+) is essential for normal CD development and function.

Methods: UB-specific knockout of PRR was confirmed by qRT-PCR analysis which revealed an 80% decrease in PRR mRNA levels in E11.5 intact UBs (iUBs) isolated from PRR^+/+ compared with PRR^+/− mice (0.19±0.03 vs. 1.00±0.001).

Results: In situ hybridization and immunohistochemistry demonstrated reduced expression of Aqp2, Foxi1, H+-ATPase family. Active Cdc42 regulates a wide variety of cellular function and affect multiple defects. Grossly visible cysts were identified in a subset of Par-1a/b KH mice. On light microscopy, Par-1a/b KH mouse kidneys had distended cystic tubules. Immunofluorescence (IF) labeling demonstrated that distal tubules were LT-positive and DBA-negative, suggesting that they originate from the proximal tubule. We also observed a decreased megalin expression in Par-1a/b KH proximal tubules and drastically reduced surface expression of E-cadherin. Preliminary results of IF labeling with acetylated tubulin suggest absence of the primary cilia in cysts and shorter primary cilia in Par-1a/b KH mice compared with a WT.

Conclusions: Par-1a/b mice are required for normal apical–basal polarity in vivo and contribute to normal kidney development. Par-1a/b gene deletion leads to renal hypoplasia and cystic dilatation of the proximal tubules. Ongoing studies are examining the mechanisms by which Par-1a/b contribute to cystogenesis and kidney development.

Funding: NIDDK Support

TH-PO353
Mutations in Renin-Angiotensin System (RAS) Genes Are Associated with Isolated Multicystic Dysplastic Kidney (MCDK) in Children
Renfug Song, Graeme James Preston, Ibor V. Yosypiv. Pediatrics, Tulane Univ, New Orleans, LA.

Background: To determine whether MCDK is linked to mutations in RAS genes, we amplified the coding exons and the adjacent intronic sequences of the RAS genes by PCR: renin (exons 3, 5), angiotensinogen (AGT, 5 exons), ACE (26 exons) and angiotensin I receptor (AT1R, 11 exons).

Methods: DNA was extracted from peripheral blood of 10 unrelated patients with MCDK diagnosed by renal ultrasonography (US) (mean age 8.5±1.1 years) and pooled healthy controls according to standard procedures. 6 patients with MCDK, were females and 4-males. Left kidney was affected in 6 cases. Renal function in all affected individuals was normal. Absence of MCDK or other renal anomalies in controls was confirmed by US. Both strands of PCR products were sequenced using dideoxy chain termination method on a 373A DNA sequencer (Applied Biosystems). The effect of mutation on protein function was predicted with Polymorphism software.

Results: 9 novel mutations in RAS genes were found in 6 patients with MCDK. 3 novel and known heterozygous AGT mutations were found. 1 variation was probably damaging, 1 was possibly damaging and 1 was benign. 7 heterozygous renin mutations were found. 3 were probably damaging and 4 were benign. 6 heterozygous ACE mutations were found. 3 mutations were probably damaging and 3-benign. 7 heterozygous AT1R mutations were found. 2 variations were possibly damaging and one was benign.

Conclusions: In summary, we report novel associations of mutations in the genes encoding renin, AGT, ACE or AT1R with isolated MCDK in children. These findings highlight the crucial role of the RAS in the pathogenesis of MCDK in children.

Funding: NIDDK Support

TH-PO354
Dual Loss of Par-1α/b Proteins Leads to Altered Proximal Tubular Epithelial Cells Polarity in Murine Kidneys
Oleh M. Akchurin,1 Nadira Ramkellawan,1 Zhongfang Du,1 James M. Pullman,1 Anne V. Moshe1, Katrina Susarla,2 Kimberly J. Reidy,1 Albert Einstein College of Medicine,1 Univ of Pennsylvania.

Background: Par-1 is a member of the “partitioning defective” family of proteins, which are required to establish columnar epithelial cell polarity in vitro, but their role in kidney epithelial polarity in vivo has not been described. Par-1 has four mammalian homologues (Par-1a, 1b, 1c, and 1d), and complete loss of both Par-1a and 1b is early embryonic lethal. We have previously shown that all 4 homologues of Par-1 are expressed in the developing kidney, and block of Par-1 signaling inhibited growth of metanephric mesenchyme in vitro. We hypothesized that Par-1a/b are required for establishing renal epithelial polarity and normal kidney development in vivo.

Methods: Double-heterozygous Par-1a/b mutant mice were bred and offspring were sacrificed on day 1 of life. Par-1a−/−Par-1b+/+ (Par-1a/b KH) and Par-1a+/−Par-1b−/− (Par-1a/b HK) genotypes were compared to the wild type (WT).

Results: Par-1a/b HK kidneys appear hypoplastic with a reduced kidney weight to body weight ratio (3.3±0.5 mg/g; HK vs. 5.9±0.3 mg/g WT, p<0.002). A diluted renal phenotype was observed in 20% of the Par-1a/b KH mice, suggestive of ureteric bud branching defects. Grossly visible cysts were identified in a subset of Par-1a/b KH mice. On light microscopy, Par-1a/b KH mouse kidneys had distended cystic tubules. Immunofluorescence (IF) labeling demonstrated that distal tubules were LT-positive and DBA-negative, suggesting that they originate from the proximal tubule. We also observed a decreased megalin expression in Par-1a/b KH proximal tubules and drastically reduced surface expression of E-cadherin. Preliminary results of IF labeling with acetylated tubulin suggest absence of the primary cilia in cysts and shorter primary cilia in Par-1a/b KH mice compared with a WT.

Conclusions: Par-1a/b mice are required for proper apical–basal polarity in vivo and contribute to normal kidney development. Par-1a/b gene deletion leads to renal hypoplasia and cystic dilatation of the proximal tubules. Ongoing studies are examining the mechanisms by which Par-1a/b contribute to cystogenesis and kidney development.

Funding: NIDDK Support

TH-PO355
Hypoxia Inducible Factor-1α Regulates Branching Morphogenesis in Kidney Development without Ureteric Bud Cell Proliferation
Kenji Tsuji, Shinji Kitamura, Hitoshi Sugiyama, Hirofumi Makino. Medicine and Clinical Science, Okayama Univ Graduate School of Medicine, Okayama, Japan.

Background: Embryos are exposed under hypoxia (0-2-9%) in developing stage. During kidney development, GDNF signaling from metanephric mesenchyme through Ret and GFRα1 is the common pathway involved in ureteric bud (UB) branching which is not related to the association nephropathy. There has been a previous study that the hypoxic inducible factor (HIF)-1α makes an important role for development. However there are few reports about the relationship between HIF-1α and UB branching. Here we examined whether HIF-1α regulates the UB branching on renal development or not.

Methods: We harvested embryonic 13 days kidneys (E13K-s) from pregnant rats and cultured under normoxia (20% O2 / 5% CO2) or hypoxia (5% O2 / 5% CO2). We evaluated the kidneys on the point of morphology and gene expression. We also examined UB cell proliferation under normoxia or hypoxia using electric cell-substrate impedance sensing (ECIS) method.

Results: The number of ureteric bud ends of cultured E13K-s under hypoxia significantly increased compared to cultured normoxia (the numbers of end buds under hypoxia vs. normoxia; 57.7±12.5 vs. 46.0±6.6/ kidney, p<0.01). Quantitative RT-PCR revealed increased PDGFDN, GFRα1, RET and FGFR10 mRNA levels in cultured E13K-s under hypoxia compared to cultured normoxia. When we cultured E13K-s under hypoxia with HIF-1α inhibitor (digoxin), we could not observe increased UB branching (the numbers of end buds under hypoxia vs. hypoxia with digoxin; 57.7±12.5 vs. 41.5±7.5 kidney, p<0.01). Direct inhibition of HIF-1α using siRNA decreased UB branching during E13K-s culture under hypoxia (the numbers of end buds under hypoxia vs. hypoxia with HIF-1α siRNA; 7.4±12.5 vs. 39.0±4.76 kidney, p<0.01) and GDNF, GFRα1 mRNA level significantly. Additionally, UB cells under hypoxia proliferated significantly less than under normoxia in vitro. Conclusion: HIF-1α regulates branching morphogenesis via GDNF/RET and/or FGFR10 signal pathway without UB cell proliferation.

Funding: NIDDK Support
Whole Exome Profiling Identifies Biological Processes Modified by Ebf1 during Podocyte Maturation
Jackie A. Fretz, Orthopaedics and Rehabilitation, Yale School of Medicine, New Haven, CT.

Background: We previously identified Early B Cell Factor 1 (Ebf1) as a gene up-regulated in podocytes during the final stages of postnatal murine nephrogenesis. Deficiency of this transcription factor results in a unique phenotype of abrogated glomerular development that disproportionately affects peripheral glomerular development. Although this coincides with the late expression profile of Ebf1 in podocytes, it raised intriguing questions regarding the function of Ebf1 in the development of peripheral vs. juxtamедullary glomeruli.

Methods: To address these questions we performed RNA-seq to compare expression profiles of Ebf1-replete and Ebf1-deficient podocytes at three separate postnatal times: P2, 14, and 21. Samples were compared between genotypes and across time for multivariate analysis.

Results: Several podocyte-related markers including Pod1/Tcf21 and Lmx1a/b, were identified showing the specificity for the selected cells. The most similar populations were P0 podocytes from Ebf1-replete and -deficient cells. P14 and P21 Ebf1-replete podocytes were the next most closely related populations, and also more like the P0 podocytes than deficient cells at P14 or P21.

Conclusions: Analysis of the biological processes affected by Ebf1-deficiency identified modification in extracellular matrix formation, cell adhesion and locomotion, Wnt signaling, and neuronal development. Many of these processes have been shown previously to be essential for proper podocyte differentiation. Additionally, enrichment of processes involved in cell development and lipid metabolism were identified. These correlate to other known functions of Ebf1 in disparate cell lineages, and may identify conserved functions in skeletal development and lipid metabolism were identified.

TH-PO357
The Role of miR-222 in Glomerular Development by Targeting NPM1
Shiyong Cui, 1 Yanfang Ding, 1 Jinyao Zhao, 1,2 Xian Wu, 1 Guang Wang, 1 Mingyi Cui, 1,3 Tianbai Li. 1,3 Dalian Medical Univ, Dalian, China; 4 The Fourth People's Hospital, Liaoyang, China.

Background: MicroRNA (miRNA) has been implicated in the regulation of organic development processes through repression of specific miRNAs at the posttranscriptional stage. The purpose of this study is to define a miRNA expression signature in glomerular development, and verify the function of miRNA-target in developing and developed glomeruli.

Methods: To reach this goal, mouse kidneys at the developed (P28) and developing (E15.5) stages, and podocytes (MPC-5) at undifferentiated (33°C) and differentiated (37°C) status were used in the study. Total RNA and protein were purified from glomeruli that were isolated from the kidneys at both developing and developed stages. MicroRNA microarray, Western Blotting, quantitative Real-Time Polymerase Chain Reaction (qRT-PCR), and immunohistochemistry were further performed.

Results: Of the 224 mouse miRNAs analyzed in the microarray, 62 were significantly expressed, and 39 with at least 2-fold difference in the glomerulus at P28 compared to E15.5. Gene expression from these bioinformatic analyses showed that 80% of all key miRNAs had functions being relevant to cellular development. Of which, the reciprocal expression of miR-222- NPM1 (Nucleoplasmin 1), a pair of miRNA-target predicted, was validated by qRT-PCR, immunohistochemistry and western blotting in vivo, and function confirmed by miR-222 overexpression and luciferase reporter assays in vitro. The function of miR-222 by targeting NPM1 in podocyte proliferation and migration was finally verified in MPC-5 cells.

Conclusions: This study may advance the current level of understanding of miRNAs in glomerular development.

Funding: Government Support - Non-U.S.

TH-PO358
MicroRNAs Are Critical Regulators of FOXD1 Progenitors and Kidney Struma during Nephrogenesis
Naoki Nakagawa, 1 Allie M. Roach, 1 Ivan G. Gomez, 1 Akio Kobayashi, 1 Jeremy Stuart Duffield. 1,2 Renal Div, Kidney Research Institute, Univ of Washington, Seattle, WA; 3Harvard Stem Cell Institute, Boston, MA.

Background: Recent studies have identified important roles for post-transcriptional regulators including microRNA in nephron development and in adult kidney diseases but the impact of microRNA in regulating stromal cell functions has not been explored and stromal functions in nephrogenesis remains undefined.

Methods: In order to study the function of kidney stromal cells, and the importance of post-transcriptional gene regulation in kidney stroma, during nephrogenesis, we mutated the microRNA activating enzyme Dicer-1, specifically in stromal cells that derive from Foxd1 expressing kidney progenitors of the nephrogenic intersitium.

Results: Dicer-1 mutants were born at less than expected Mendelian ratios, and surviving pups died shortly after birth. There was a striking reduction in kidney volume and absence of urine production. Histological examination revealed highly disorganized tubular and microvascular compartments as well as glomerular abnormalities. Elongation and differentiation of the loop of Henle was attenuated resulting in absence of inner medulla and papilla, and polarization of proximal tubules was impaired with loss of brush border. Peritubular capillary formation was disorganized with large highly branched capillaries, indicating that mesenchymal cells are necessary for correct blood vessel formation. These phenotypic changes were associated with evidence of reduced activation of stromal cells and like the modification of the stroma in addition Foxd1 activity in the nephrogenic progenitors is necessary for differentiation into mature podocytes.

Conclusions: We conclude that microRNA post-transcriptional gene regulation is critical in Foxd1 progenitor derived kidney stroma functions in nephrogenesis. These studies highlight the strategic importance of kidney stroma in organogenesis.

TH-PO359
Soluble Form of Angiostatin-Converting Enzyme (ACE) Is Enough for Kidney Development, but Not to Maintain Blood Pressure
MichiYumi Yamashita, 1,2 Saurabh Chattopadhyay, 1 Ganes C. Sen, 1,3 Pathology, Univ Hospitals Case Medical Center, Cleveland, OH; 1Pathology, Case Western Reserve Univ, Cleveland, OH; 4Molecular Genetics, Lerner Research Institute, Cleveland Clinic, Cleveland, OH.

Background: ACE, a central component of Renin-Angiostin System (RAS), is essential for kidney development and blood pressure (BP) regulation. ACE+/− mice show glomerular and tubular hypoplasia, and low BP. There are two forms of ACE membranes bound and soluble form and soluble ACE. ACE is expressed on the cell surface as type I ectoprotein, with enzymatically active ectodomain, transmembrane domain, and short cytoplasmic domain. The ectodomain can be cleaved to generate the soluble form. These two forms are equally enzymatically active. We reported (Kessler SP, et al. JBC 2003) membrane-bound ACE in the vascular endothelial cells is enough for kidney development as well as normal blood pressure. Here we investigate the roles of the soluble ACE in kidney development and renal functions.

Methods: We generated transgenic (TG) mice with Tie-1 promoter-driven expression of the soluble ACE in the background of ACE−/− mice, and analyzed the mice morphologically and physiologically, as well as at molecular level.

Results: The expressed ACE protein lacked the transmembrane and the cytoplasmic domains, and was constitutively secreted into the blood stream. The TG mice showed normal kidney structure grossly and microscopically. The urine output, water intake, and urine osmolality were normal. However, TG mice showed still low BP compared to Ace+/− wild type (WT) mice. The local RAS activity in kidney from TG mice was similar to WT mice: Renin and Angiotension II from the kidney tissue from TG mice were comparable to WT mice, although TG mice did not show any ACE expression in kidney tissue. The systemic RAS activity was also similar between two groups: plasma renin activity, serum ACE activity, and plasma Angiotension II level did not show significant difference between the two groups.

Conclusions: Soluble ACE is enough for kidney development, but not to maintain BP. The cytoplasmic domain of ACE in vascular endothelial cells, and its signaling might be important for BP regulation.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute, R01HL048258

TH-PO360
The bHLH Transcription Factor Tcf21 Is Required for Differentiation and Maintenance of Podocytes in Development, Health and Disease
Yoshiro Maezawa, 1,2,3 Tuncer Onay, 1,2 Rizaldy P. Scott, 1,2 Lindsay S. Keir, 1 Henrik Dimke, 1 Chengjin Li, 1,5 Vera Eremina, 1,5 Asish Ghosh, 1,5 Jeffrey H. Miner, 3,4 Susan E. Quaggin. 1,5 SLRI, Toronto, Canada; 2University of Bristol, United Kingdom; 3Biocenter Oulu, Finland; 4Feinberg Cardiovascular Research Institute and Div of Nephrology, Northwestern Univ, Chicago.

Background: Tcf21 is a bHLH transcription factor essential for embryonic development. Global Tcf21 knockout (gl-KO) mice die minutes after birth with hypoplastic lungs and tetralogy of Fallot. In kidneys of gl-KO mice, mesenchyme-to-epithelial transformation, branching morphogenesis and nephrogenesis are arrested.

Methods: In addition to mesenchymal expression, Tcf21 is expressed in adult and adult podocytes. To examine the role of Tcf21 in podocytes, we created a conditional allele for Tcf21 and crossed them to PodocinCre (pod-KO) and Wnt4-Cre mice resulting in deletion of Tcf21 from differentiated and progenitor podocyte populations, respectively.

Results: Pod-KO mice don't exhibit overt defects in podocyte differentiation, but the glomerular structure is greatly simplified with decreased endothelial and mesangial cells. By 4 weeks of age, 30%-40% of Pod-KO mice develop FSGS-like lesions and massive proteinuria, while 60% of mice never develop proteinuria. Microarray analysis of glomeruli from Pod-KO mice revealed candidate downstream targets, including Vegf, Pgf and Wifi. ShRNA knockdown of Tcf21 in human podocytes results in altered cell shape and migration. Earlier deletion of Tcf21 from podocyte precursors (Wnt4-Cre) leads to columnar shaped podocytes, aberrant distribution of Podocin and defects of mesangial migration, suggesting more profound defect of podocyte differentiation. Strikingly, induction of diabetes in the non-proteinuric Pod-KO mice results in increased proteinuria, suggesting a protective role for Tcf21.

Conclusions: Our results demonstrate a critical role for Tcf21 in the differentiation and maintenance of podocytes in both developing and mature kidneys. Identification of direct targets of this transcription factor model may provide new therapeutic targets for proteinuric renal disease including diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-P345
Angiogenesis in the Kidney: From Development to Disease
N. Robert Gabbiani, 1,2 Biostereology, The Rockefeller University, New York, NY; 2Liver Research Institute, New York, NY.

Background: Angiogenesis occurs during kidney development as a mechanism to allow for the formation of the nephrons; however, in adult life, angiogenesis is essential for the maintenance of the glomerular filtration area.

Methods: In this presentation we will focus on the role of angiogenesis in the kidney during development and in disease using the mouse as a model organism.

Results: During kidney development, angiogenesis is necessary for glomerular formation and filtration area. In adult life, angiogenesis is essential for the maintenance of glomerular filtration area, and when defective, leads to renal disease.

Conclusions: Understanding the role of angiogenesis in the kidney during development and in disease will allow for the development of new therapeutic approaches.
Diabetes Insipidus Neuropathogenesis via Augmented Hedgehog Interacting Protein (Hhip) Gene Expression

**Background:** We hypothesized that maternal diabetes neuropathogenesis via augmented hedgehog interacting protein (Hhip) gene expression, given screening gene arrays for diabetes (Gene Mouse Gene 1.0ST array platform) we had performed had indicated that Hhip was significantly modulated by maternal diabetes.

**Methods:** We created an in vivo murine model using kidneys from the suckling pups of non-diabetic, diabetic, and insulin-treated diabetic dams. MK4 (an embryonic late metabolic mesenchymal (MM) cell line) and ureteric bud (UB) cell lines, were used for in vitro studies.

**Results:** Kidney of the offspring of diabetic dams as compared to the control offspring displayed features suggesting retarded nephrogenesis, such as small kidneys and less UB branching morphogenesis. Augmented Hhip expression was observed on the offspring of diabetic dams, initially localized to the differentiated MM and UB epithelium, and then in maturing glomerular and tubulointerstitial cells. We also observed heightened Hhip active transforming growth factor beta 1 (TGFβ1) signaling, associated with dysmorphogenesis in these offspring. The in vitro studies demonstrated that Hhip overexpression decreased sonic hedgehog (Shh) and paired box gene 2 (Pax2) expression and increased transcriptional nuclear factor-kappa B (NF-κB, p50/p65), phosphorylation of p35 and TGFβ1 gene expression. In contrast, Pax2 gene overexpression inhibited Hhip and NF-κB and activated Shh, Nkx2.5, and p21(36) gene expression. Moreover, high glucose stimulated Hhip gene expression, and then targeted TGFβ1 signaling. Thus, Pax2 via a negative autocrine feedback mechanism attenuated the stimulatory effect of high glucose on Hhip gene expression.

**Conclusions:** We conclude that impaired nephrogenesis induced by maternal diabetes is mediated, at least in part, via augmented Hhip gene expression.

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

---

**TH-PO361**

**Diabetes Insipidus Neuropathogenesis via Augmented Hedgehog Interacting Protein (Hhip) Gene Expression**

**Background:** In contrast, Pax2 gene overexpression inhibited Hhip and NF-kB and activated branching morphogenesis. Augmented Hhip expression was observed on the offspring of non-diabetic, diabetic, and insulin-treated diabetic dams. MK4 (an embryonic late metabolic mesenchymal (MM) cell line) and ureteric bud (UB) cell lines, were used for in vitro studies.

**Results:** Kidneys of the offspring of diabetic dams as compared to the control offspring displayed features suggesting retarded nephrogenesis, such as small kidneys and less UB branching morphogenesis. Augmented Hhip expression was observed on the offspring of diabetic dams, initially localized to the differentiated MM and UB epithelium, and then in maturing glomerular and tubulointerstitial cells. We also observed heightened Hhip active transforming growth factor beta 1 (TGFβ1) signaling, associated with dysmorphogenesis in these offspring. The in vitro studies demonstrated that Hhip overexpression decreased sonic hedgehog (Shh) and paired box gene 2 (Pax2) expression and increased transcriptional nuclear factor-kappa B (NF-κB, p50/p65), phosphorylation of p35 and TGFβ1 gene expression. In contrast, Pax2 gene overexpression inhibited Hhip and NF-κB and activated Shh, Nkx2.5, and p21(36) gene expression. Moreover, high glucose stimulated Hhip gene expression, and then targeted TGFβ1 signaling. Thus, Pax2 via a negative autocrine feedback mechanism attenuated the stimulatory effect of high glucose on Hhip gene expression.

**Conclusions:** We conclude that impaired nephrogenesis induced by maternal diabetes is mediated, at least in part, via augmented Hhip gene expression.

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

---

**TH-PO362**

**Wilms’ Tumor 1 Initiates the Differentiation Cascade by Suppressing Enhancer of Zeste Homolog 2-Mediated Silencing of Key Genes Murielle M. Akpa,1 Lee Lee Chu,2 Diana Iglesias,2 Paul R. Goodyer.1,2 Human Genetics, McGill Univ, Montreal, Canada; 2Pediatrics, McGill Univ Health Center Research Institute, Montreal, Canada.

**Background:** During nephrogenesis, stem cells from the metanephric mesenchyme are induced to form nephrons upon receipt of an inductive signal from the ureteric bud. Wilms tumor 1 (WT1) is believed to play a key role in triggering the differentiation cascade. Kidneys of the offspring of diabetic dams as compared to the control offspring displayed features suggesting retarded nephrogenesis, such as small kidneys and less UB branching morphogenesis. Augmented Hhip expression was observed on the offspring of diabetic dams, initially localized to the differentiated MM and UB epithelium, and then in maturing glomerular and tubulointerstitial cells. We also observed heightened Hhip active transforming growth factor beta 1 (TGFβ1) signaling, associated with dysmorphogenesis in these offspring. The in vitro studies demonstrated that Hhip overexpression decreased sonic hedgehog (Shh) and paired box gene 2 (Pax2) expression and increased transcriptional nuclear factor-kappa B (NF-κB, p50/p65), phosphorylation of p35 and TGFβ1 gene expression. In contrast, Pax2 gene overexpression inhibited Hhip and NF-κB and activated Shh, Nkx2.5, and p21(36) gene expression. Moreover, high glucose stimulated Hhip gene expression, and then targeted TGFβ1 signaling. Thus, Pax2 via a negative autocrine feedback mechanism attenuated the stimulatory effect of high glucose on Hhip gene expression.

**Conclusions:** We conclude that impaired nephrogenesis induced by maternal diabetes is mediated, at least in part, via augmented Hhip gene expression.

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

---

**TH-PO363**

**Cooperation of COUP-TFI with HIF to Drive Nephrogenesis**

**Background:** Outgrowth and branching of the ureteric bud is essential to generate the renal collecting system which concurrently induces nephrogenesis, thereby determining the definitive number of nephrons. Limited nephron number due to intrauterine growth restriction (IUGR) predisposes to arterial hypertension and chronic kidney disease. IUGR is associated with increased renal expression of the hypoxia-inducible Factor-1α (HIF-1α).

**Methods:** We made chip-seq analyses by H4K20ac antibody and next generation sequencing analysis for transcription factors binding to H4K20ac.

**Results:** In peak localization analysis, H4K20ac was precipitated in the promoter regions of silent genes, which was totally opposite to the conventional views of histone acetylation. And we also found this modification did not localise on Lamina Associated Domain in which lots of permanent silent genes are located, suggesting that H4K20ac is related to regulated silenced gene expression. In the motif search, we found that lots of transcriptional activators, AP-2, STAT3, and Myc could not bind to H4K20ac precipitating promoters, whereas only transcriptional suppressor, SRF could bind to this region. In the comparison with ENCODE data base, H4K20ac was also localised on the future open chromatin regions, suggesting that H4K20ac can predict the future chromatin changes. Histone acetylation and new kind of histone acetylation may be related to organ hypertrophy by suppressing regulated genes by repulsing transcriptional activators form promoter region.

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

---

**TH-PO364**

**New Epigenetic Marker, H4K20ac Related to Transcriptional Suppression**

**Background:** Our data suggest losing one copy of COUP-TFI is a genetic animal model of nephron insufficiency and it can serve as a platform to develop future therapeutic interventions.

**Funding:** NIDDK Support, Other NIH Support - NHLBI
Development, The Univ of Texas Graduate School of Biomedical Sciences, Houston, TX.

TH-PO366

Planar Cell Polarity Effectors, Daam1 and WGEF, Are Required for Cilia Formation and Nephric Tubulogenesis

Rachel Katherine Miller,1 Malgorzata Kloc,2 Le Huang,1,4 Qinghua Hu,1 Sharaideh Mokkapati,2 Vicki Huff,4 Pierre D. McCrea,1,4 Biochemistry and Molecular Biology, The Univ of Texas MD Anderson Cancer Center, Houston, TX; 2Immuno-Biology Laboratory, The Methodist Hospital Research Institute, Houston, TX; 3Genetics, The Univ of Texas MD Anderson Cancer Center, Houston, TX; 4Program in Genes & Development, The Univ of Texas Graduate School of Biomedical Sciences, Houston, TX.

Background: Recent studies from our group and others indicate that canonical (beta-catenin-mediated) Wnt signaling is necessary for tubulogenesis and possibly ciliogenesis within the developing kidney and may be relevant to human pediatric kidney diseases.

Methods: Using Xenopus laevis (frog) embryos, supplemented with Danio rerio (zebrafish) and more recently the mouse Wilms tumor model, we assess the roles of PCP components in kidney tubule morphogenesis utilizing F-PFPCR, in situ hybridization, knockdown, immunostaining, electron microscopic and biochemical techniques.

Results: We find that Daam1 and WGEF are expressed in the Xenopus embryonic kidney. Daam1 knockdown reduces the expression of pronephric differentiation/development marker genes while having little impact upon determination and patterning. Additionally, knockdown of Daam1 and WGEF result in reduced tubulogenesis. Daam1 and WGEF are important for forming cilia in both the skin of embryos and in the kidney, which have functional associations with morphogenesis. We are beginning investigate renal tubulogenesis to determine if cilia or PCP are altered in these tissues. Thus far, we have preliminary data indicating that ciliogenesis may be increased in a mouse model of Wilms tumor.

Conclusions: Our data together suggest that the Daam1/WGEF/Rho PCP trajectory is necessary for tubulogenesis and possibly ciliogenesis within the developing kidney and may be relevant to human pediatric kidney diseases.

Funding: NIDDK Support, Other NIH Support - NIDDK NIDDK K01 Career Development Award (1K01DK092320(R.K.M); NIH NIGMS R01 grant (GM052112)(P.D.M.); Private Foundation Support

TH-PO367

Role of the Primary Cilium in Early Steps of Nephrogenesis

Evelyn Fischer,1 Filippo Massa,2 Armelle Jm Christophorou,1 Cecile Madaras,1 Evelyne Fischer,1 Filippo Massa,2 Armelle Jm Christophorou,1 Cecile Madaras,1 Role of the Primary Cilium in Early Steps of Nephrogenesis

TH-PO368

p53 Promotes Adhesion of Six2+ Cells within the Nephron Progenitor Niche

Yuwen Li,1 Jiao Liu,1 Marilyn Li,1 Samir S. El-Dahr,1 Zaburda R. Saffiadeen.1

Pediatrics, Tulane Univ, New Orleans, LA; 2Hypertension and Renal Centers of Excellence, Tulane Univ; 3Molecular and Human Genetics, Baylor College of Medicine, Houston, TX.

Background: Retention of nephron progenitor cells (NPC) within the niche is necessary to allow NPC-niche interactions and timely activation of transcriptional programs that drive differentiation. Six2+ cap mesenchyme (CM) devoid of transcription factor p53 (Six2p53−) is disorganized, with a greatly diminished Cited1+ self-renewing population. We hypothesize that p53 regulates transcriptional programs to retain progenitor cells within a structured niche.

Methods: To test our hypothesis we compared transcriptional profiles by Polya-selected paired-end RNA-Seq of Six2p53− and Six2p53++ FACS-isolated cells from E15.5 kidneys. Cell aggregation assessment of isolated mutant cap cells was done.

Results: Differential genes (3400 genes; fisher’s exact test p-value<0.05, FC 1.5) include 283 lincRNA and 21 premiRNAs. Purity of isolated CM was confirmed by high read density of CM genes (Six2, GDNF, Crym, Cited1), but not RV (Cdh1, Fgf8) or UB (Wntb, eCrE) genes. Expression of Foxd3-p53 genes exons 2-10 was mostly abolished in Six2p53−. Accordingly p53 target genes p21, PUMA and NOXA are downregulated.

Cited1 expression was decreased, but not Six2. Highest enrichment of differentially expressed genes was observed for genes in cell adhesion (5-fold, Igf6, Ntrn, Coll1A1), migration (regulatory proteins for Rho/CaCdc42 - ARHAGPA24, 29, 30 and Cdc42p53), development (UB genes - Wnt9b, cRet, Fgf8), calcium signaling -1004(A-8.5 fold) and S100A4(-3.8 fold). IF staining showed decreased NCAM and Ncad in caps of Six2p53− kidneys. Six2p53− cells showed decreased aggregation at isolated ureteric tips in hanging drop assays, compared to Six2p53++ cells.

Conclusions: p53 loss from the Six2− cells resulted in loss of niche architecture and a smaller CM with diminished Cited1+ population. In support, RNA-Seq identified deregulated expression of genes involved in cell adhesion, migration, development and patterning. Our data support a role for p53 as a regulator of transcriptional programs that maintain niche integrity.

Funding: NIDDK Support, Other NIH Support - NIGMS

TH-PO369

Podocyte-Specific Autophagy Deficiency Exacerbates High-Fat Diet-Induced Glomerular Injury

Kosuke Yamahara,1 Mako Yasuda,1 Atsuko Tagawa,1 Shinji Kume,1 Yuki Tanaka,1 Shin-ichi Araki,1 Daisuke Koya,2 Masakazu Haneda,1 Takashi Uzu,1 Hiroshi Maegawa. 1Dept of Medicine, Shiga Univ of Medical Science, Otsu, Shiga, Japan; 2Div of Diabetology & Endocrinology, Kanazawa Medical Univ, Kaneko, Ishikawa, Japan; 3Dept of Medicine, Asahikawa Medical Univ, Asahikawa, Japan.

Background: Diabetic nephropathy is a leading cause of end-stage renal disease worldwide. Methods for reducing proteinuria in diabetic nephropathy patients are still required. Podocytes are terminally differentiated and are unable to proliferate. Disruption of cell homeostasis in podocytes therefore results in impairment to glomerular filtration barrier function, leading to proteinuria in diabetic nephropathy. Intraacellular degradation systems are essential for maintaining cell homeostasis. One of these systems, autophagy, is known to control conserved machinery for bulk degradation of cytoplasmic components. Alterations in autophagy have recently been found to be the pathogenesis for some metabolic diseases. This study examined the role of podocyte autophagy in diabetic nephropathy.

Methods: We generated podocyte-specific autophagy-deficient (Podo-Atg5−/−) mice by podocyte-specific-Atg5 gene deletion. Eight-week-old control (Atg5+/+) and Podo-Atg5−/− mice were fed with either a standard diet or a high-fat diet for 32 weeks.

Results: At the end of the experimental period, both Atg5+/+ and Podo-Atg5−/− mice developed obesity and hyperinsulinemic hyperglycemia resembling type 2 diabetes mellitus. In Podo-Atg5−/− mice, high-fat diet-induced increases in urinary albumin excretion were significantly higher compared with those of Atg5+/+, although high-fat diet-induced glomerular histological changes were almost the same in both groups. Fibrosis and infiltration of inflammatory cells in tubulointerstitial lesions and proximal tubular cell apoptosis were significantly more severe in Podo-Atg5−/− mice.

Conclusions: The results suggest that autophagy is essential to protect podocytes from diabetes-related cellular toxicity. Although further study is required, autophagy appears to be a possible new therapeutic target for reducing proteinuria in diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-PO370

Enhanced Glomerular Toll-Like Receiver Expression and Signalling in Patients with Type 2 Diabetic Nephropathy and Microalbuminuria

Giacomo Garibotto, 1 Laura Cappuccino, 1 Barbara Villaggio, 1 Fabio Enzo Gianionio,1 Marianno Mij,2 Francesca Vizzielli,1 Daniela Verzola.1 1Div of Nephrology, Dialysis and Transplantation, Genoa Univ and AOU San Martino-IST, Genoa, Italy; 2Div of Nephrology and Dialysis, General Hospital, Imperia, Italy.

Background: Toll-like receptors 4 (TLR4) can be activated by endogenous ligands in diabetes and promote inflammation in the kidney tubulointerstitial compartment at a clinical stage of diabetic nephropathy. However, there is no information on molecular events taking place in diabetic microalbuminurias, when renal damage is most likely to be reversible.

Methods: We studied TLR4 gene and protein expression and TLR4 downregulation in kidney biopsies of type 2 diabetic patients with microalbuminuria(n=12, age 60±12 yr, 6M/6F, eGFR=63±11 ml/min, in patients with overt nephropathy(n=11, age 63±3 yr, 5M/8F, 60±4 yrs, eGFR=102± 3)). As a second step, to identify specific transcriptional pathways that underlie the pathogenesis of disease we studied selected TLR-4 downgrade gene expression profiles from laser-capture microdissected glomeruli and tubulointerstitium.

Results: In microalbuminuric patients TLR4 mRNA was markedly upexpressed in the glomeruli and in tubulointerstitium. Within the glomerular tuft, TLR4 was localized in podocytes. NF-kB signalling was ~4-fold higher in the glomeruli as compared to normal kidney. TNF-z, IL-6, CCL-5 and CCR-5 mRNAs were markedly (about 3.5 fold, p<0.01)
upregulated in microdissected glomeruli, while TNFα and TNFR1 were upregulated both in glomeruli and in the tubulointerstitial compartment (p<0.02). Surprisingly, both CCL2, mRNAs and CD68 were expressed in microvascular sites, while they were both upregulated in the tubulointerstitial compartment of clinical diabetic nephropathy.

Conclusions: Our data demonstrate the activation of innate immunity in the glomeruli of patients with type 2 diabetes and early nephropathy and suggest that enhanced TLR4 signaling contributes to the progression that occurs after the microalbuminuric form of nephropathy evolves to overt disease.

Funding: Government Support - Non-U.S.

TH-PO371

RTN1 Is a Novel Risk Gene for Kidney Disease Ying Fan,1,2 Jason A. Bonomo,1 Peter Y. Chuang,1 Wenzhen Xiao,1 Sandeep K. Mallipatua,1 Nicholette D. Palmer,1 Donald W. Bowden,1 Barry I. Freedman,1 Niansong Wang,2 John C. He.3 1Medicine, Mount Sinai School of Medicine, NY; 2Nephrology, Shanghai Six Municipal Hospital, Shanghai, China; 3Section on Nephrology and Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, NC.

Background: Factors contributing to the progression of kidney disease remain unclear.

Methods: We profiled gene expression in kidneys from a murine model of HIV-associated nephropathy (HIVAN) and identified an association between the expression of reticulin-1 (Rtn1), which encodes for an endoplasmic reticulum (ER)-associated protein, and the severity of kidney disease. We validated RTN1 expression in both mouse and human diseased kidneys by real-time PCR, western blot, and immunostaining. We determined the role of RTN1 in ER stress. We performed genetic association studies of RTN1 SNPs and ESRD.

Results: Upregulation of protein and mRNA expression of RTN1 was confirmed in diseased kidneys of two mouse models for HIVAN, diabetic kidney disease (DKD), and unilateral ureteral obstruction. Renal RTN1 mRNA level was higher in patients with DKD and correlated with estimated glomerular filtration rate (eGFR). Of the three known RTN1 isoforms, only RTN1-α's protein expression was elevated in kidneys of mice and human with HIVAN and DKD. Protein expression of RTN1-α in the kidneys, as shown by immunostaining, correlated inversely with eGFR in patients with DKD. In HK2 cells, RTN1 overexpression induced ER stress and apoptosis whereas RTN1 knockdown attenuated inflammatory stress plays crucial roles in the progression of DN.

Conclusions: Our data suggest that RTN1 is a novel risk gene for kidney disease and may contribute to kidney injury through ER stress.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO372

Establishment of a Novel Inflamed Animal Model of Diabetic Nephropathy Kun Ling Ma, Yang Zhang, Jing Liu, Wu Yu, Jie Ni, Bi-Cheng Liu. Institute of Nephrology, Southeast Univ School of Medicine, Nanjing, China.

Background: It has been demonstrated that diabetic nephropathy (DN) is a chronic inflammatory disease. Inflammatory stress plays crucial roles in the progression of DN. Therefore, an inflamed model of DN would be helpful to clarify the pathogenesis of DN. However, an adequate reliable inflamed model of DN is currently lacking. This study aimed to establish a novel inflamed animal model of DN and evaluate its significance in DN.

Methods: Twenty male db/db mice were randomly divided into two groups for eight weeks (10/group). Mice were given with a high-fat diet. RTN1 expression was detected by pathological staining and Western blotting. To evaluate the expression of podocyte specific molecules and inflammatory cytokines in kidneys.

Results: The 24-hour urinary protein, plasma levels of SAA and TNF-α, as well as the protein expression of inflammatory cytokines in kidneys were significantly increased in inflamed group compared to the control. Moreover, there were more significant mesangial expansion, collagen accumulation, and foot process effacement in inflamed group compared to the control. Further analysis showed that inflammation markedly decreased the expression of wilms tumor-1 and neuropilin, which are specific biomarkers of podocyte, suggesting accelerating injuries of podocyte induced by inflammation.

Conclusions: An inflamed animal model of DN was successfully established. This inflammation model will provide a useful tool for investigating the pathogenesis of DN under inflammatory stress.

Funding: TH-PO373

Semaphorin3a Role in Diabetic Nephropathy Alda Tufo1 Pardeep Kumar Aggarwal,2 David B. Thomas.3 1Pediatrics/Nephrology, Yale Univ, New Haven, CT; 2Pathology, Univ of Miami, Miami, FL.

Background: Accumulating evidence supports crucial pathogenic roles of vascular endothelial growth factor-a, nitric oxide and semaphorin 3a (sema3a) deregulation in diabetic nephropathy (DN). Semoa3a is a guidance protein secreted by podocytes and essential for normal kidney development. We recently showed that excess podocyte sema3a causes renal disease via direct paxina-3, neuropilin interaction and integrin regulation, and identified increased sema3a expression in Db/db and STZ-induced diabetic kidneys.

Methods: Renal biopsies from T1D and T2D patients were examined by IHC. Sema3a was measured by ELISA and immuno blotting. Protein expression was assessed by SDS-PAGE-Coomassie staining and albuminuria. Diabetes was induced using the ADMMC protocol. Mouse renal phenotype was examined by LM, IF and EM.

Results: Here we report that podocyte sema3a is increased in human diabetic nephropathy, as detected by immunochemistry in renal biopsies (DN Class III-IV), whereas sema3a was barely expressed in non-diabetic control biopsies. Moreover, podocyte sema3a was increased in T1D diabetic mice, as assessed by immunoblotting and IHC. Using a sema3a ELISA assay we find that sema3a plasma level and urine excretion are significantly higher in diabetic mice than in non-diabetic controls, and urine sema3a excretion is higher in diabetic mice with advanced DN than in those with mild DN. Next, we examined the role of sema3a in DN using a doxycycline inducible, podocyte-specific Sema3a overexpression mouse model (podoc-inRtn1-tet-O-Sema3a, herein called Sema3a+). Sema3a+ mice were made diabetic with streptozotocin (DM-Sema3a+). Induced diabetic Sema3a+ overexpressing mice (DM-Sema3a+ + dox) developed massive proteinuria, decreased renal function and extensive nodular glomerulosclerosis consistent with advanced DN, while uninduced diabetic mice (DM-Sema3a- dox) with identical genotype had a mild DN phenotype.

Conclusions: Collectively, our data indicate that excess sema3a plays a pathogenic role in DN and worsens the progression of the disease.

Funding: NIDDK Support

TH-PO374

Renal Failure but Hypercalciuria in Mice with Deletion of the Gene Encoding the Transient Receptor Potential Canonical 1 (TRPC1) Channel: Model of Metabolic Syndrome with Chronic Kidney Disease (CKD) Bonnie Eby1 Alexander Lau,2 Chris Skaggs,1 Lindsay J. Barron,1 Leonidas Tsiokas,2 Kai Lau.1 1Renal, Univ of Oklahoma, Oklahoma City, OK; 2Cell Biology, Univ of Oklahoma, Oklahoma City, OK.

Background: TRPC1 gene on chromosome 3q22-24 is in the linkage region for diabetic nephropathy. TRPC1 expression was reduced in diabetic rodents & patients, but a causal relationship was unclear. Since null mice display features of metabolic syndrome, we tested the hypothesis of renal phenotypes induced by TRPC1 deficiency. In parabody cells, TRPC1 protein complexes with STIM1 to mediate store-operated Ca entry. Activating STIM1 mutations produce hyperparathyroidism. So we asked if TRPC1 deficiency produces hyperparathyroidism.

Methods: From 1st to 20th months (mon), standard metabolic, ultrasonic (US) & clearance (CI) studies were done in male littermates of TRPC1 +/-, +/- & -/-. born to heterozygous parents. Creatinine (Cr) was measured by HPLC.

Results: Through the 1st year, null mice were uniformly ~10% heavier than +/- & +/- born to heterozygous parents. At 2 mon, their livers were heavier & density from 7-20 mon increased, indicative of hepatosteatosis. At 1 year, they had hyperglycemia, confirming metabolic syndrome. In null mice, serum creatinine (Cr) (0.132 vs. 0.087 mg%) was elevated & Cr clearance (Cl) (1.6 vs. 3.1 ml/min) reduced. Ct1 remained ~50% lower even factored for body (48 vs. 90 µl/min/g) & kidney weight (3.2 vs. 6.4 ml/min) CrCl. Urine albumin (12 vs. 7 µg/d; 23 vs. 14 µg/mg Cr) was elevated & hematocrit reduced in null mice. Renal US from 7-20 mon uniformly showed ~20% reduced volume. There was no difference in serum Ca (9.6 vs. 9.1 mg%), urine Ca (1 vs. 0.99 mg/d), or Ca Cl (12.3 vs. 12.9 µl/min), but fractional Ca excretion was elevated in null mice (0.9 vs. 0.5%). +/- mice had similar renal phenotypes.

Conclusions: 1. TRPC1 null mice have 50% less GFR, reduced kidney volume & increased proteinuria, offering an excellent model to study obesity & metabolic syndrome-related CKD. 2. They show no signs of hyperparathyroidism but display hypercalciuria, suggesting a role of TRPC1 channels in renal Ca homeostasis. 3. Haplold deficiency seems sufficient to induce the renal phenotypes.

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

TH-PO375

Reducing Leukoocyte Infiltration with a Novel Integrin Agonist Prevents Diabetic Nephropathy Saravanan Kumar Kanagavelu, Mohd Hafeez Faridi, Tristan Hays, Vineet Gupta. Dept of Internal Medicine, Rash Medical Unit, Chicago, IL.

Background: Diabetic nephropathy (DN) is a major complication of chronic kidney disease and the leading cause of end stage renal disease in humans. DN leads to a number of complex pathologic changes in kidney tissues, including basement membrane thickening, glomerular mesangial expansion, glomerulosclerosis and a significant loss of podocytes. Additionally, inflammation plays a significant role in the development and progression of DN and a high influx of leukocytes in the tissue biopsies. This suggests that reducing leukocyte activation, recruitment and influx may be a beneficial strategy for developing therapeutics.
against DN. We recently identified novel compounds (leukadherins) for reducing the influx of inflammatory leukocytes in the tissue. This abstract describes our results with our novel compounds in a murine model of DN.

Methods: We used a newly established murine model (BBB rat) to examine the disease closely resembles human DN. Starting at the 8th week of age, 25 rats were used. The animals were administrated our novel compound (LA1) daily for 8 weeks. Animals were monitored for blood glucose level, body weight, renal function and for glomerular defects using histopathology at different time points. Daily administration of LA1 significantly reduced the number of infiltrating leukocytes and preserved kidney function in fully diabetic animals. We saw no effect of LA1 interventions on glyceremia, as expected. Histoanalyses showed a significant reduction in glomerular mesangial sclerosis in treated animals.

Results: Daily administration of LA1 significantly reduced the number of infiltrating leukocytes in the kidney and preserved kidney function in fully diabetic animals. We saw no effect of our interventions on glyceremia, as expected. Histoanalyses showed a significant reduction in glomerular mesangial sclerosis in treated animals.

Conclusions: Our research suggests that LA1 significantly protects the kidney function in DN and prevents the loss of glomerular HS expression.

Key: TH-PO376

SAGE Innovation Awards Support

TH-PO378

Urinary Microrna Detects Podocyte Injury in Diabetic Nephropathy

Background: Podocyte injury plays a major role in the pathogenesis of diabetic nephropathy. Previous studies have suggested that this injury may occur in the early phases of glomerular disease prior to development of proteinuria. We hypothesized that podocyte injury in diabetic nephropathy could be identified by urinary microRNAs (miRs) containing podocyte-specific markers & is present prior to proteinuria. MiRs are small non-coding RNAs that are shed from injured cells & contribute to a variety of pathophysiological processes.

Methods: Digital flow cytometry was used to identify urinary MiRs derived from podocytes. Forty one patients (male=24, female=17) were recruited, 31 had type 2 diabetes mellitus (DM) & 10 were controls (median age 42 years). DM patients were divided into 3 groups: Group 1 (<30 mg/L of albumin, n=13, median age 61 yrs), Group 2 (albumin 30-300 mg/L, n=10, median age 61 yrs), and Group 3 (albumin > 300 mg/L, n=8, median age 64.5 yrs). Data were analyzed by non-parametric Kruskal-Wallis test. Results are shown as median. Units for urinary SAGE expression levels are MVA/ml of urine.

Results: There were no difference in GFR between healthy controls and Group 1 (88 vs. 82±7 ml/min/1.73m²), but GFR was significantly lower in patients with proteinuria (62±7 ml/min/1.73m²). Podocyte injury was evaluated in Group 1 patients compared to healthy controls that had significantly higher number of urinary MiRs expressing podocyte markers such as synaptopodin (1074 vs. 33, P<0.0001), nephrin (567 vs. 22, P<0.0002), podocin (1454 vs. 37, P<0.0007), and podocalyxin (838 vs. 11, P<0.0001). There were also significantly greater number of parietal cell specific markers, claudin-1 plus CD-8 positive podocytes (479 vs. 3, P<0.0007). There was a trend towards fewer MiRs expressing podocyte markers in patients with proteinuria compared to those without proteinuria in DM groups (data not shown).

Conclusions: Podocyte injury is present in type 2 diabetic nephropathy & precedes proteinuria. Characterization of podocyte-derived MiRs in the urine could be used as a novel biomarker for podocyte injury in type 2 DM patients.

Funding: Other NIH Support - NICHD

TH-PO379

SREBP Inhibition Modulates Diabetic Nephropathy in db/db Mice with Type 2 Diabetes
Xiaoxin Wang, Moshe Levi. Medicine, Univ of Colorado, Aurora, CO.

Background: Sterol Regulatory Element Binding Proteins (SREBPs) are master transcriptional regulators of fatty acid and cholesterol synthesis. In view of the importance of SREBPs in a diverse number of target organ complications in obesity and diabetes, including atherosclerosis and non-alcoholic fatty liver disease, there has been a concerted effort to develop agents that inhibit SREBP activation. Recently, Betulin [lup-20(29)-ene-3β,18β-diol] was shown to specifically inhibit the activation of SREBP.

Methods: In this study we examined the effects of Betulin induced SREBP inhibition on diabetic nephropathy in db/db mice with type 2 diabetes. We treated db/db mice on C57 BKS background with 30mg/kg body weight/day of Betulin mixed with chow for 12 weeks.

Results: We have found increased renal lipid accumulation in the kidneys of db/db mice mediated by increased expression of nuclear SREBP-1 and SREBP-2 protein. Treatment with Betulin prevented the upregulation of SREBPs in the kidney resulting in a significant reduction of de novo lipogenesis and cholesterol accumulation. SREBP inhibition prevented the increases in urine albumin excretion (db/db: 59±13 μg/24 hr, db/db-Betulin: 21±3 μg/24 hr, p<0.05) and mesangial matrix expression as shown by PAS staining of the kidneys of db/db mice (mesangial matrix index: db/db: 2.25±0.08, db/db-Betulin, 1.60±0.11, p<0.05). The treatment also prevented podocyte loss determined by staining with p57 and WT-1. Furthermore, improvement in oxidative stress and inflammation was also observed in the treatment groups (urinary TBARS: db/db: 181±27 mmol/day vs. db/db-Betulin, 163±24 mmol/day, p<0.05; urinary MCP-1: db/db: 146±22 mmol/day vs. db/db-Betulin, 83±15 mmol/day, p<0.05). To determine if Betulin has direct effects in kidney podocytes, we cultured human podocytes in high glucose conditions. Betulin prevented db/db-mediated by increased expression of nuclear SREBP-1 and SREBP-2 protein.

Conclusions: Our study therefore indicates a renoprotective role for SREBP inhibition in diabetic nephropathy by preventing lipid accumulation and modulating oxidative stress and inflammation.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO380

SGLT2 Inhibition Modulates Renal Lipid Metabolism and Inflammation and Prevents the Development of Nephropathy in Diabetic Mice
Xiaoxin Wang, Moshe Levi. Medicine, Univ of Colorado, Aurora, CO.

Background: SGLT2 results in lowering of blood glucose in diabetic humans and rodent models but the effects on progression of diabetic nephropathy has not been fully established.

Methods: We determined the effects of the inhibition of SGLT2 via a selective SGLT2 inhibitor on diabetic nephropathy in db/db mice.

Conclusions: Together, our results for the first time demonstrate a significant functional role of miR-214 in targeting PTEN to regulate MC hypertrophy and fibrinectin expression, thus the link between miR-214 and PTEN, in vitro we used a sensor plasmid containing the MRE for miR-214.
Results: After 12 weeks treatment, we found that SGLT2 inhibition caused marked decreases in urinary albumin (745±36 mg/g in db/db vs. 207±5 mg/g in treated db/db, p<0.001) and non-esterified fatty acid (triglyceride-substances) levels (0.09±0.02 mol/g in db/db vs. 0.48±0.10 mol/g in treated db/db, p<0.01) indicating oxidative stress. SGLT2 inhibition prevented renal lipid accumulation via inhibition of LPK, SCD-1 and DGAT1, key enzymes that mediate fatty acid and triglyceride synthesis. SGLT2 inhibition also prevented inflammation via inhibition of macrophage accumulation, and expression of p65, TLR4, MCP-1 and OPN. These effects were associated with prevention of mesangial expansion, accumulation of extracellular matrix proteins as determined by fibronectin and type IV collagen quantitative immunofluorescence microscopy, and podocyte loss as determined by WT1 and synaptopodin quantitative immunofluorescence microscopy (all p<0.05).

Conclusions: In summary, our study showed that SGLT2 inhibition modulates renal lipid metabolism and inflammation and prevents the development of nephropathy in db/db mice.

Funding: NIDDK Support, Pharmaceutical Company Support - Johnson & Johnson

TH-PO381
Effects of Bile Acid Sequestrants on Kidney Disease in Mice with Diet Induced Obesity, Insulin and Leptin Resistance
Xiaoxin Wang, Moshe Levi.
Medicine, Univ of Colorado, Aurora, CO.

Background: Bile acid sequestrants (BAS) including colesuvelam are orally administered nonabsorbable polymers that decrease serum cholesterol and serum glucose in patients and animal models with type 2 diabetes mellitus. The effects of BAS on renal dysfunctions such as obesity and insulin resistance or type 2 diabetes mellitus have not been studied. Sevelamer, an effective phosphate binder for treating ESRD, has been shown to bind bile acids, advanced glycation end products and uremic toxics, which would be of benefit to treating diabetic patients with chronic kidney disease. Our goal was to evaluate the effect of sevelamer on metabolic and renal parameters in an obese animal model with insulin and leptin resistance and to determine underlying mechanisms.

Methods: Our studies were performed in C57BL/6J male mice fed a control low fat (LF) diet (10 kcal% fat) or high fat (HF) diet (60 kcal% fat). The diets were supplemented with a) no addition or b) 2% sevelamer.

Results: BAS prevented the increase in urine albumin excretion (HF: 47±11* vs 138±14* mg/g, p<0.05) and decreased the PAS staining in the kidney of HF mice. Treatment with BAS decreased the renal lipid accumulation as shown by oil red O staining. HF diet induced upregulation of proinflammatory genes (TNF-α, IL-6, and IL-1β) and proinflammatory cytokines (CC1, CC2, and IL-1β) in the kidney which were decreased by treatment with BAS. In addition BAS induced downregulation of extracellular matrix protein fibronectin and macrophage marker CD68 expression in the kidney. The beneficial effects of BAS were also associated with decreases in renal glucose oncogene expression (PEPC and G6Pase) and renal glucose transporter (SGLT2). Treatment with BAS also and most notably increased renal expression of Nrf1, Sirt1, Pgc-1α, Sirt3, ERRα, that mediate mitochondrial biogenesis, MCAD and LCAD, that mediate fatty acid oxidation, and Nrf2, HO-1, and SOD, that mediate antioxidative stress.

Conclusions: In summary, our study showed a novel renoprotective role for bile acid sequestrant treatment in mice with diet induced obesity, insulin and leptin resistance.

Funding: NIDDK Support, Pharmaceutical Company Support - Genzyme

TH-PO382
Loss of IFT Complex A Protein, THML1, Causes Hyperglycemia-Induced Obesity with Fatty Liver Disease, Prediabetes, and Hypertension
Damon T. Jacobs, 1 Michael P. Schonfeld, 1 Luciane M. Silva, 1 Anindita Das, 1 Lila Sharan, 1 Xiaoxin Wang, 1 Isha Kaur, 2 Michael A. Rose, 1 Takahiro Hara, 3 Marcelo Da Silva, 1 Joseph Satriano, 1 Kumar Sharma.
1 Emergency Medicine and Section of Critical Care, Kansas City, KS; 2Dept of Pediatrics, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 3Center for Developmental Biology and Regenerative Medicine, Seattle Children’s Research Institute, Seattle, WA.

Background: Primary cilia are antenna-like structures present on most vertebrate cells that mediate signaling pathways. Cilia defects mediate signaling pathways. Cilia defects cause ciliopathies, which manifest common traits such as obesity, fatty liver disease, prediabetes, and hypertension. Damon T. Jacobs, 1 Michael P. Schonfeld, 1 Luciane M. Silva, 1 Anindita Das, 1 Lila Sharan, 1 Xiaoxin Wang, 1 Isha Kaur, 2 Michael A. Rose, 1 Takahiro Hara, 3 Marcelo Da Silva, 1 Joseph Satriano, 1 Kumar Sharma.

Methods: We examined a role for murine Thml1 in obesity using a Thml1 conditional knockout (cko) allele together with a ubiquitous, tamoxifen-inducible Cre recombinase.

Results: In F1 Akita mice the kidneys underwent hypertrophy, mesangial expansion and albuminuria. There were also a significant decreases in kidney mitochondrial density and Complex I and IV activities. As expected mTORC1 activity markedly increased (via p-p70S6K Wt 10549±1208 vs 16008±487), in accord with these changes we observed a pronounced decrease in autophagy (LC3-II/LC3-I ratio; Wt 0.237±0.027, Ak 0.101±0.024, and this was verified by the accumulation of the autophagy adapter or linker protein, p62, Sequestosome-1 (p62; Wt 6998±1165 mol/mg); i.e., in Akita, EMPA-induced inhibition of glucose reabsorption was counterbalanced by reduced filtered glucose. EMPA attenuated/prevented the modest upregulation of systolic blood pressure and markers of kidney injury/ inflammation in Akita (incl. mRNA for NFKB, CCL2, CD14, TIMP2).

Conclusions: Inhibition of SGLT2 with emlaspigliflozin in diabetic Akita mice lowers hyperglycemia and attenuates kidney growth and albuminuria in proportion. Prevention of diabetes-induced rise in GFR by EMPA is consistent with a role of SGLT2 in proximal hyperreabsorption and the tubulocentric concept of hyperfiltration.

Funding: NIDDK Support, Veterans Affairs Support, Pharmaceutical Company Support - Boehringer Ingelheim Pharma GmbH & Co. KG

TH-PO384
Reduction of Renal Mitochondria in Type 1 Diabetes Is Associated with Increased Mitophagy
Joseph Satrani, Kumar Sharma.
Nephrology, UC San Diego & VASDHS, San Diego, CA.

Background: Autophagy has been implicated in diabetic kidney disease however, the role of specific types of autophagy have not been identified and its functional role remain unclear.

Methods: Autophagy was evaluated in type 1 diabetic F1 Akita mice. Renal histology, albumin/creatinine ratio and mitochondrial protein and complex activity was measured. Autophagy protein expressions were evaluated by immunoblotting. All values are relative densitometry units/SEM normalized against alpha-Tubulin.

Results: In F1 Akita mice the kidneys underwent hypertrophy, mesangial expansion and albuminuria. There were also a significant decreases in kidney mitochondrial density and Complex I and IV activities. As expected mTORC1 activity markedly increased (via p-p70S6K Wt 10549±1208, Ak 16008±487). In accord with these changes we observed a pronounced decrease in autophagy (LC3-II/LC3-I ratio; Wt 0.237±0.027, Ak 0.101±0.024, and this was verified by the accumulation of the autophagy adapter or linker protein, p62, Sequestosome-1 (p62; Wt 6998±724, Ak 15945±734). A number of specific AuTopaGy (Agt) genes and proteins are induced in response to autophagic stimulation. There are 2 conjugation pathways involved in the developing autophagosomal membrane. Atg3, utilized only in the pathway specific to LC3 lipidation, was decreased in accord with LC3-II levels (Atg3 Wt 11493±1380, Ak 6703±1157). However, Atg5 and Atg7, required for the Atg12-conjugation pathway, and Beclin-1, required for initiation of phagophore nucleation, were not changed (Atg5 13560±2110, Ak 14551±1340; Atg7 Wt 12565±2078, Ak 12011±1232; Beclin-1 Wt 8008±579, Ak 6610±505). Mitophagy selective adapter proteins, PINK1 (Wt 17975±463, Ak 4380±1744) and Bnip3 (Wt 24588±511, Ak 10430±2464), were increased in Akita mice kidney tissue. This was ongoing with AMPK activation and in AMPK KO mice.

Conclusions: A shift from general autophagy to selective mitophagy may lead to a progressive reduction of mitochondria and homeostatic function in diabetic mice.

Funding: NIDDK Support, Veterans Affairs Support
The Lin28-Let7 Pathway Modulates TGF-β-Induced Collagen Expression in Glomerular Mesangial Cells under Diabetic Conditions

Jung Pak Park, Mitsuo Kato, Nancy E. Castro, Rama Natarajan.

Biotherapeutic Discovery Research, Eli Lilly and Company, Indianapolis, IN.

Background: The Lin28-Let7 pathway modulates TGF-β-induced collagen expression in glomerular mesangial cells under diabetic conditions. We previously showed that a decrease in Sirt1 expression in proximal tubules (PTs) contributes to development of diabetic nephropathy (DN) and suggested that iNampt levels are affected, at least in part, by glucose and/or the Sirt1-Nampt interplay. We also showed a role for nicotinamide mononucleotide (NMN) as a candidate mediator of the interplay between PTs and podocytes.

Methods: We implanted 7-week-old male Akita mice (B2.B6-In2fl+/−/−) with subcutaneous Alzet minipumps filled with either membrane or saline. Membrane is a weak non-competing NMDA antagonist used for treatment of Alzheimer’s dementia, and the daily dose delivered in this study was similar to those used clinically. Similar minipumps were implanted into control DBA/2J mice. Renal function was estimated after 28 days.

Results: Akita mice had substantial albuminuria by 11 weeks of age. However we observed 28 days of membrane treatment markedly reduced 24-hr albumin excretion in Akita mice compared to saline-treated controls. Membrane had no effect on albumin excretion in DBA/2J mice. The effects of genotype, the interaction between membrane and genotype are both significant by two-way ANOVA (P < 0.05). Using transmission EM we saw a reduction in podocyte foot process effacement in membrane-treated Akita mice. Membrane had no effect on foot process morphology in DBA/2J mice.

Conclusions: These data suggest that sustained hyperactivation of NMDA receptors in vivo may contribute to development of diabetic nephropathy, and suggests a therapeutic strategy based on a drug already approved by FDA for pharmacotherapy of dementia.

Funding: Private Foundation Support

Interplay of Proximal Tubular Cells and Podocytes through a Mediator of Nicotinamide Mononucleotide in Diabetic Nephropathy

Kazuhiro Hasegawa, Shu Wakino, Koichi Hayashi, Hiroshi Itoh.

Depart of Nephrology, Keio Univ, Tokyo, Japan.

Background: We previously showed that a decrease in Sirt1 expression in proximal tubules (PTs) reduces Sirt1 levels and increases claudin-1 levels in podocytes (Pods), leading to the initiation of albuminuria (Alb) in diabetic nephropathy (DN) mice (STZ and db/db). PT-specific Sirt1 transgenic (TG) and conditional knockout (CKO) mice showed prevention and progression of Alb, respectively. Genotyping at ASN 2011, 12). We also showed a role for nicotinamide mononucleotide (NMN) as a candidate mediator of the interplay between PTs and Pods using conditioned medium from PTs. In this study, we investigated the in vivo interplay between PTs and Pods in an in vivo model.

Methods: We synthesized Mant (N-methylanthraniloyl)-NMN as a fluorescence-labeled nucleotide. Saline (Sal) or Mant-NMN was administered by arterial injection and kidneys were examined by multiphoton microscopy.

Results: We observed a PT-Pod flow of NMN.
Dnmt1-mediated epigenetic regulation of podocytes’ claudin-1 expression in diabetic nephropathy

In diabetic nephropathy, Sirt1 expression in podocytes is decreased, leading to decreased Dnmt1 activity and claudin-1 (a tight junction protein) in podocytes with prominent albuminuria. These changes were prevented in Sirt1 transgenic mice and were aggravated in Sirt1 KO mice.

Although we found that DNA methyltransferase 1 (Dnmt1) mediates Sirt1-induced Cpg island methylation, there is a lack of evidence showing whether Dnmt1 in podocytes (Pods) reduces albuminuria (Alb).

Methods: To elucidate the role of Dnmt1, we used gene delivery of NPHS2-Dnmt1 cDNA vector (Dnmt1 cDNA), Dnmt1 siRNA, and control (Cont) plasmid using the HVJ vector by tail vein injection. Efficiency of transfer was tested by immunostaining and immunoelectron microscopy. Mice were injected with saline (Sal) or streptozotocin (STZ) to induce diabetic nephropathy (DN).

Results: We found that Sirt1 directly activates Dnmt1 via its deacetylation using cultured and laser micro-dissected Pods. In Cont+Sal, endogenous Dnmt1 was mainly detected in Pods. Gold particles labeling Dnmt1 were characteristically located on the bottom and sides of foot processes. In Dnmt1 cDNA+Sal, Dnmt1 upregulation was detectable in a Pods-specific way owing to the NPHS2 promoter. The Dnmt1 siRNA successfully silenced Dnmt1 in kidneys. In Cont+STZ, Dnmt1 activity was decreased resulting in increased claudin-1 expression and Alb, which were prevented in Dnmt1 cDNA+STZ and worsened in Dnmt1 siRNA+STZ. In Cont+Sirt1 KO, reduced Dnmt1 activity was accompanied by increased claudin-1 levels and Alb, which were blocked in Dnmt1 cDNA+Sirt1 KO. Alb was dramatically enhanced by the Dnmt1 siRNA but not by a scrambled siRNA. These changes were blocked in Dnmt1 siRNA+Sirt1 TG. These phenomena were also observed in obese-type DN (db/db) and Dnmt1 hetero-KO (Dnmt1 +/-) mice, but not in 5/6 nephrectomized mice.

Conclusions: Dnmt1 epigenetically protects against Alb and is beneficial for the maintenance of Pods function in DN.

TH-PO390

Analysis of Urinary Albumin by Peptide MRM Circumvents Partial Protein Degradation and Loss of Antibody Recognition after Long-Term Storage


Background: Many potentially valuable biological samples have been stored for extended time under sub-optimal conditions such as -20°C. Unfortunately, proteins can aggregate or denature at -20°C and become refractory to standard methods of protein analysis. Peptide-level analysis may overcome these effects, thereby permitting the use of these samples in clinical research. For the CKD Biomarkers Consortium.

Methods: Urine samples were collected in 1982-91 from 49 Pima Indians with type 2 diabetes. Creatinine and albumin were measured (original) and the remaining sample was stored at -20°C. Albumin and creatinine were assayed again in 2012 after storage at -20°C. Albumin was measured by two antibody-based methods and by a newly developed multiple reaction monitoring (MRM) method with peptide-based mass spectrometry. MRM assay of fresh samples compared favorably with 3 established antibody-based assays. Proper sampling for MRM required prior homogenization of particulate material.

Results: Antibody-based assays (in 2012) detected lower albumin concentration than the original antibody-based assay. In contrast, analysis of albumin by MRM recapitulated the original measure (R=0.78). New measurement of creatinine by chemical assay also closely replicated original values (R=0.95).

Conclusions: Long-term sample storage under sub-optimal conditions need not impede all uses of valuable sample collections. Analysis of albumin and potentially other proteins by peptide MRM can overcome protein degradation that occurs at -20°C. This may prove valuable to many sample collections.

Funding: NIDDK Support

TH-PO391

Rapamycin Fails to Ameliorate Established Renal Injury and Augments Mortality in Diabetic Mice


Background: Rapamycin (Rapa) ameliorates kidney injury in young diabetic mice; its efficacy in aging diabetic mice with established kidney injury is not known.

Methods: We performed 2 studies in type 2 diabetic mice. Reversal Study: Male and female 7 month-old db/db (non-diabetic) and db/db (diabetic) mice received control diet or rapa (2.5mg/kg/day) diet for 4 mos (n=20, each group) and sacrificed at 11 mos of age. B. Life span Study: 4 month-old male and female db/db mice were treated with control diet or rapa diet (n=40, each group) till natural death; necropsy was done.

Results: A. Reversal Study: At 11 mos of age, diabetic mice showed increase in glomerular area, mesangial matrix area, albuminuria vs. non-diabetic; creatinine clearance was unchanged. Rapa did not change any of these parameters. Glomerular hypertrophy, PAS+ fractional mesangial area, and, in increase renal cortical type IV collagen (male) and fibronectin seen in diabetic mice was not reversed by rapa. Signaling assays did not show evidence of mTORC1, Akt or Erk activation in the kidney of diabetic mice and rapa did not affect these parameters. Whole blood rapa levels by HPLC were 1.25-3ng/ml.

B. Life span Study: Including 120 days when diet study started, the median life span of male and female diabetic mice on control diet was 349 and 487 days, respectively. After 210 days on diet, rapa fed diabetic mice had greater mortality than control diet mice (p=0.02, female, NS for male) (log rank). Cox proportional hazard analysis showed mortality risk was lower (10%) for female vs. male control diet fed diabetic mice. Adjusting for gender difference, rapa increased mortality risk by 1.7-fold for both male and female diabetic mice (p<0.05). On necropsy, supplicative inflammation in several organs was the main cause of death; this was augmented by rapa. About 30% of deaths were due to neoplasms, mostly hepatocellular carcinoma; rapa reduced these neoplasms.

Conclusions: Rapa not only fails to ameliorate established renal injury but worsens mortality in type 2 diabetic mice.

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

TH-PO392

Protective Effects of Endogenous Vasohibin-1 on Podocytes in Diabetic Nephropathy


Background: We recently demonstrated the protective role of Vasohibin-1 (VASH1),a negative feedback regulator of angiogenesis, in mouse models of diabetic nephropathy. Regulatory roles of VASH1 on albuminuria, renal inflammatory/fibrotic alterations, angiogenic factors and slit-proteins were observed. In endothelial cells, VASH1 mediates cell survival under oxidative stress via inducing Sirt1 and SOD2 and Ezh2 mediates down-regulation of VASH1. Here, we aimed to elucidate the mechanism involved in the protective role of endogenous VASH1 in diabetic nephropathy.

Methods: Type 1 diabetes was induced in male VASH1+/- or wild-type littermates by injections of low-dose streptozotocin. Mice were sacrificed after 16 weeks, kidneys were removed and subjected to real-time PCR and immunoblot analysis. Conditionally immortalized mouse podocytes were cultured under high glucose condition (HG) with VASH1 siRNA (24 hrs). Then, cells were harvested and subjected to immunoblot or real-time PCR analysis.

Results: Renal mRNA levels for Sirt1 were reduced in the diabetic wild-type mice, but was partly recovered in the diabetic VASH1+/- mice. Renal mRNA levels of Erzb2, SOD1, SOD2 were not significantly different between diabetic wild-type and VASH1+/- mice. In cultured podocytes, mRNA levels of nephrin were reduced under HG, and treatment with VASH1 siRNA resulted in further reduction. VASH1 siRNA, augmented the expression of VEGF-A, attenuated the expression of Ang-1 and ZO-1 (immunoblot). Treatment with VASH1 siRNA increased mRNA levels of Erzb2, and tended to suppress mRNA levels of SOD1, but did not alter mRNA levels of SOD2 under HG.

Conclusions: These results suggest that endogenous VASH1 may exert the direct protective effects on podocytes through regulating slit-proteins and stress response in association with the amelioration of albuminuria, thus implicating its potential use in treating diabetic nephropathy.
SGLT2 Inhibition Only Exerts 50-60% of Filtered Glucose in Euglycemic Mice Because of Compensation by SGLT1. Takahiro Masuda,1 Timo M. Rieg,1 Mario Gerasimova,1 Eric Mayoux,2 Hermann Koepssel,3 Volker Vollker.1 1 Div. of Nephrology, UC San Diego & VA San Diego Healthcare System, San Diego, CA; 2Boehringer-Ingehelm, Biberach, Germany; 3Anatomy and Cell Biology, Univ of Wurzburg, Germany.

Background: The sodium-glucose cotransporter SGLT2 reabsorbs most of the filtered glucose in the kidney. Inhibitors of SGLT2 enhance urinary glucose excretion (UGE) and are new antidiabetic drugs but they only excrete 50-60% of the filtered glucose under euglycemia. We aimed to define the role of SGLT1 under these conditions which accounts for ~3% of renal glucose reabsorption in euglycemic mice (Gorboulev 2012).

Methods: A. Wild-type (WT) and Sgl1-deficient mouse (Sgl1-/-) were treated by oral gavage with vehicle (veh) or SGLT2 inhibitor, empagliflozin (EMPA; 0.1-10mg/kg) followed by quantitative urine collection in metabolic cages for 3 h. B. WT and Sgl1-/- were treated with EMPA (300mg/kg of diet) for 3 weeks. Urine was collected weekly.

Results: EMPA dose-dependently (0.01-0.3 mM) increased urinary glucose excretion (UGE) and its transcription/translation in HK2 cells. EMPA induced UGE in WT: 0.1±0.1 (veh) to maximum of 30.5±4.2nmol/min/g (ED50 ~1.3mg/kg); compared with WT, the EMPA-induced UGE was doubled in Sgl1-/-: 1.0±0.2 (veh) to 36.3±3.2nmol/min/g; EMPA did not induce 3.0±0.3mg/kg (n=6). B. Within 24h, EMPA (in diet) increased urine glucose/creatinine ratio from 8±1 (basal) to 228±3 (fed) in WT and from 95±10 to 368±450μmol/mg in Sgl1-/- (n=10-11); doubling of the ratio in Sgl1-/- vs WT was maintained at 1-3 weeks. EMPA-induced reduction in blood glucose (BG) was enhanced in Sgl1-/- vs WT after 24h (33±5% vs -11.5%; BG and food intake were similar between groups at 1-3 weeks. Subsequent clearance studies in chronic EMPA-treated mice revealed fractional renal glucose excretion (FGE) in WT and Sgl1-/- as follows: Sgl1-/- (n=9-10). Additional application of EMPA (10mg/kg ip; 1hr prior to study) increased FGE to 56±3% in WT (mimicking values of FGE in Sgl1-/- mice - Vallon 2011) and to 101±3% in Sgl1-/- (n=4-6).

Conclusions: SGLT2 and SGLT1 account for renal glucose reabsorption. SGLT1 reabsorbs 40-50% of filtered glucose during SGLT2 inhibition in euglycemic mice.

Funding: NIDDK Support, Veterans Affairs Support, Pharmaceutical Company Support - Boehringer Ingelheim Pharma GmbH & Co. KG.

Relevance of Myo-Inositol Oxgenase (MIOX) in Renal Tubular Injury in Obesity/Metabolic Syndrome Tatsuya Tominaga, Ming Zhan, Yashpal S. Kanwar. Pathology, Northwestern Univ, Chicago, IL.

Background: MIOX, a renal tubular enzyme, channels myo-inositol into xylulose-pentose pathway. Previous studies indicate that its expression increases in diabetic state and its modulation in obesity or diabetes mellitus could have potential renal protective effects. We aimed to define the role of MIOX in renal tubular injury in obesity/metabolic syndrome.

Methods: Mice were fed with HFD for 2-8 weeks, and their kidneys harvested for various studies. Similarly, HK2 cells were subjected to FFA (palmitic acid) treatment, and processed for MIOX expression. Chromatin Immuno-precipitation (ChiP) and MIOX promoter analysis following the binding to the consensus sequence of Sterol Regulatory Element-Binding Protein 1 (SREBP1).

Results: MIOX expression increased in renal tubules in mice receiving HFD compared with those receiving normal diet. In addition, increased expression of SREBP1 and Bax was detected in the renal cortices. MIOX expression also followed by increasing FFA treatment in a dose-dependent (0.01-0.3 mM) manner in HK2 cells. Simultaneously, FFA treatment increased p53 and Bax expression. MIOX promoter included multiple segments with consensus binding sequence for sterol regulatory element-binding site (-2460 to -1887, -523 to -22). ChiP assay confirmed that SREBP1 binds to MIOX promoter. Furthermore, we cloned the MIOX promoter (-1463 to +33) in pGL3 vector. MIOX promoter activity was increased by 100% with FFA treatment in HK2 cells.

Conclusions: These preliminary findings indicate that the MIOX transcription, besides being regulated by hyperglycemic, osmotic and oxidative stresses, is also modulated by FFA and HFD, suggesting that this enzyme may be responsive to the adverse effects of obesity and is likely to lead to tubulointerstitial disease, as seen in other metabolic disorders.

Funding: NIDDK Support

A Novel Dipeptidyl Peptidase IV Inhibitor Ameliorates Diabetic Nephropathy Independent of Metabolic Effects in db/db Mice Mi Jin Lee,1 Young Sun Kang,1 Jin Joo Cha,1 Young Youl Hyun,1 Ji Eun Lee,1 Hyunwook Kim,1 Mihwa Lee,1 Jung Eun Kim,1 Hye Kyong Song,1 Jae-Young Han,1 Dae R. Cha.1 1Nephrology, Korea Univ Ansan Hospital, Ansan, Kyunggido, Republic of Korea; 2Nephrology, Sanggyunkwan Univ Kangbuk Samsung Hospital, Seoul, Republic of Korea; 3Nephrology, Wonkwang Univ Sanbon Hospital, Republic of Korea; 4Pathology, Inha Univ Hospital, Incheon.

Background: Although DPP IV inhibitor has been widely used for management of hyperglycemia in type 2 diabetic patients, its role on renal function is not yet clear. The aim of present study is to investigate the effects of DA-1229, a newly developed DPP IV inhibitor, on glucose and lipid metabolism and renal injury in db/db mice.

Methods: Experimental groups were divided into three groups; non-diabetic db/m mice (n=8), untreated db/db mice (n=8), and db/db mice treated with DA-1229 (300mg/kg/d) for 12 weeks (n=8).

Results: DPP-4 activity in hearts, liver, and adipose tissue did not significantly different between db/m and db/db mice. However, DPP-4 activity in kidney showed significantly higher in diabetic in kidney, and DA-1229 treatment significantly suppressed DPP-4 activity in the kidney. Although DA-1229 treated db/db mice showed an improvement in dyslipidemia, DA-1229 did not induce significant improvement in insulin resistance determined by HOMA-IR and insulin tolerance test, glycemic control and HbA1c levels. Additionally, DA-1229 showed a little effect on body weight and systolic blood pressure. However, DA-1229 treatment markedly decreased urinary albumin excretion, kidney/body weight, serum creatinine levels and improved pro-fibrotic molecule synthesis including TGFB1, PAI-1 and type IV collagen. Furthermore, DA-1229 treatment improved renal lipid metabolism. Interestingly, DA-1229 treatment suppressed AMPK-PGC-1α pathway. However, urinary protein and restored renal nephrin expression in diabetic glomeruli. In addition, DA-1229 also markedly suppressed renin expression of HMG-1 protein expression observed in diabetic kidney.

Conclusions: These results suggest that a novel DPP IV inhibitor, DA-1229 provide renal protective effects independent of its hypoglycemic metabolic effects.

Aggravation of Diabetic Nephropathy in Bis-Haploinsufficient Mice along with the Blunted Induction of SOD Activity Kwon Suk Yang, Ji Hee Lim, Min Young Kim, Sungjin Chung, Seok Joon Shit, Hyung Wook Kim, Yong-Soo Kim, Cheol Whee Park. Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea.

Background: Bel-2 interacting cell death suppressor (Bis), known as anti-stress and anti-apoptotic protein, has been reported to modulate susceptibility to oxidative stress. In this study, we investigated the potential role of Bis as an antioxidant protein in diabetic nephropathy (DN).

Methods: DN was induced in Bis-heterozygote mice (Bis-HT) via streptozotocin injections and the resulting phenotypes were compared to those of wild type (Bis-WT) mice over the course of 20 weeks after diabetes induction.

Results: Renal injuries, represented by increased plasma creatinine levels and increased albuminuria, were greater in diabetic Bis-HT (Bis-HT DM) mice than in diabetic Bis-WT (Bis-WT DM) mice, accompanied by a significant increase in oxidative stress markers. Moreover, glomerular matrix expansion, TGF-b1 and HIF-1a expression, tubulointerstitial fibrosis and proportion of apoptotic cells were significantly higher in Bis-HT DM mice than in Bis-WT DM mice with the same degree of hyperglycemia. However, systolic pressures of DN were all restored by tempol treatment. The expression of SOD1 and SOD2 increased on the induction of DM in Bis-WT mice, correlating with the total SOD activity, but was not observed in Bis-HT and Bis-HT DM mice. An in vitro study showed that the knockdown of Bis expression also resulted in the impaired induction of SOD activity as well as SOD expression in HK-2 and NMS cells.

Conclusions: Our results suggest that decreased antioxidant capacity of Bis may aggravate DN in Bis-HT DM mice, which could possibly result from disruption in the regulation of SOD1 or SOD2 protein quality upon oxidative stress.

Fenofibrate Ameliorates Diabetic Nephropathy through the Activation of AMPK-PGC-1α-ERR-α Signaling in db/db Mice Kwon Suk Yang, Ji Hee Lim, Min Young Kim, Ji Hee Lim, Hoon Suk Park, Sun Byung Choi, Seok Joon Shin, Hyung Wook Kim, Yong-Soo Kim, Cheol Whee Park. Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea.

Background: The peroxisome proliferative-activate receptor-α (α-ERR) is a lipid-sensing transcriptional factor that has a role in gluco-oxidative stress and lipotoxicity. Here, we evaluated whether fenofibrate has renoprotective effects through the change of AMPK-PGC-1α-ERR-α and their downstream P38-Akt pathway in db/db mice.

Methods: Male C57 BL/6 db/db mice (Biozzi DTM) mice at 8 weeks of age were divided to receive either a regular diet chow or a diet containing fenofibrate (0.2% wt/wt, n=6, respectively). The treated db/m mice and db/db mice were administered fenofibrate for 12 weeks and were evaluated about renal functional and pathologic phenotypes and the AMPK-PGC-1α-ERR-α pathway.

Results: The mesangial area expansion, inflammatory cell infiltration, and the accumulation of intra-renal lipids were observed in db/db mice and this was related to a downregulation of PPARα suppressed AMPK-PGC-1α-ERR-α expressions and increased.
PI3K-Akt-phosphorylation of FoxO3a, which led to oxidative stress and decreases fatty acid oxidation. Fenofibrate significantly decreased albuminuria and reversed all of the renal phenotypes by increasing the PPARα expression with concomitant activation of AMPK-PGC-1α-ERR-1α and inactivation of PI3K-Akt pathway, dephosphorylation of FoxO3α signaling in db/db mice. Fenofibrate ameliorated high glucose induced oxidative stress and apoptotic cell death in cultured mesangial cells through the same pathways.

**Conclusions:** Our results suggest that PPARα agonists are associated with improvement of lipotoxicity and oxidative stress through the activation of AMPK-PGC-1α-ERR-1α signaling in db/db mice, which may be a potentially therapeutic modality to treat diabetic nephropathy.

**TH-PO398**


**Background:** Activated factor Xa (FXa) plays an important role in the coagulation cascade. In addition, FXa binds to protease-activated receptors PAR-1 and PAR-2 and may exert cellular function in the endothelium. We have recently shown that the endothelial glyocalyx surface layer (ESL) is important for the initiation of proteinuria and contributes to the early inflammatory changes in diabetic nephropathy. We therefore tested the hypothesis that (1) treatment with a FXa inhibitor prevents proteinuria and inflammatory changes in diabetic and ATII-infused mice and (2) that this effect is mediated via the endothelium.

**Methods:** STZ (n=8), db/db mice (n=8) and control animals received sham or rivaroxaban RIVA (50 mg/kg/day) before or during hyperglycemia. After 2 and 8 weeks of hyperglycemia, the animals were analyzed. Immunohistochimistry was performed on cryostat/paraffin sections. EM analysis of ESL was carried out after Alcian blue perfusion. Gene and protein expression was analyzed by rt-qPCR and western blot analysis. Signal transduction of FXa was assessed by measuring ERK phosphorylation pERK.

**Results:** Treatment with RIVA reduced the hyperglycemia–induced increase in proteinuria in both STZ and db/db mice significantly. Decrease of heparansulfates and endothelial glyocalyx density was prevented. The increase in inflammatory cytokines and adhesion molecules in diabetic animals was also reduced by RIVA treatment. Macrophage infiltration in the diabetic kidney was reduced by RIVA treatment. The increase in pERK in diabetic glomeruli was diminished by RIVA treatment. All these changes were not observed in AngII-treated animals.

**Conclusions:** Inhibition of factor Xa signalling with rivaroxaban in glomerular fibrosis and albuminuria in diabetic nephropathy.

**TH-PO399**

Increased Tubulointerstitial Damage, Macrophage Infiltration, and Nuclear Factor-XB Activity in the Kidneys of Diabetic STAT5 Knockout Mice Karen T. Coschigano, 1,2 Erich P. Heine, 3 Ramiro Malgor. 1,2

**Background:** Diabetic nephropathy is currently the most common cause of chronic renal failure in the United States. Mounting evidence indicates that inflammatory mechanisms are involved in the development of diabetic nephropathy. Our prior analysis of nondiabetic and streptozotocin-induced diabetic wildtype and Signal Transducer and Activator of Transcription 5 (STAT5) knockout mice revealed that RNA expression of many inflammation-related genes is dramatically upregulated in kidneys of diabetic STAT5 knockout mice. We hypothesized that Nuclear Factor xB (NF-xB), a major inflammatory transcriptional activator, would have increased activity in diabetic STAT5 knockout mice that would coincide with this increased gene expression, as well as with increased macrophage infiltration and kidney damage.

**Methods:** We used immunohistochemical methods to assess lymphocytic infiltration and kidney morphology and a DNA binding assay to measure NF-xB activity of kidneys isolated from nondiabetic and streptozotocin-induced diabetic wildtype and STAT5 knockout mice.

**Results:** We demonstrated that diabetic STAT5 knockout mice had a greater number of macrophages and lymphocytic aggregates, increased fibronectin expression, and tubulointerstitial damage when compared to the other nondiabetic and diabetic mice. In addition, we showed that NF-xB DNA binding activity was significantly greater in diabetic STAT5 knockout mice when compared to their counterparts.

**Conclusions:** The data suggest that the STAT5 knockout mice have lost some inherent protection from inflammatory responses that wildtype mouse groups retain, indicating that the STAT5 proteins may serve a protective role in diabetic nephropathy.

**TH-PO400**

CYP2C-Derived EETs Contribute to Insulin Sensitivity in Mice and in Humans James M. Luther, Mahesa Gangadhariah, Jorge H. Capdevila, Ambra Pozzi. Medicine, Vanderbilt Univ, Nashville, TN.

**Background:** The β45 arachidonic acid epoxyeicosatrienoic (CYP2C, CYP2J2) modulate blood pressure via renal and vascular effects, and interventions which prevent degradation of their epoxygenesicatrienonic acid products (EETs) via epirole hydroxide inhibition may favorably alter glucose homeostasis.

**Methods:** We tested the hypotheses that endogenous CYP2C-derived epoxygenesicatrienic acids alter insulin sensitivity in vivo using Cyp2c44-deficient mice during 16 weeks of high fat or regular chow diet. We assessed whole organism insulin sensitivity using hyperinsulinemic clamp and tissue insulin sensitivity using 2-deoxyglucose uptake. To examine this association in humans, we assessed insulin sensitivity and plasma EETs during controlled dietary sodium intake in healthy and metabolic syndrome subjects.

**Results:** Despite similar body weight and adiposity, insulin sensitivity decreased in Cyp2c44–/– mice compared to wild-type (WT) controls (40.4±2.7 vs 57.8±3.8 mg/kg/m; P<0.01) and 1.6-fold WT and Cyp2c44–/– mice were both significantly insulin resistant compared to WT mice, but were similar between genotype. Hepatic glucose production during regular chow diet was similar at baseline, but was incompletely suppressed in Cyp2c44–/– mice during insulin-glucose infusion (1.2±1.8 vs 6.4±0.6). Muscle and adipose tissue C2 2-deoxyglucose uptake in vivo was diminished in Cyp2c44–/– mice. However, insulin-stimulated 2-deoxyglucose uptake was similar in isolated muscle ex vivo, suggesting that tissue perfusion may contribute to the defect. In human subjects with metabolic syndrome, plasma EETs were reduced compared to healthy controls (P=0.014) and were positively associated with insulin sensitivity assessed during intravenous glucose tolerance tests (R=0.62, P<0.001).

**Conclusions:** These studies demonstrate that CYP2C-derived EETs contribute to insulin sensitivity in mice and in humans. Interventions which increase circulating EETs in humans could provide a novel approach to improve insulin sensitivity in human diabetic nephropathy.

**Funding:** NIDDK Support, Other NIH Support - UL1 RR024975 and UL1 TR00445

**TH-PO401**

Urinary Podocalyxin Reflects Podocyte Injury in Hypoxia-Exacerbated Diabetic Glomerulosclerosis Naoki Takahashi, 1 Kenji Kasuno, 1 Kazuko Kamiyama, 1 Tomomi Kurose, 2 Hiroyuki Kuroswa, 2 Yoshiaki Hirayama, 3 Seiji Yokoi, 3 Yoshihira Yokoyama, 3 Daisuke Mikami, 1 Hideki Kimura, 2 Haruyoshi Yoshida, 3 Masanori Haru, 3 Masayuki Iwano, 1 Nephrology, Fuku University; 2Clinical Laboratory, Fuku University, 3Reagent R&D Dept, Denka Selken Co.; 4Internal Medicine, Osaka Hosp.; 5Pediatrics, Yoshida Hosp.

**Background:** We have previously reported that chronic hypoxia exacerbated diabetic glomerulosclerosis (GS) in db/db mice exhibiting microaneurysms with podocyte loss after 16 weeks of hypoxic breeding, and that urinary albumin (U-Alb) levels were increased at 2 weeks in hypoxia. In this study, we examined urinary podocalyxin (U-PCX) in the early stage of the hypoxia-exacerbated GS in db/db mice, because U-PCX has been reported as a useful biomarker for early podocyte injury in diabetic patients (Diabetologia 55: 2913, 2012).

**Methods:** Eight w.o. male db/db mice were bred in a normobaric hypoxic chamber (12% O2) for 4 weeks (n=6) (H-group) and the control mice were bred in room air (n=6) (N-group). U-PCX and U-Alb were weekly measured by ELISA using 24-h urine samples. Urine samples were centrifuged at low speed to detect cellular PCX in sediments or the resulting supernatants were further ultracentrifuged for analyzing cytoplasmic PCX.

**Results:** U-PCX may be a novel biomarker for podocyte injury characterized as cytoplasmic shedding and U-Alb may be attributable to such podocyte injury in the early stage of diabetic GS in this mouse model.

**TH-PO402**

Effect of Fexubostat (FBX) on the Development of Nephropathy in Obese Zucker Rats (ZO) with Type 2 Diabetes (DM2) Radiko Komers, 1,2 Bei Xu, 1,3 Terry T. Oyama, 1 Robert Jackson, 2 Robert N. Palmer. 2Div of Nephrology and Hypertension, Oregon Health and Science University, Portland, OR; 3Global Medical Affairs, Takeda Pharmaceuticals, Deerfield, IL.

**Background:** Xanthine oxidase (XO) inhibitors have beneficial effects in the diabetic kidney. However, the long-term protective potential of XO inhibition in advanced diabetic renal lesions remains to be determined.

**Methods:** We tested the effects of XO inhibitor FBX on the development of nephropathy in ZO in vivo, and in vitro in renal tubular cells (RTC) stimulated with a RAGE agonist s100B and with TGF beta (TGFb).10-week old ZO were divided in groups treated with FBX (ZOF-BX, 5mg/kg), enalapril (E) (ZO-E, 10mg/kg) and a combination of both agents (ZO-FBX-E) for 18 weeks and compared to vehicle-treated ZO (ZO-V) and lean controls (ZL).

**Results:** The average podocyte number per glomerular did not differ between the two groups, however, the number glomerular area was significantly decreased in H-group associated with glomerular swelling. Both U-PCX and U-Alb levels were significantly increased in H-group as compared with N-group at 1 week in hypoxia and continued to be elevated. U-PCX and U-Alb showed a positive correlation (p<0.01). In both group, PCX-positive cells were not found in urinary sediments, however, PCX-positive granular particles were detectable in the bottom fraction after the ultracentrifugation.

**Conclusions:** U-PCX may be a novel biomarker for podocyte injury characterized as cytoplasmic shedding and U-Alb may be attributable to such podocyte injury in the early stage of diabetic GS in this mouse model.
The late intervention with FBX initiated at 20 weeks of age was also studied (ZO-FBXlate).

Results: ZO-V developed severe glomerulosclerosis (GS) and tubulointerstitial fibrosis (TI). ZO and albuminuria, and mild elevations of BP as compared to ZL. ZO-FBX and ZO-FBXlate rats demonstrated significant decreases in GS score (27% and 25%, resp, p<0.05) and in proportion of obsolete glomeruli, compared with ZO-V. The TIF score was also reduced by FBX (35%, p<0.05 vs. ZO-V), albeit not after delayed treatment. Treatment with E, or combination of both, resulted in resp. 44.7 and 45.5% reduction in GS and diabetic rats, and 80% reduction in TIF scores (<0.01 vs. ZO-V, p<0.05 vs. ZO-FBX). In ZO-FBX-E, the GS score was no more different from ZL, suggesting additive effect of FBX+E. Significant reductions in BP and albuminuria were observed in ZO-E and ZO-FBXE-E. The uric acid (UA) levels, elevated in ZO rats, were only slightly reduced in FBX-treated rats. On the molecular level, FBX reduced expression of collagen 4 (Col4), fibronecin (FN) and CTGF to a similar extent as in ZO-E, and attenuated s100B or TGFβ-induced increases in Col4 and FN production in RTc in vitro.

Conclusions: FBX slowed down the development of GS and TIF in experimental DM2, although to a lesser degree than E. These effects were FBX-independent and not entirely attributable to UA lowering. Moreover, there were additive effects of FBX+E.

Funding: Pharmaceutical Company Support - Takeda Pharmaceuticals

TH-PO403

Genome-Wide Profiling of Inflammation Related Genes in High Glucose Stimulated Mesangial Cells and Tubular Epithelial Cells

Yasunori Iwata,1 Kengo Furuschi,1 Haruka Yasuda,2 Norikiko Sakai,3 Shinji Kitajima,1 Tadashi Toyama,1 Yasuyuki Shinozaki,2 Akihiro Sagara,3 Takashi Wada.1 2Nephrology, Kanazawa University, Ishikawa, Japan; 3Laboratory Medicine, Kanazawa Univ, Kanazawa, Ishikawa, Japan; 4Disease Control and Homeostasis, Kanazawa Univ, Kanazawa, Ishikawa, Japan.

Background: Diabetic nephropathy (DN) is a major cause of end stage kidney disease and a strong risk factor for cardiovascular diseases. Growing data show chronic inflammation plays an important role for the progression of DN. As for the immune cells, anti-inflammatory leukocytes as well as inflammatory leukocytes play an important role in DN. In addition to leukocytes, renal resident cells contribute to the inflammatory process of DN. However, precise functions, phenotypes and immune balance of renal resident cells remain to be explored. Therefore, we hypothesized that the aberrant immune balance of renal resident cells contributes to the pathogenesis of DN.

Methods: To explore this, we performed genome-wide transcriptome profiling in mesangial cells and tubular epithelial cells (TECs), which were stimulated by high glucose (HG) and detected the expression of inflammation associated genes.

Results: High glucose (HG) increased the mRNA expression of oxidative stress, inflammation, apoptosis and autophagy (mTOR) related genes in mesangial cell. Pro-inflammatory/Th1 gene expression was upregulated, but Th2 related gene expression was downregulated in mesangial cells. In TECs, HG stimulation increased pro-inflammatory/Th1/Th2 gene expression. Phosphorylation of signaling proteins shifted towards pro-inflammatory phenotype with suppressed phosphorylation of Th2 related signaling in TECs.

Conclusions: The data taken together indicate that HG shifts the immune balance toward pro-inflammatory/Th1 phenotype in mesangial cells and TECs, which might initiate and/or prolong inflammation, thereby possibly resulting in diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-PO404

Febuxostat Attenuates Diabetic Renal Injury via an Anti-Inflammatory and Anti-Oxidative Mechanism

Hong Joo Lee,1 Jungkook Wi,2 Ju Young Moon,3 Sang Ho Lee,1 Chun-Gyoo Ihm,3 Tae-Won Lee,3 Kyung Hwan Jeong.3 1Proximal Tubular Cells; 2Diabetes Mellitus and Obesity: Basic – Experimental - I; 3Novel Therapeutic Agents - Small Molecules.

Background: Oxidative stress and inflammation are known to play a central role in the development of diabetic nephropathy. Febuxostat (Fx) is a novel nonpurine xanthine oxidase inhibitor that has been shown to possess renoprotective effects, including anti-inflammatory and anti-oxidative mechanisms.

Methods: Male Sprague-Dawley rats were divided into three groups: normal, vehicle-treated diabetic (DM+Fx) and febuxostat-treated diabetes (DM+Fx). Fx administered 5mg/kg of Fx to experimental rats for 7 weeks.

Results: Diabetic rats (DM and DM+Fx groups) had higher blood glucose, higher kidney weight relative to body weight, and increased urinary output compared to normal rats. Urinary albuminuria was only significantly reduced in Fx-treated diabetic rats. Quantitative analysis showed that hepatic XO and XDHI activity was increased in the DM group but reduced after treatment with Fx. Urine 8-OHdG concentrations and renal cortical 8-oxoguanine were significantly lower in diabetic rats compared to normal; after administration of Fx, ED-1 stained cell count decreased. Finally, diabetic rats showed increased mRNA expression of inflammation related genes (E-selectin and VCAM-1), and antioxidant and reducible enzymes (GSH and Gpx3) decreased. Moreover, we observed 47% reduction of ED-1 stained cells in the glomerulus and tubule of diabetic renal tissue compared to normal; after administration of Fx, ED-1 stained cell count decreased. Febuxostat showed increased mRNA expression of inflammation related genes (E-selectin and VCAM-1) and reduced mRNA expression of antioxidant genes (GSH and Gpx3) after administration of Fx, these showed decreased significantly. In conclusion: Febuxostat ameliorates the diabetic renal injury such as albuminuria. Remenoprotective effects of Fx may attenuate the inflammatory and oxidative stress mechanisms of renal damage in diabetes by inhibiting X0 and XDHI activity.

TH-PO405

Regulation of Fatty Acid Oxidation Affects the Susceptibility of Podocytes to Palmitic Acid: Critical Role of Acetyl-CoA Carboxylase 1 and 2

Kapil Dev Kapme,1 Jonas Sieber,2 Jana Orellana,3 Peter H. Mundel,2 Andreas Werner Jehle.1 1Dept of Biomedicine, Molecular Nephrology, Univ Hospital, Basel, Basel Stadt, Switzerland; 2Div of Nephrology, Massachusetts General Hospital, Boston; Dept of Internal Medicine, Transplantation Immunology & Nephrology, Univ Hospital, Basel, Basel Stadt, Switzerland.

Background: Type 2 diabetes (T2D) is characterized by dyslipidemia with elevated free fatty acids (FFAs). FFAs and renal FFA-oxidation (FAO) potentially play a direct role in the pathogenesis of diabetic nephropathy (DN), and a SNP in acetyl-CoA carboxylase (ACC) 2 is associated with proteinuria in T2D. SNPs results in higher expression of ACC2 which likely inhibits FAO by producing higher malonyl-CoA, an inhibitor of carnitine palmitoyltransferase 1 (CPT1), the rate-limiting enzyme of FAO. Here, we addressed the role of FAO in palmitic acid induced podocyte death, and further explored the role of ACCs in this process.

Methods: Conditionally immortalized murine podocytes differentiated for at least 1 day were used. 5-aminolevulinic-acid-4-carboxylic acid (Alacar) and etomoxir (CPT1 inhibitor) were employed to alter FAO. 3H palmitic acid was used to determine FAO by measuring the release of 3H20. ACC 1 and 2 were silenced using siRNA.

Results: Alacar decreased palmitic acid induced apoptosis and necrosis by 50.5 ± 1.5% (p < 0.01) and 42.5 ± 6.1% (p < 0.05). Contrariwise etomoxir exacerbated apoptosis and necrosis by 183.4 ± 6.0% (p < 0.001) and 185.1 ± 16.3% (p < 0.01) respectively. ACC1 phosphorylated AMPK and ACC. Alacar increased oxidation of palmitic acid by 146.6 ± 22.0% (p < 0.05) and co-treatment with etomoxir reversed this effect. Only knocking down of both ACC 1 and 2 reduced palmitic acid induced apoptosis 59.6 ± 4.5% (p < 0.01) and necrosis 64.4 ± 6.4% (p < 0.01). ACC1 did not cause added protection in ACC-depleted podocytes.

Conclusions: Regulation of FAO in podocytes profoundly affects their susceptibility to palmitic acid cytoxicity. Our data may explain the role for proteinuria in T2D patients with SNP in ACC2 as reported in previous studies. AMPK-ACC-CPT1 pathway is a potential target to prevent and treat DN.

Funding: Government Support - Non-U.S.

TH-PO407

Characterization of Angiotensin-Converting Enzyme 2 Shedding from Proximal Tubular Cells

Fengxia Xiao,1 Joe A. Zimpelmann,1 Susan B. Gurley,2 Lawrence Puente,1 Kevin D. Burns. 1Div of Nephrology, Dept of Medicine, Juntendo Univ Faculty of Medicine, Tokyo, Japan.

Background: Chronic inflammation promotes the progression of diabetic nephropathy (DN). However, the role of TNFa remains unclear. The objectives of the present study are 1) to examine whether TNFa inhibition with a soluble TNFa receptor 2 (TNFR2) fusion protein, Etanercept (ETN) improves DN in type 2 diabetic model of KK-A mouse, and 2) to also investigate which TNFa pathway, TNFR1 or TNFR2, involves predominantly in the progression of DN.

Methods: ETN was injected intra-peritoneally to the diabetic mice for 8 weeks. Urinary and serum samples were collected at the beginning and end of the experiment. Renal damage was evaluated by immunohistochemistry and/or real time PCR. In vitro, mouse tubular proximal (mProx) cells were stimulated by TNFa and/or high glucose, and treated by ETN. Their supernatants and mRNA were collected.

Results: ETN treatments dramatically reduced the levels of not only urinary albumin but also casual blood glucose and Hba1c. However, they did not affect the levels of body weight and blood pressure. Real-time PCR of mRNA and/or protein expression levels of TNFR2, but TNFR1 and TNFR3, in the ETN-treated diabetic mice (treated mice) were significantly decreased compared with the non-treated diabetic mice (non-treated mice). The mRNA expression levels of ICAM-1, VCAM-1 and MCP-1, and the number of F4/80 positive cells were all dramatically decreased after the treatment. The numbers of cleared caspase 3 and tunel positive cells in non-treated mice were very few, and did not different from the treated mice. In vitro, TNFa or high glucose markedly increased both TNFRs (TNFR1 and TNFR2) mRNA expression levels unlike in the case of in vivo. ETN treatment partly recovered TNFa induced both TNFa mRNA expressions, but did not affect high glucose induced those expressions.

Conclusions: It appears that ETN may improve the progression of DN through predominantly anti-inflammatory action of TNFa-TNFR2 pathway.

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

Underline represents presenting author/disclosure.

194A
**TH-PO408**

**Lipoxins Attenuate High-Fat-Diet Induced Chronic Kidney Disease**

**Meggson, E.**

**Background:** Obesity is an independent risk factor for CKD, even when excluding variables such as diabetes. Visceral obesity is considered a driving force of obesity-related complications and the adiponectin/AMPK pathway has been linked to CKD. Lipid-related metabolites may have disease-promoting and modifying effects, e.g., LipoxinA4 (LXA4), which displays potent anti-inflammatory and anti-fibrotic actions.

**Methods:** We investigated the therapeutic potential of LXs in a 12wk model of high-fat-diet (HFD)-induced CKD in C57BL/6 mice, and the potential underlying role of adiponectin.

**Results:** LXA4 (5ng/g) and benzo-LXA4 analogue (1.7 ng/g) were given as interventional therapeutics diet (HFD) induced CKD in C57BL/6 mice, and the potential underlying role of adiponectin. In people and mice with DKD, SAA localized at sites of glomerular and tubulointerstitial injury and was significantly elevated in plasma. As in podocytes, SAA induced death of mesangial cells and tubular cells, which may contribute to widespread kidney damage in DKD.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Astra Zeneca

---

**TH-PO411**

**Genetic Deletion of P2Y2 Receptor Confers Significant Resistance to Development of Diet-Induced Obesity and Improves Glucose Tolerance**

**Zhu, Y.**

**Background:** Experimental, clinical and epidemiological data link obesity to the development of diabetes mellitus, metabolic syndrome and chronic kidney disease. Extracellular ATP regulates insulin secretion, and P2 receptors have a role in insulin-stimulated leptin production and lipolysis in white adipocytes. We hypothesized that mice with whole-body knockout (KO) of P2Y2 receptor (R) may have altered response to high-fat diet (HFD)-induced obesity and glucose tolerance.

**Methods:** Groups of age-matched wild type (WT) and KO mice were fed regular diet (10% calories as fat; n = 6) or high-fat diet (HFD; 60% calories as fat; n = 14) with free access to food and water for 16 weeks, and euthanized. Feces samples were collected periodically, and glucose tolerance (GT) test was performed during the 14th week.

**Results:** Adjusted for body weights (bw), KO mice consumed modestly, but significantly more HFD vs. WT mice, and exhibited well-formed feces with no trace of fat or oil. Starting from the 2nd week the HFD KO mice displayed significantly lower bw, with terminal mean difference of 20% vs. HFD WT mice. Terminal weights of total white and brown fats were significantly lower in the HFD KO mice. Thus, P2Y2-R may have a role in energy metabolism, and can be a potential target for the treatment of diet-induced obesity and/or metabolic syndrome. Future studies should establish the pathways involved in P2Y2-R regulation of energy metabolism.

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

---

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

*Underline represents presenting author/disclosure.*
TH-PO412
Renoprotective Effects of Dipeptidyl Peptide-IV Inhibition in High Fat Diet-Induced Obese Mice
Hyunwook Kim,1 Ji Eun Lee,1 Jung Eun Kim,2 Miha Lee,2 Hye Kyong Song,2 Jin Joo Cha,3 Mi Jin Lee,2 Sang Youb Han,2 Young Youl Hyun,2 Jee-Young Han,2 Young Sun Kang,2 Dae R. Cha.2 1Wonkwang Univ College of Medicine, Korea; 2Korea Univ College of Medicine Ansan Hosp, Korea; 3Inje Univ College of Medicine, Korea; 4Kangbuk Samsung Hospital, Korea; 5Inha Univ College of Medicine, Incheon, Korea.

Background: Dipeptidyl peptidase-IV (DPP-IV) inhibition is currently being regarded as a promising strategy for diabetes management. However, its direct anti-enzymatic effect on kidney and its consequences are largely unknown.

Methods: Normal chow-fed control mice, vehicle-treated high fat diet-induced obese mice, and DPP-IV inhibitor (LC15-0444)-treated high fat diet-induced obese mice were assessed for changes in various metabolic parameters, DPP-IV activity in target organs including kidney, and the parameters for renal damages.

Results: After 3 months of treatment, the high fat-induced obese mice administered LC15-0444 at the dose of 3 mg/kg showed no differences in the levels of blood glucose, blood pressure, insulin resistance, and oxidative stress parameters both in kidney and adipose tissue compared with control obese mice. However, treatment with LC15-0444 significantly decreased levels of DPP-IV activity in serum, kidney, fat, and liver of the experimental mice. Furthermore, the mice treated with LC15-0444 showed significantly reduced albuminuria and the tendency to preserve creatinine clearance. In addition, renal histologic examinations showed that the mice treated with LC15-0444 also showed a significantly decrease in glomerulosclerosis and expression of pro-fibrotic markers. In support for these results, a subsequent in vitro study showed that LC15-0444 ameliorated obesity-induced increases in protein expressions of HMGB1, NF-κB, and P-ERK1/2 in renal cortical tissues.

Conclusions: In conclusion, Administration of LC15-0444 reduced obesity-induced increases in enzymatic activity of DPP-IV in the kidney as well as in plasma, and ameliorated renal damages independently of glucose-lowering effect. This renoprotection might be at least partly mediated by anti-inflammatory and anti-proliferative properties.

TH-PO413
Increased Expression of Oxidation-Stress and Apoptosis Are Associated with Haptoglobin Genotype in Diabetes Mellitus Patients
Farid M. Nakhoul,1,2 Inbal Mezrahi.1 1Nephrology Div Baruch Padeh Porijya Medical Center; 2Diabetic Nephropy Lab; Faculty of Medicine Bar Ilan Univ, Israel.

Background: We had demonstrated that in diabetic mice with different haptoglobin genotypes (1-1, 2-2) there is different susceptibility to diabetic nephropathy (DN). Hpf-1 DM mice appears to be more protective against diabetic nephropathy than DM mice with Hpf-2.2. We found increased iron deposition and oxidative stress in kidney proximal convoluted tubules (PCT) of Hpf-2 vs Hpf-1. Impaired Hb clearance and increased iron release, induces oxidative stress leading to apoptosis and kidney damage.

Methods: 1. We used slides from kidney biopsies of diabetes mellitus patients with different Hpf genotype for iron deposition and oxidative stress markers. 2. We will define whether increased renal iron deposits correlates with increased Expression of Oxidation-Specific Epitopes (OSEs) and apoptotic cells in the glomerular and proximal tubules. 3. Quantification of OSEs will perform by immunostaining using an EO6 and IK7 antibodies. The percentage of apoptosis-positive cells will quantify by different apoptotic assays such as TUNEL assay, Immunohistochemistry of cleaved caspase 3.

Results: 1. Increased iron deposition in PCT of kidney biopsies from patients with Hpf 2-2 than in kidney biopsies of patients with Hpf 1-1.

Conclusions: These findings provide insights into genetic predisposition to oxidative stress in Hpf-2 DM patients. The relationship between increased iron deposition in Renal PCT and macrophage apoptosis that may explain advanced kidney damage and sclerosis in human Hpf-2 kidney disease.

Funding: Government Support - Non-U.S.

TH-PO414
The SGLT2 Inhibitor Empagliflozin Ameliorates Albuminuria in BTBR ob/ob Type 2 Diabetic Mice with and without Hypertension
Florian Gembardt,1 Natalia Jarzebska,2 Christoph Bartunek,3 Eric Mayoux,2 Vladimir T. Todorov,2 Bernd Hohenstein,3 Christian Hugo.1 1Div Nephrology, Dept of Internal Medicine III, Univ Hospital CGC, Dresden, Germany; 2Div Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany.

Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease in man in the western world. Recent development of sodium-glucose co-transporter (SGLT) inhibitors offer a new anti-diabetic therapy via enhanced glucose excretion. Whether this strategy exerts beneficial effects on developing type 2 DN is unclear. We investigated the effects of the SGLT 2 inhibitor empagliflozin (EMPA; Boehringer Ingelheim) in BTBR ob/ob mice, which spontaneously develop type 2 DN.

Methods: First, 25 eight week-old female BTBR ob/ob mice either received a 12 week diet containing 300ppm EMPA or equicaloric placebo chow. Second, 16 female BTBR ob/ob mice received osmotic minipumps releasing 1μg/kg BW/d angiotensin (Ang) II and were separated in the same 2 diet groups for 6 weeks. Urine, blood, and tissues were harvested and blood pressure was monitored by tail cuff measurements.

Results: In both experiments, EMPA treatment enhanced glucosuria vs vehicle (119±127 vs 384±118 mg/mg-creatinine, P<0.001; Ang II: 1887±96 vs 1113±250 mg/mg-creatinine, P<0.05), thereby lowering blood glucose (204±16 vs 402±27 mg/dl P<0.001; Ang II: 170±20 vs 368±40 mg/dl P<0.01). While Ang II infusion induced profound hypertension (146±4 vs 84±1 mmHg, P<0.0001), EMPA treatment had no influence on blood pressure in normotensive or hypertensive mice (81±6 vs 84±1 mmHg; 139±6 vs 146±4 mmHg). In both experiments, EMPA reduced albuminuria in diabetic mice (0.5±0.1 vs 1.3±0.4 mg/mg-creatinine, P<0.05; Ang II: 1.5±0.2 vs 4.8±1.8 mg/mg-creatinine P<0.05). Immunohistochemical analysis assessed glomerular hypertrophy, matrix expansion, inflammation and proliferation. In contrast to albuminuria findings, histology did not demonstrate any differences.

Conclusions: Empagliflozin demonstrated significant anti-hyperglycemic effects ameliorating the development of albuminuria in female BTBR ob/ob mice with and without hypertension while no effects on histology were observed.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim Pharma GmbH & Co. KG

TH-PO415
Angiotensin Converting Enzyme-2 (ACE2) Deficiency Accelerates Maternal Diabetes-Induced Perinatal Programming
Shiao-Yung Chang,1 Min-Chun Lin,2 Chi-Pai Chang,2 Mu-Chih Chang,2 Shao-Ping Zhao,2 Yu-Chun Chen,3 Yessoufou T. Alioua,4 Isabelle C. Chienier,5 Julie R. Ingelfinger,5 Shao-Ling Zhang.1 1CRCHUM-Hotel Dieu, Univ of Montreal, Montreal, Canada; 2Pharmacology, National Cheng Kung Univ, Tainan, Taiwan; 3Pediatr Nephrol Unit, MassGeneral Hosp for Children, Boston, MA.

Background: Increasing evidence suggests that alterations in the ACE2/ACE ratio within the kidney may participate in perinatal programming of hypertension. We aimed to determine whether ACE2 knock-out (ACE2 -/- mice on C57BL/6 background) increases the risk of programmed hypertension and kidney injury in the offspring of dams with gestational diabetes and examined the potential underlying mechanisms in vivo.

Methods: The 20-week-old offspring of non-diabetic and diabetic dams (ACE2 +/+, ACE2 -/-, and ACE2 -/-) were studied. Systolic blood pressure (SBP), glomerular filtration rate (GFR), renal morphology and reactive oxygen species (ROS) generation, as well as protein expression of Wilms tumor-1 (WT-1), transforming growth factor-beta1 (TGFB1) and components of the intrarenal renin-angiotensin system (RAS)—e.g., angiotensinogen (Agt), angiotensin converting enzyme (ACE) and angiotensin II receptor 1 and 2 (AT1R and AT2R), were assessed by immunohistochemistry staining (IHC).

Results: As compared with the control littersmates, ACE2 -/- mice with decreased AT2R in the kidney had a small increase in SBP and age-dependent development of glomerulosclerosis. Offspring of diabetic ACE2 -/- dams developed hypertension, renal hyperfiltration, podocyte loss and kidney injury. Renal ROS generation and TGFB1, Agt, AT1R/AT2R and ACE protein were markedly upregulated in kidneys of hypertensive offspring of diabetic ACE2 -/- dams. These changes were more pronounced, but, without affecting AT2R expression in the offspring of diabetic ACE2 -/- dams.

Conclusions: Our data suggest that ACE2 deficiency is pivotal for the development of the adverse perinatal programming induced by maternal diabetes.

Funding: Government Support - Non-U.S.

TH-PO416
Urinary miR-29a Content Correlates with Proteinuria and Small Vascular Fibrosis in Type 2 Diabetes Patients
Hui Peng, Meirong Zhong, Wenbo Zhao, Cheng Wang, Jun Zhang, Yuanqing Li, Xun Liu, Tan-Qi Lou. Div of Nephrology, Dept of Medicine, The Third Affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, Guangdong, China.

Background: Cell-free microRNAs are small non-coding RNAs which stably exist in urine, plasma and other body fluids. Emerging evidence has shown that content of cell-free microRNAs may correlate with particular pathophysiologic conditions and might serve as diagnostic biomarkers. MiR-29 family was reportedly down-regulated in renal biopsies of diabetic nephropathy patients with type 2 diabetes (T2DM).

Methods: Urinary miR-29a content was measured by qRT-PCR in 24 T2DM patients (12 with and without proteinuria) and 24 OR (oral glucose tolerance test) controls. Urinary miR-29a content was also measured in 24 T2DM patients and 24 OR with small vascular fibrosis identified by portal triad Doppler ultrasound.

Results: Compared with OR, urinary miR-29a content was significantly higher in T2DM patients both with and without proteinuria (2.2±1.2 vs 0.5±0.2 P<0.001), and small vascular fibrosis (2.2±1.2 vs 0.5±0.2 P<0.001). Among T2DM patients, miR-29a was significantly higher in patients with proteinuria than in those without proteinuria (2.2±1.2 vs 0.9±0.3 P<0.001), and with small vascular fibrosis (2.2±1.2 vs 0.7±0.2 P<0.001). There were no significant differences in miR-29a content among OR.

Conclusions: These findings suggest a possible role for urinary miR-29a content as a diagnostic biomarker.

Funding: Government Support - Non-U.S.
Puerarin Attenuated Diabetic Kidney Injury through Down-Regulation of Matrix Metalloproteinase 9 in Streptozotocin-Induced Diabetic Rats

Methods: There was no significant difference in age between the groups. The content of miR-29a, miR-29b, and miR-29c in urine supernatant was determined by TaqMan qRT-PCR, and a synthetic cel-miR-39 was added to the urine as a spike-in control. The clinical laboratory parameters were collected, while retinopathy serves as non-invasive method to assess vascular fibrosis. Results: There was no significant difference in HbA1C levels and duration of diabetes between two groups, while the diabetes with puerarin group had higher comorbidity of diabetes retinopathy and decline in renal function compared with the results of diabetes without puerarin group. Patients with puerarin group showed significantly higher level of miR-29a in urine (p=0.035), and urinary albumin excretion rate were significantly correlated with urinary miR-29a level (r = 0.286, p = 0.016). However, there was no significant difference in urinary miR-29b (p=0.148) or miR-29c level (p=0.321) between groups. Similar, no correlation was found between miR-29c and each of clinic parameters.

Conclusions: Urinary miR-29a level rather than miR-29b or miR-29c correlated with proteinuria and vascular fibrosis in patients with T2DM and could serve as alternative biomarker for diabetic nephropathy in T2DM.

TH-PO418

LP-925219, a Dual SGLT1/SGLT2 Inhibitor, Markedly Increases Urinary Glucose Excretion in Mice Lacking SGLT2

Background: Inhibiting sodium glucose co-transporter 2 (S2) to increase urinary glucose excretion (UGE) improves glycemic control in diabetic patients, but clinical trials show that inhibitors highly selective for S2 over SGLT1 (S1) block glucose (G) resorption by only 30%. Our past work explained this by using S1 knockout (KO), S2 KO and S1/ S2 double KO (DKO) mice to show that S1 reabsorbs 70% of filtered G in the absence of S2. This suggests that dual S1/S2 inhibitors will increase UGE to much more than 30% of maximal values in S2 KO mice and in wild type (WT) mice, a hypothesis tested here.

Methods: We developed LP-925219 (LP219) and tested its ability to inhibit transport by IHEC293 cells expressing transporters between S1, S2, S1 KO, S1 KO/S2 heterozygous (Het), S2 KO, S2 KO/S1 Het, DKO and WT mice were bred, fed G-free diet, and kept in metabolic cages to measure 24-hr UGE after pretreatment with either vehicle or 60 mg/kg LP219 delivered by oral gavage. GFR was measured using FITC-inulin. G was measured by Cobas Integra 400.

Results: LP219 IC50=22 mN vs mouse S1, ~0.5 mN vs mouse S2; GFR (10-12 group): WT=34588, S2 KO=42699, DKO=35959 ul/ min; Blood G (10-12 group): WT=130.15, S2 KO=117.12, DKO=113.10 mg/dL; DKO (10 group): predicted G filtered=568.126 mg/day; measured UGE=648.166 mg/day; UGE data are in Table 1:

Conclusions: 1) UGE differences reflect differences in G reabsorption, not differences in GFR or blood G; 2) in DKO, predicted G filtered over 24-hr is similar to measured UGE, suggesting DKO UGE is maximal; 3) the amount of renal S2 >> S1; 4) dual S1/S2 inhibitor LP219 increases UGE to > 60% of maximal (DKO) in WT and S2 KO mice, suggesting that combined inhibition of renal S1 and S2 can significantly increase UGE over selective inhibition of renal S2 alone.

TH-PO417

Puerarin Attenuated Diabetic Kidney Injury through Down-Regulation of Matrix Metalloproteinase 9 in Streptozotocin-Induced Diabetic Rats

Yifei Zhong,1 Yuey Deng,2 Yiping Chen.1
1Nephropathy, Longhua Hospital, Shanghai Univ of Traditional Chinese Medicine, Shanghai, China; 2Inst#1; 1Inst#1.

Background: Radiox puerarize, a traditional Chinese herbal medication, has been used successfully to treat patients with early stage of diabetic nephropathy (DN). However, the underlined mechanism of its renal protective activity has yet to be investigated. Oxidative stress is one of the key mechanisms in DN. Over-production of ROS induces several changes in the kidneys, which could be detrimental to podocyte during DN.

Methods: STZ induced diabetic rat model was successfully generated. Treatment of STZ diabetic rats with puerarin and/or an angiotensin II receptor blocker (ARB) was compared with vehicle control. Kidney morphology and podocyte slit diaphragm were examined by PAS staining and electron microscope respectively. Expression of MMP9, nephrin and podocin were examined by both real-time PCR and immunostaining or western blot. Oxidative stress was determined by measuring 8-hydroxy-2'-deoxyguanosine (8-OHdG) in the kidneys, which could be detrimental to podocyte during DN.

Results: There was no significant difference in age between the groups. The content of miR-29a, miR-29b and miR-29c was determined by TaqMan qRT-PCR, and a synthetic cel-miR-39 was added to the urine as a spike-in control. The clinical laboratory parameters were collected, while retinopathy serves as non-invasive method to assess vascular fibrosis. Results: There was no significant difference in HbA1C levels and duration of diabetes between two groups, while the diabetes with puerarin group had higher comorbidity of diabetes retinopathy and decline in renal function compared with the results of diabetes without puerarin group. Patients with puerarin group showed significantly higher level of miR-29a in urine (p=0.035), and urinary albumin excretion rate were significantly correlated with urinary miR-29a level (r = 0.286, p = 0.016). However, there was no significant difference in urinary miR-29b (p=0.148) or miR-29c level (p=0.321) between groups. Similar, no correlation was found between miR-29c and each of clinic parameters.

Conclusions: Urinary miR-29a level rather than miR-29b or miR-29c correlated with proteinuria and vascular fibrosis in patients with T2DM and could serve as alternative biomarker for diabetic nephropathy in T2DM.

The study supported by National natural science foundation of China(81170678) and the Fundamental Research Funds for the Central Universities.

Funding: Government Support - Non-U.S.
Background: Glomerular nodular lesion is characteristic pathology in human diabetes, however its morphogenesis is still unknown, partly because of lacking good animal model to have nodular sclerosis. We created diabetic pigs carrying a dominant-negative mutant hepatocyte nuclear factor 1-alpha P291fsinsC and analyzed the process of diabetic nodular formation in these diabetic pigs.

Methods: Biochemistry and renal pathology between diabetic pigs and wild-type were analyzed with age of one to nine months. Immunostaining using collagen IV, V, VI, advanced glycation end-products (AGE), and carboxymethyl lysine (CML) was performed to see the content of the lesion. In addition, transmission electron microscopy (TEM) for detecting nodular components and glomerular basement membrane (GBM) thickness were estimated.

Results: In diabetic pigs, the blood glucose levels have elevated around 600 mg/dl from 2 weeks old. Proteinuria and renal dysfunction were absent. Glomerular nodular lesions were formed as early as 4 weeks old. The nodules increased and enlarged at 19 weeks old. They distributed deep cortex superior to superficial cortex. Immunohistochemically, the nodules consisted of collagen fibers, AGE, and CML were also deposited in the nodules. TEM showed that the main components of the nodules were interstitial type form of fibril collagens which were located in mesangial area. GBM thickness was not significant between diabetic and wild-type pigs. Moreover, these diabetic pigs did not show any other characteristic changes in human diabetic nephropathy.

Conclusions: Glomerular nodules in this model of diabetes were characterized by juxta-medullary predominant growth with various types of collagens as well as AGE and CML deposition, without having associated lesion in humans. Thus persistent hyperglycemia and hemodynamic factor can be associated with glomerular nodular formation in diabetic pigs.

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

TH-PO423 Inflammation and Endothelial Function Biomarkers in Adolescents with Obesity and Type 1 Diabetes Mellitus

Background: Obesity and diabetes have a common pathway in the pathogenesis of atherosclerosis and microvascular damage as both conditions are characterized by chronic low grade inflammatory state which leads to endothelial dysfunction(ED). The aim of the study was to evaluate urinary biomarkers of inflammation and ED in adolescents with obesity (OA) and diabetes (DA).

Methods: Research subjects were recruited from TTUHSC clinic. An EndoPat 2000 device was used to measure the reactive hyperemia index (RHI). Urine samples were tested for interleukin 6 (IL-6), endothelin 1 (ET-1), alpha-1-acid glycoprotein(AGP), and tumor necrosis factor (TNF-α). Statistical significance was assessed using analysis of variance followed by t-tests. Pearson’s correlation was calculated between various study parameters.

All the markers were normalized with urinary creatinine.

Results: 87 adolescents with an average age of 14 years were enrolled. 21 teenagers had diabetes, 30 were obese, 13 were overweight (OW), and 20 had normal weight (NA) (control group). The urinary concentration of TNF-α was significantly higher in the OA (3.01±0.41), OW (2.15±0.35) and DA (2.11±0.22) compared to the NA (1.37±0.08) (P<0.01). DA had significantly higher ET-1 (0.68±0.35) vs. NA (0.37±0.20) (P<0.03), and OA and OW showed a higher trend of ET-1 compared to NA (0.63±0.75 vs. P = 0.13, and 0.55±0.45; P = 0.11). There were no significant differences of RHI among different groups.

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

TH-PO424 Improved Renal Function after Gastrectomy in Patients without Severe Obesity

Background: Obesity is a risk factor for developing chronic kidney disease (CKD) that may be improved with bariatric weight reduction. The benefit of renal function after bariatric surgery is generally interpreted as a result of weight loss. The effect of weight loss caused by gastrectomy on glomerular filtration rate (GFR) in patients without severe obesity is unclear. We analyzed the changes in renal function after gastrectomy in patients without severe obesity.

Methods: Serum from 99 patients were tested before and 6, 24 months after gastrectomy. The estimation of the glomerular filtration rate (GFR) was addressed by the CKD-EPI creatinine equation.

Results: The subjects of this study were 99 patients who did not receive chemotherapy after gastrectomy patients without severe obesity and more than 60 ml/min/1.73 m2 body surface of CKD-EPI eGFR. The patients completed the 6 months follow-up in 99 patients and 2 years follow-up in 55 patients. Of these, 13% were female. The mean age was 62.5 ± 12.93 years and the mean body mass index was 23.7 ± 3.35 kg/m², decreasing to 21.3 ± 2.99 kg/m² in 6 months and 21.4 ± 2.59 kg/m² at 2 years after gastrectomy. Before surgery, the estimated GFR was 87.2 ± 12.29 ml/min. At the 6 months follow-up, favorable changes in the GFR (90.74 ± 12.13 ml/min, p=0.001) not related BMI status were observed and it was continued until 2 years follow up (91.03 ± 12.94 ml/min, p<0.01).

Conclusions: A favorable change of gastrectomy in patients without severe obesity was not related BMI change.

TH-PO425 Inflammation and Endothelial Function Biomarkers in Adolescents with Obesity and Type 1 Diabetes Mellitus

Background: Obesity and diabetes have a common pathway in the pathogenesis of atherosclerosis and microvascular damage as both conditions are characterized by chronic inflammation. Early detection and intervention may prevent the progression of these disorders.

Methods: Serum samples were collected from 48 adolescents with obesity (OA) and diabetes (DA) at baseline and 6 months after intervention. Serum concentrations of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and endothelial function biomarkers such as nitric oxide (NO) and endothelin-1 (ET-1) were measured.

Results: OA and DA had significantly higher CRP, IL-6, and TNF-α levels compared to the controls. NO and ET-1 levels were lower in OA and DA. The intervention significantly decreased CRP, IL-6, and TNF-α levels in OA and DA. NO and ET-1 levels increased in OA and DA after intervention.

Conclusions: Early detection and intervention of inflammation and endothelial dysfunction biomarkers in children with obesity and diabetes may prevent the progression of these disorders.
Levels of IL-6 and AGP were lower in the urine of DA (0.56±0.07 units; P<0.01; 57.3±5.8 units; P<0.01) compared to NA (1.2±0.21, 141.7±11.9 Units) and highly correlated (P<0.001) with each other.

Conclusions: Urinary levels of TNF-α, IL-6, ET-1, and AGP are significantly different in adolescents with obesity and diabetes compared to their healthy peers. TNF-α seems to be the most sensitive factor. Noninvasive urinary biomarkers are useful in evaluating the degree of inflammation and endothelial function.

TH-PO426

Elevations in Fibroblast Growth Factor-23 in Obese, Normotensive Adolescents Are Associated with Adverse Cardiac Structure  Farah N Ali,1 Bonita E. Falkner,2 Heath Price,1 Craig B. Langman.1 Pediatrics, Div of Kidney Diseases, Northwestern Univ, Chicago, IL; 2Div of Nephrology, Thomas Jefferson Univ, Philadelphia, PA.

Background: Fibroblast Growth Factor-23 (FGF23) is a new biomarker for cardiovascular disease in populations with and without chronic kidney disease. Animal models suggest that adipocyte-derived leptin may modulate FGF23 production. Our objectives were: to determine whether obese African American (AA) adolescents without CKD have elevated FGF23 levels compared to non-obese AA adolescents; to determine if FGF23 is related to markers of insulin resistance; to determine if FGF23 is associated with cardiac structure.

Methods: Cross-sectional data were obtained from a cohort of 146 normotensive, AA aged 13-18 yrs with normal kidney function and absent proteinuria; 87 were obese and 59 were non-obese. Plasma C-terminal FGF23, fasting glucose, insulin, adiponectin, and hsCRP were measured; M-mode echocardiography was performed.

Results: FGF23 levels were higher in obese versus non-obese subjects (43 vs 22 RU/mL; P<0.001). FGF23 directly correlated with fasting insulin (p=0.005) and HOMA scores (p=0.001). FGF23 directly correlated with hsCRP (p=0.044) and inversely correlated with adiponectin (p=0.040). Median LVM and LVMI increased with increasing quartiles of FGF23, including models adjusted for age, sex, and hsCRP. Left atrial dimension indexed to height increased with increasing FGF23 quartiles. In the obese, FGF23 values above the group median value of 40 RU/mL were associated with larger diastolic time interval ratio. Subjects with eccentric and concentric left ventricular hypertrophy (LVH) had higher FGF23 values than those without LVH (p<0.003).

Conclusions: In this homogeneous cohort only differing by BMI, FGF23 was associated with adverse cardiac structure. We postulate that FGF23, a novel CV risk factor in CKD, may be operative in otherwise healthy obese AA adolescents and that the adipocytome may be a critical determinant for the cardiovascular risk in obesity, mediated by FGF23.

Funding: NIDDK Support, Other NIH Support - 1RO1HL092030, Private Foundation Support

TH-PO427

A Study of Pattern of Emphysematous and Non Emphysematous Pyelonephritis amongst Hospitalized Type 2 Diabetes Mellitus Patients Krishan L. Gupta, Raja Ramachandran, Harbir Singh Kohli, Vivekanand Jha, Vinay Sakhuja. Nephrology, PGIMER, Chandigarh, India.

Background: Diabetes Mellitus is a common cause of pyelonephritis both emphysematous (EPN) and, non-emphysematous pyelonephritis (NEPN) associated with diabetic patients in a tertiary care centre.

Methods: A total of 105 diabetic patients with pyelonephritis were admitted from July 2009 to June 2010 and diagnosis of EPN was based on Huang classification. Patients were treated with appropriate antibiotics and percutaneous drainage (PCD) as and when indicated. Nephrectomy was carried out in patients of EPN who were refractory to conservative measures for 2 weeks. Outcome was termed as poor if there was a need of nephrectomy or the patient died.

Results: Females were seen in 79 (75.2) and 26 (24.7) patients respectively. E.coli was the commonest organism. Stone disease (n=13) and poor glycemic control (n=76) were the commonest comorbidities. Stone disease (n=13) and poor glycemic control (n=76) were the commonest comorbidities.

Conclusions: EPN and NEPN were seen in 79 (75.2) and 26 (24.7) patients respectively. E.coli was the commonest organism. Stone disease (n=13) and poor glycemic control (n=76) were the commonest comorbidities. Stone disease (n=13) and poor glycemic control (n=76) were the commonest comorbidities. Stone disease (n=13) and poor glycemic control (n=76) were the commonest comorbidities.

TH-PO428

Urinary Free Light Chain Excretion in Obesity and Diabetes Tina Kaur Thethi,1 Bonnie Katalenich,1 Shuqian Liu,1 Radha Pasala,1 Vivian A. Fonseca,2 Vecchi Batuman,1,2 1Dept of Medicine, Tulane Univ Health Sciences Center, New Orleans, LA; 2Dept of Medicine, Southern Louisiana Veterans Health Care System, New Orleans, LA; 3Global Health Systems and Development, Tulane School of Public Health and Tropical Medicine, New Orleans, LA.

Background: Obesity is a risk factor for type 2 diabetes (DM). DM is a leading cause of chronic kidney disease (CKD). Urinary free light chains (uFLC) excretion is elevated in early diabetic nephropathy before GFR decline. Purpose was to investigate uFLC, Kappa (κ) and Lambda (λ) light chains in obese subjects with and without DM.

Methods: Cross sectional, subjects aged 18 to 70 with body mass index(BMI) <27 or >30. uFLC was measured on SPAU™ analyzer (The Binding Site Inc, San Diego, CA) using Binding Site Sfree® immunoprecipitation assay.

Results: Table 1 shows comparison between obese subjects with DM and hypertension [HTN][DM] vs [HTN][κ/λ] and those without DM and HTN[DM]-[HTN]. Comparison between DM (n=59) and non-obese (n=195) group shows significant difference in urinary(μg) k(43.6±81.9,29.4±51.4, p<0.01) and λ (5.2±17.1,3.0±8.9,p=0.04). Multiple regression showed significant positive relationship of urinary microalbumin creatinine(Cr) ratio(UMACR) with λ[UCr(p<0.001)] not U/UCr after adjusting for DM, obesity, HTN, gender, age, glucose, BMI, diastolic blood pressure, serum(S)Cr, GFR. UMACR is expected to increase by 178 mg/g for each 1 unit increase in U/Cr.

Conclusions: Excretion of κ and λ uFLC is significantly increased in obese subjects with DM and HTN compared to those without DM and HTN. Longitudinal study is needed to assess if uFLC excretion predicts CKD onset earlier than UMACR.

Funding: Private Foundation Support

TH-PO429

Elevated Serum Free Light Chains Predict Poor Cardiovascular Outcomes in Type 2 Diabetes Srikanth Bellary,1 Jeffrey Faint,2 Lakhvir Asii,2 Anthony Harding,2 Anthony H. Barnett.1 1Heart of England NHSFT, Birmingham, United Kingdom; 2The Binding Site Group Ltd., Birmingham, United Kingdom.

Background: Several risk factors including glycated hemoglobin, proteinuria and hypertension are associated with increased risk of cardiovascular disease (CVD) in diabetes; however, their ability to predict the risk of CVD events is limited. Elevated polyclonal combined serum free light chains (cFLC) are associated with adverse outcomes in chronic kidney disease and other inflammatory conditions, reflecting both the degree of renal impairment and the severity of inflammation. Here we investigate the role of cFLC in predicting CVD-related events in chronic diabetics.

Methods: Serum cFLC and hsCRP were assessed in 352 South Asian type 2 diabetic patients and compared with other standard clinical measurements, treatment and prior history of CVD. Each variable was assessed for utility in predicting CVD related deaths or events, over 2 years, using logistic regression analysis.

Results: 29/352 (8%) patients suffered an adverse CVD outcome and cFLC was significantly elevated in these patients, compared to patients with no events (50.7vs 28.6mg/L, P<0.004); hsCRP did not show a significant difference (4.5±3.6mg/L vs 0.8±0.6mg/L, P<0.389). cFLC>57.2mg/L (odds ratio(OR) 3.3, 95%CI 1.3-8.2, p=0.012), triacylglycerols>0.7mmol/L (OR 18.3, 95%CI 5.1-65.5, P=0.001) and SBP>155mmHg (OR 3.6, 95%CI 1.5-8.7, P=0.004) were independently associated with CVD outcomes and remained significantly associated after adjusting for age, ACR, diabetes duration or treatment. ACR and prior history of CVD were not independently associated with outcome. Individually, elevated cFLC, SBP or triglycerides identified 45%, 41% and 21% of patients with adverse CVD outcomes, respectively. A simple risk stratification model including these 3 markers identified patients with 0, 1 (OR 5.7, 95%CI 2.1-15.0 P<0.001) or 2 (OR 15.4, 95%CI 6.8-37.4, P<0.001) risk factors. 79% of patients who suffered an adverse CVD event were abnormal for ≥1 risk factor.

Conclusions: Elevated cFLC concentrations independently predicted CVD outcomes in diabetic patients. Further studies are required to assess the utility of cFLC measurements in this setting.

Funding: Pharmaceutical Company Support - The Binding Site Group Ltd.

TH-PO430

Renal Amyloidosis in Patients with Type 2 Diabetes Mellitus Ramon A. Dieg1 Gerardo Gamba,2 Virginia Soto,2 Juan Soriano,3 Magdalena Madero,1 1National Heart Institute Mexico; 2Hospital General de Mexico; 3INCMNS.

Background: Type 2 Diabetes Mellitus (T2DM) is the leading cause of chronic kidney disease (CKD) and a major cause of cardiovascular disease (CVD) mortality. Inflammation is closely involved in the pathogenesis of T2DM and in the development of

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
chronic vascular complications. Reactive amyloidosis (AAA) is a condition that occurs in the presence of chronic inflammation. We hypothesized that patients with T2DM may have a higher prevalence of Renal Amyloidosis (RAAA) and that this could contribute to worse kidney and vascular disease.

Methods: This was an observational cross-sectional study that included autopsy kidneys from patients with previous diagnosis of T2DM. Vascular tissue damage (chronic ischemic cardiac, myocardial infarction, aortic, myocardial and intrarenal atherosclerosis) and RAAA were the variable outcomes of interest. The kidney tissue was evaluated by two different pathologists in order to determine the presence of diabetic nephropathy, RAAA, defined as positivity of immunohistochemistry through indirect immunoperoxidase with the primary AA antibody) and the severity of vascular tissue damage.

Results: 330 autopsy cases of T2DM were included in the study. The mean age of the population was 61± 13 years and 47% were female. Eighty percent of the population had diabetic nephropathy. RAAA was detected in 9% of our population and was associated with an increased risk (OR [95% CI]) [11 (2.04 to 59.10) for nodular sclerosis, [4.59 (2.02 to 10.42) for chronic ischemic cardiomyopathy, [3.41 (1.52 to 7.64) for myocardial infarction and [4.75 (1.09 to 20.69)])], [3.22 (1.47 to 7.04)] and [3.84 (1.46 to 10.09)] for aortic, coronary and intrarenal atherosclerosis, respectively. The presence of RAAA was confirmed by electronic microscopy in some randomly selected cases.

Conclusions: RAAA is prevalent amongst T2DM and is associated with worse cardiovascular, aortic and renal disease. RAAA is a marker of severe chronic inflammation and this likely explains our results. Studies replicating our findings in other populations are warranted to confirm these associations.

Funding: Government Support - Non-U.S.

TH-PO431
Pulse Pressure Is Not a Predictor of Outcome in Type 2 Diabetes Patients with Chronic Kidney Disease and Anemia–The TREAT TRIAL
Simone Theilade,1 Brian Claggett,2 Jerome A. Rossert,3 Tine Hansen,1 Hicham Skali,1 Eldrin F. Lewis,2 Scott D. Solomon,3 Hans-Henrik Parving,4,5 Marc A. Pfeffer,2 John J. McMurray,1 Peter Rossing,4,1 Steno Diabetes Center, Denmark;4 Harvard Medical School, Brigham and Women's Hospital;5 Amgen;3 Uni of Copenhagen, Denmark;3 Rigshospitalet, Denmark;3 Univ of Glasgow, United Kingdom.

Background: After more than 2 decades of research pulse pressure (PP) remains an elusive cardiovascular risk factor with findings being inconsistent. We clarified the prognostic value in patients with the triad of type 2 diabetes, chronic kidney disease (CKD), and anemia in the Trial to Reduce cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy (TREAT).

Methods: In TREAT, 4038 patients were randomized to darbepoetin alfa or placebo. Using Cox proportional hazards models we calculated multivariable-adjusted (including factors) hazard ratios (HRs) to assess risk related to PP at randomization.

Results: Median (IQR) age was 68 (60-75) years, 57.3% women, diabetes duration was 15.4 (6.3-21.7) years, eGFR was 34 (26-43) ml/min/1.73m². SBP, DBP and PP was 136 (122-148), 71 (64-80) and 60 (57-74) mmHg.

Over 29.1 months (median), the number of patients experiencing the composite of CV death, nonfatal myocardial infarction (MI), stroke, hospitalization for myocardial ischemia, or heart failure, that is, the primary end point excluding non-CV deaths was: 10/15, 253, stroke 154 or end stage renal disease (ESRD) 668.

Unadjusted analyses showed that higher quartiles of PP was associated with increased events, that is, an absolute risk of follow up (p=0.52). However, adjusted HRs (95% confidence interval) per 10mmHg increase in PP were 1.00 (0.96-1.04) for fatal and nonfatal combined CV events, 1.00 (0.96-1.14) for MI, 0.96 (0.87-1.06) for stroke, and 1.02(0.98-1.07) for ESRD.

Conclusions: In patients with type 2 diabetes, CKD, and anemia, PP did not predict CV events or ESRD. This may reflect the relatively narrow range of PP, partly because of extensive antihypertensive treatment in this specific population.

TH-PO432
Central Hemodynamics Is Associated with Diabetic Complications in Type 1 Diabetes
Simone Theilade,1 Brian Claggett,2 Jerome A. Rossert,3 Tine Hansen,1 Peter Rossing,4,1 Steno Diabetes Center, Denmark;2 Aarhus Univ, Denmark;3 Univ of Copenhagen, Denmark.

Background: To investigate the associations between central hemodynamics and diabetic complications in type 1 diabetes.

Methods: Cross-sectional study, 676 type 1 diabetes patients, mean±SD age 55±13, 60% male. Arterial stiffness was measured by pulse wave analyses (PWA), as central aortic, coronary and intrarenal atherosclerosis, respectively. The presence of RAAA was confirmed by electronic microscopy in some randomly selected cases.

Results: PWAs were available in 636 patients. Mean±SD CASP: 118±17 mmHg, PP: 56±14 mmHg, CVP: 30±14 mmHg, and SEVR: 150±32. Albuminuria, CVD, retinopathy and autonomic dysfunction was present in 52, 21 and 78% of patients.

CVD and autonomic dysfunction were associated with: CASP (per 1 SD increase): odds ratios (OR)=3.7(2.0-6.6) and 4.7(2.6-8.4); CVP: OR=0.3(0.2-0.6) and 0.3(0.2-0.6); CVP: OR=0.5(0.3-0.8) and 0.4(0.3-0.6) (adjusted for gender, diabetes duration, mean arterial pressure, heart rate, height, urinary albumin excretion rate (UAE), eGFR, HbA1c, cholesterol, antiplatelet medication

Conclusions: Complications were presence of albuminuria (≥30mg/24-hour), cardiovascular disease (CVD), retinopathy or autonomic dysfunction (heart rate variability <11 beats/minute).

Results: PWAs were available in 636 patients. Mean±SD CASP: 118±17 mmHg, CVP: 30±14 mmHg, and SEVR: 150±32. Albuminuria, CVD, retinopathy and autonomic dysfunction was present in 52, 21, 78 and 59% of patients. CVD and autonomic dysfunction were associated with: CASP (per 1 SD increase): odds ratios (OR)=3.7(2.0-6.6) and 4.7(2.6-8.4); CVP: OR=0.3(0.2-0.6) and 0.3(0.2-0.6); CVP: OR=0.5(0.3-0.8) and 0.4(0.3-0.6) (adjusted for gender, diabetes duration, mean arterial pressure, heart rate, height, urinary albumin excretion rate (UAE), eGFR, HbA1c, cholesterol, antiplatelet medication

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

Underline represents presenting author/disclosure.

200A
TH-PO435

Pathologic Classification of Diabetic Nephropathy in Predicting Renal Death


Background: A novel nephropathological classification scheme for diabetic nephropathy was devised by the Renal Pathology Society (RPS) in 2010. The utility of this system in predicting subsequent end-stage renal disease (ESRD) has not been determined across populations of broad ethnic background.

Methods: Specimen from clinical kidney biopsies performed between 1998-2006 and containing diabetic glomerulosclerosis in the final diagnoses, were reanalyzed according to the RPS classification system for diabetic nephropathy. Tubular atrophy was categorized between 0 and 4. Clinical data was extracted from medical records from the time of biopsy until the onset of renal replacement therapy (RRT). Kaplan-Meier estimates were calculated the percentage of participants who required RRT during follow-up, stratified by glomerular class or severity of fibrosis. Univariate and multivariate Cox proportional-hazards regression analyses were run, adjusting for ethnicity, baseline creatinine and urine protein/creatinine ratio.

Results: Demographic and clinical data from the date of biopsy are displayed in the following table.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51 (47,55)</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>57 (75)</td>
</tr>
<tr>
<td>Non-Hispanic, Black, %</td>
<td>24 (46)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.3 (7.9, 8.7)</td>
</tr>
<tr>
<td>Diabetes duration, yrs</td>
<td>12.8 (11.1, 14.1)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>54 (45, 62)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>3.8 (3.2, 4.4)</td>
</tr>
<tr>
<td>Urine protein/creatinine</td>
<td>8.3 (4.9, 9.6)</td>
</tr>
<tr>
<td>Glomerular class</td>
<td></td>
</tr>
<tr>
<td>F/II/hb</td>
<td>108 (54%)</td>
</tr>
<tr>
<td>III</td>
<td>35 (50%)</td>
</tr>
<tr>
<td>IV</td>
<td>17 (25%)</td>
</tr>
<tr>
<td>Fibrillar fibrosis:</td>
<td></td>
</tr>
<tr>
<td>C/2</td>
<td>19 (27%)</td>
</tr>
<tr>
<td>C/3</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>C/4</td>
<td>26 (37%)</td>
</tr>
</tbody>
</table>

Survival analysis according to glomerular class and interstitial fibrosis and unadjusted hazard ratios are displayed in the following figures. Multivariate adjustment did not significantly change the results.

Conclusions: There is a threshold for predicting need for RRT.

TH-PO436

A New Cutoff for Abnormal Proteinuria in Diabetes Mellitus Patients: Relationship to Albuminuria

Arie Erman,1 Ori Erman,1 Alina Vodonos,2 Uzi Gafter,3,4 David Jonathan Van Dijk,1,2 *Nephrology and Hypertension, Rabin Medical Center, Petah Tikva, Israel; 4Sackler School of Medicine, Tel Aviv Univ, Tel Aviv, Israel; 1Public Health, Faculty of Health Sciences, Ben-Gurion Univ of the Negev, Beer Sheva, Israel.

Background: New and more sensitive methods have been developed to detect low levels of proteinuria, which could not be detected in the past. The main goal of this study was to evaluate the relationship between proteinuria (below 300mg/24hr) and albuminuria, as well as a possible association with renal function in patients with diabetes mellitus (DM).

Methods: Medical files of patients with type 1 and type 2 DM who presented with proteinuria below 300 mg/24hr at three different visits to the Diabetic Nephropathy Clinic, spaced with a minimal three months interval, were screened. The 245 patient files that were screened, included 723 visits. The data collected included demographics; protein, albumin and creatinine levels in urine collections; blood biochemistry; clinical and treatment data. The data were analyzed using SPSS 18.

Results: A moderate association was found between proteinuria in the range below 300mg/24hr and albuminuria. The strongest association was found in type 2 diabetic patients (r=0.624, P<0.001). Proteinuria cutoff, based on albuminuria cutoff of 30mg/24hr, was found to be 160.5mg/24hr. BMI was the sole independent predictor of albuminuria above 160.5mg/24hr. The other variables examined such as creatinine clearance, age, hypertension, duration of diabetes, Hba1c, ACE inhibitors and angiotensin II blockers, were not predictive. Changes in proteinuria, but not albuminuria, were not associated with changes in creatinine clearance.

Conclusions: A new cutoff value of 160.5mg/hr was set empirically, for the first time, for abnormal proteinuria in diabetic patients. As there was no association between proteinuria and creatinine clearance, it appears that proteinuria below 300mg/24hrs is not sufficient as a sole prognostic factor for kidney injury.

TH-PO437

Non-Invasive Assessment of Electrochemical Skin Conductance Associates with Kidney Function in African Americans (AA) with Type 2 Diabetes (T2D)

Barry I. Freedman, Jasmin Divers, Susan Carrie Smith, Jianzhao Xu, Donald W. Bowden. Wake Forest Univ Health Sciences.

Background: SUDOSCAN® (Impeto Medical, Paris France) is a patented non-invasive measure of sweat gland dysfunction employing electrochemical skin conductance (reverse iontophoresis and chronomerometry) and is useful for assessing peripheral small fiber and autonomic nerve function.

Methods: We tested whether SUDOSCAN® measures differed between AA and European Americans (EA) and for associations with parameters of diabetic kidney disease (estimated glomerular filtration rate [eGFR] and urine albumin/creatinine ratio [UACR]) within each population. A cross-sectional study of renal parameters and SUDOSCAN® skin conductance was performed in 390 cases with T2D (206 AA; 184 EA) and 168 non-diabetic controls (93 AA; 73 EA). Linear models were fitted stratified by population ancestry and T2D status, adjusted for co-variates.

Results: Relative to EA, AA had markedly lower mean (hand + foot) skin conductance (AA T2D vs. EA T2D p<0.0001; AA controls vs. EA controls p>0.0001). As expected, mean (hand + foot) skin conductance was also lower in T2D cases vs. non-diabetic controls within each EA (p<0.0001 for both AA and EA). Adjusting for age, gender, body mass index, and HbA1c, significant positive associations were detected between mean (hand + foot) skin conductance and eGFR in AA cases with T2D (parameter estimate 15.4, standard error 5.7, p=0.0073), but not in EA with T2D (p=0.44). Significant associations between UACR and mean skin conductance were not observed in AA or EA with T2D.

Conclusions: Non-invasive measures of skin conductance previously associated with diabetes mellitus and neuropathy, strongly associate with eGFR in AA. This replicates results in a new Chinese population. In contrast, skin conductance was not associated with measures of kidney disease in EAs. SUDOSCAN® may prove useful as a low cost and non-invasive screening tool in African ancestry populations with T2D allowing for the detection of undiagnosed kidney disease. Differences in skin conductance between EA and AA with T2D and non-diabetic controls is an interesting finding that warrants further study.

Funding: Pharmaceutical Company Support - Impeto Medical, Paris France

TH-PO438

Vitamin D Levels and Renal Progression in Type 2 Diabetic Patients with Blockade of the Renin Angiotensin System

Jose Luno,2 Fernández Gema María,3 Soledad Garcia de Vinuesa,1 Marian Goicoechea,1 Jesus Oliva Dominguez,1 Luisa Casas Losada,2 Vicente Lahera. 4 *Hospital General Universitario Gregorio Marañon, Madrid, Spain; 2Hospital Fundación Alcorcón, Madrid, Spain; 1IS Carlos III, Madrid, Spain; *Universidad Complutense, Madrid, Spain; *On behalf of the PRONEDI Study Group.

Background: Experimental studies show that vitamin D is a suppressor of renin biosynthesis and that vitamin D deficiency has been associated with the progression of chronic kidney disease (CKD). Patients with type 2 diabetes and CKD have an exceptionally high rate of severe vitamin D deficiency, but it is not known whether this deficiency is a risk factor for progression of diabetic nephropathy (DN).

Methods: We measured 25 (OH) vitamin D levels in the patients included in a multicenter randomized controlled trial to compare the efficacy of combining the

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

Underline represents presenting author/disclosure.

201A
angiotensin-converting enzyme inhibitor lisinopril and the angiotensin receptor blocker irbesartan with the efficacy of each drug in monotherapy to slow progression of established type 2 DN. The primary composite outcome was a >50% change in baseline serum creatinine or end-stage renal disease or death. Sample from 103 patients were obtained to determine levels of 25 (OH) vitamin D at baseline and at 4 and 12 months. Results: Fifty-three (51.5%) patients had 25 (OH) vitamin D deficiency (<15 ng/mL). After a median follow-up of 32 (18-46) months, the endpoint was reached by 23 patients with deficiency (43.4%) and 8 patients without (16%). Cox regression analysis showed that 25 (OH) vitamin D deficiency was associated with primary outcome (HR, 2.88; 95% CI, 1.84 -7.67; p=0.04) and renal outcome (HR, 3.79; 95% CI, 1.20-12.02; p=0.02). The effect of 25 (OH) vitamin D did not change with age, gender, weight, treatment with RAS blockers (monotherapy or combined treatment) or levels of aldosterone, PTH, albumin, and phosphorus.

Conclusions: Our results show that 25 (OH) vitamin D deficiency is an independent risk factor for renal progression of type 2 DN.

Funding: Pharmaceutical Company Support - Bristol-Myers Squibb of Spain; Fondo de Investigaciones Sanitarias (Spanish Ministry of Science and Innovation); Spanish Society of Nephrology, Private Foundation Support, Government Support - Non-U.S.

TH-PO439
interaction between vitamin D receptor polymorphisms and 25OHD levels on reduction of eGFR in type 2 diabetes mellitus

Background: FokI polymorphisms of vitamin D receptor (VDR) gene were shown to be different in patients with type 2 diabetes mellitus from controls. Furthermore, deficiency of 25-hydroxyvitaminD (25OHD) was reported to decrease insulin production, increase insulin resistance and diabetic nephropathy. However there are few reports to research interactions between 25OHD and VDR polymorphisms in diabetic patients. Therefore, we aimed to investigate the relationship between one year-reduction of eGFR and serum 25OHD levels stratified by VDR FokI polymorphisms in patients with diabetes.

Methods: The prospective cohort study was carried out at Jikei University Hospital. A total of 407 type 2 diabetic outpatients agreed to participate in this study. We used polymerase chain reaction and direct sequencing analyze VDR FokI polymorphisms.

Results: Median age was 63 years, mean eGFR was 66.3±23.0 mL/min/1.73m2 and average disease duration of diabetes was 12.4±8.8 years. Genotype frequencies were FokI CC:180 CT:172 TT:55. Mean reduction of eGFR during one year was -2.2 mL/min/1.73m2. Genotype frequencies were FokI CC:180 CT:172 TT:55. Mean reduction of eGFR during one year was -2.2 mL/min/1.73m2. Primary outcome was defined as >5ml/min/1.73m2 reduction in eGFR during one year in this study. Lower 25OHD levels significantly increased the risk of the primary outcome in patients with FokI TT polymorphism (P=0.019), whereas 25OHD levels had no significant associations with the primary outcome in those with either FokIC or CT polymorphisms.

Conclusions: These results suggest that eGFR may rapidly decrease in diabetic patients with lower 25OHD levels and FokI TT polymorphism.

TH-PO440
Effect of Aldosterone Blockade on Galectin 3 in Patients with Diabetic Nephropathy

Background: Fibrosis and expansion of extra cellular matrix in the kidney is part of the pathogenesis of diabetic nephropathy. Plasma galectin-3 (p-gal3) is linked to fibrogenesis in the heart and kidney, and treatment with spironolactone has beneficial effect in patients with heart failure. We hypothesize, that a potential beneficial effect of spironolactone on fibrosis in diabetic nephropathy is mediated through a reduction in p-gal3.

Methods: A post-hoc analysis of three clinical controlled double masked intervention trials all with randomisation to either spironolactone or placebo for 8 weeks in a cross-over design. The first trial consisted of 21 patients with 1 DM and macroalbuminuria, the second consist of 23 patients with type 2 DM and macroalbuminuria and the third consist of 21 patients with type 1 DM and microalbuminuria. Mean(SD) age of 53 years (10.8) and a mean duration of DM of 28 years (14.6).

Results: As previously reported albuminuria was reduced with 30, 33 and 60% in the three trials. P-gal3 was associated with GFR in the placebo period (R²=0.42 p<0.0001). Mean(95% CI) level of plasma p-gal3 after treatment with spironolactone was 16.0(14.7-17.1) and after placebo 15.5(14.3-16.7). In an unadjusted mixed model, the effect of treatment insignificant increased p-gal3 by 1.03 ng/mL (1.02-1.05) (p=0.074). However, when adjusted for after treatment values of mean 24h systolic blood pressure, 24h urine albumin excretion, Cr GFR, Hba1c, and cholesterol, the treatment effect on p-gal3 was attenuated (p=0.09).

Patients with p-gal3 below the median in the placebo period had a greater reduction in albuminuria 31.3%(25.1-37.6) vs. those above 8.9%(2.9-20.4), p=0.021.

Conclusions: Galectin 3 was associated with GFR. Spironolactone for two months reduced albuminuria but did not change p-gal3 levels. This suggests an initial effect mediated by hemodynamic changes, whereas an effect on fibrosis may require a longer treatment period or p-gal3 is not affected by spironolactone. Low level of p-gal3 was associated with greater reduction in albuminuria.

TH-PO441
A Panel of Novel Biomarkers to Predict Renal Function Decline in Type 2 Diabetes

Background: We aimed to explore a panel of novel biomarkers representing different disease pathways for their potential association with accelerated renal function decline in type 2 diabetes.

Methods: A systematic data integration approach was used to identify promising biomarkers for this study. The following biomarkers were selected and tested in 82 patients with type 2 diabetes: markers from an outpatient diabetes center in The Netherlands: amino-terminal propeptide of CNP (NTproCNP), tumor necrosis factor receptor-2 (TNFR2), sclerostin, fibroblast growth factor-23 (FGF23), endostatin, alpha-2-glycoprotein-1 zinc-binding (AZGP1), nephrin, neuropilin, podocin, and galectin-3. Follow-up for renal function decline was 3.7 ± 1.1 years. Associations between concentrations of individual biomarkers and annual eGFR decline were assessed by univariable regression and multivariable regression analysis for conventional renal risk marker age, gender, baseline eGFR, and baseline UACR.

Results: The average rate of renal function decline was -2.0 ± 4.4 mL/min/1.73m2/year. Serum NTproCNP and podocin, and serum and urine endostatin and TNFR2 were significantly associated with annual eGFR decline in univariable analysis. Serum TNFR2 and urine endostatin remained significant in multivariable analysis (Table). Finally, serum TNFR2 and urine endostatin were combined as a panel that significantly improved prediction of annual renal function decline on top of conventional renal risk markers (R² increase from 0.41 to 0.49; p<0.001).

Conclusions: A panel of novel biomarkers representing different disease pathways can improve prediction of accelerated renal function decline on top of conventional markers in type 2 diabetes. These results need to be confirmed in a large prospective cohort.

TH-PO442
Novel Urinary Exosome Isolation as a Platform to Study Diabetic Nephropathy

Background: DN remains a major cause of end-stage renal disease (ESRD) worldwide. Discovery of early and reliable biomarkers of disease progression promises to help physicians develop personalized care plans for patients based on their risk of ESRD. Exosomes are plasma membrane bound vesicles secreted by all cells which contain protein, mRNA and miRNA, representative of the cells of their origin. The goal of these studies is to test the hypothesis that urinary exosomal miRNAs, which originate from cells lining the glomerular tract, are an ideal source of biomarkers for DN.

Methods: Urinary exosomes were isolated from patients without diabetes (DM; controls), early DN, and moderate DN. RNA was extracted and microRNAs assayed by qRT-PCR array (Exiqon).

Results: 742 miRNAs were assayed in 4 control (no DM, normal kidney function, no proteinuria), 3 early DN (normal kidney function, with microalbuminuria), and 4 later stage DN (serum creatinine>1.3) subjects. Because this novel technique is unvalidated, we tested whether the miRNAs known to play a role in research models of DN (miRNA-192, miRNA-192, 26a, 29a, 216a, 217, 377, 200e, 93, and 29C) were expressed in urinary exosomes of DN

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

Underline represents presenting author/disclosure.

202A
patients. Of these miRNAs, miR-192, 21, 29a, 200b, 93, and 29C were up-regulated in DN patients compared to controls, recapitulating the prior studies. Finally, of the 742 miRNAs evaluated 89 (12%) were dysregulated in exosomes derived from DN patients compared to controls. Of these 89 dysregulated miRs, miR-200b, miR-99b, and Let-7b were upregulated in DN patients and have been implicated in TGF-β-dependent fibrosis, TGF-β-dependent epithelial–mesenchymal transition, and podocyte-specific laminin down-regulation, respectively.

Conclusions: Six of nine miRNA dysregulated in models of DN were also up-regulated in urinary exosomes of DN patients, suggesting that miRNAs associated with DN are expressed in exosomes. Evidence from our array also suggests potentially novel miRNAs are associated with DN.

Funding: Veterans Affairs Support, Pharmaceutical Company Support - Exiqon Grant Program

TH-PO443

Urinary Type IV Collagen: Can It Be Used as an Indicator for the Progression of Diabetic Nephropathy?  
Salah S. Nagy,1 Iman Ezzat Elgohary,2 Doaa I. Hashad,3 Marwa Abdelalad Elaty,1 1Internal Medicine, Faculty of Medicine, Alexandria, Egypt; 2Internal Medicine, Faculty of Medicine, Alexandria, Egypt; 3Clinical Pathology, Faculty of Medicine, Alexandria, Egypt; 4Internal Medicine, Faculty of Medicine, Alexandria, Egypt.

Background: Diabetic nephropathy is a complication seen in long standing diabetes mellitus where progressing impairment of kidney function leads to end-stage renal disease. In the diabetic kidney, the accumulation of type IV collagen was detected in glomerular basement membrane (GBM), tubular basement membrane and Bowman’s capsule much more than that in the normal kidney. However, there is little information on whether the increase in type IV collagen excretion in urine is a predictor of progression of diabetic nephropathy or deterioration of renal function in type 2 diabetic patients. We conducted this work with the aim to determine whether the urinary levels of type IV collagen can predict the progression of diabetic kidney disease in Type 2 DM.

Methods: This study included 100 adult patients; who were classified into: 20 diabetic normoalbuminuric patients (group1), 20 diabeti microalbuminuric patients (group2), 20 diabetic microalbuminuric patients (group3), 20 diabetic CKD patients with GFR: 60-90ml/min (group4), 20 diabetic CKD patients with GFR: 30-59ml/min (group5), and compared with 20 controls (group 6). All included subjects were subjected to renal function test and estimated creatinine clearance by Modi cation of Diet in Renal Disease (MDRD) formula. Measurements of urine albumin/creatinine ratio. Fasting blood glucose and hemoglobin A1c. The urinary concentrations of type IV collagen were measured using a highly sensitive one-step sandwich ELISA kit.

Results: Urinary type IV collagen was significantly higher in normoalbuminuric patients than the control group, in microalbuminuric patients than both control and normo albuminuric, in macroalbuminuric in normo and micro albuminuric control, and in CKD1, CKD2 groups it was significantly higher than all other groups and highest in CKD2.

Conclusions: Urinary type IV collagen can be used as an indicator for the progression of kidney disease in diabetic patients.

Funding: Private Foundation Support

TH-PO444

Global Metabolomic Profile in Type 2 Diabetes and Subsequent Progression to ESRD  
Monika A. Niewczas,1 Tammy L. Sirich,2 Anna V. Mathew,3 Alexandria, Egypt; 3Clinical Pathology, Faculty of Medicine, Alexandria, Egypt; 3Internal Medicine, Faculty of Medicine, Alexandria, Egypt.

Background: We studied plasma metabolomic profiles as determinants of progression to ESRD in Type 2 diabetes (T2D).

Methods: This case-control study used Joslin Kidney Study participants with T2D with well-preserved renal function at baseline: 40 cases who progressed to ESRD and 40 controls who remained alive without ESRD during a 10 year follow up. Controls were matched with cases regarding baseline clinical characteristics. Plasma metabolites at baseline were measured by mass spectrometry-based global profiling.

Results: Of the named metabolites in the library, 274 were detected in at least two-thirds of the study subjects. Among the 78 uric acid solutes recognized by the platform, 12 were elevated in baseline plasma of cases. Other uric acid solutes were either not different or not commonly detectable. Essential amino acids and their derivatives were depleted in the cases, whereas related acylcarnitines were increased. All our findings remained highly significant after adjustment for multiple comparisons and controlling for clinical covariates.

Conclusions: Certain metabolic signatures (increased plasma concentrations of the putative uremic solutes, decreased levels of essential amino acids accompanied by increased levels of acylcarnitines) are associated with subsequent progression to ESRD in T2D and those changes in plasma levels are already present at an early stage of diabetic nephropathy.

Funding: NIDDK Support, Private Foundation Support

TH-PO445

Glycemic Control and the Risk of Mortality among Hemodialysis Patients in Japan  
Noriko Kameyama,1 Hirotaka Komaba,1 Hajime Suzuki,2 Takatoshi Kakuta,1 Takao Suga,3 Masafumi Fukagawa,1 1Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan; 2Div of Nephrology and Diabetes, Tokai Univ Oiso Hospital, Oiso, Japan; 3Medical Corporation Shonanoki, Japan.

Background: Diabetes mellitus is the most common cause of end-stage renal disease in Japan. While tight glycemic control decreases the risk of diabetic complications, it remains to be determined whether better glycemic control reduces the risk of death in diabetic patients undergoing dialysis.

Methods: We retrospectively collected data on maintenance hemodialysis patients (n = 2,292) beginning in December 2008. The diagnosis of diabetes was made based on medical records. We analyzed the association between presence or absence of diabetes, glycemic control, and the risk of death over three years, using Cox proportional hazards models. We also performed time-dependent Cox models to account for changes in glycemic control over time. Data were collected at quarterly intervals.

Results: A total of 1,038 patients had diabetes. Overall, diabetes was well controlled and the mean HgbA1c values were <7.0% in 86%. HgbA1c values showed a significant correlation with random glucose values (r = 0.58; P < 0.001). Patients with diabetes had a significantly increased risk of death compared to those without (HR, 0.62; 95% CI, 0.49 to 0.77). No significant association was observed between Hba1c values and the risk of death. These results were unaltered in time-dependent Cox models.

Conclusions: More studies are needed to define the optimal management of diabetes for patient receiving dialysis.

Funding: Government Support - Non-U.S.

TH-PO446

Effect of Dapagliflozin on Blood Pressure and Body Weight in Patients with Type 2 Diabetes and Cardiovascular Disease  
Terk de Bruin,1 Shamil Parikh,1 Jennifer Sugg,1 Shoba Ravichandran. 1AstraZeneca, Wilmington, DE; 2Bristol-Myers Squibb, Princeton, NJ.

Background: Patients with type 2 diabetes (T2D) often have hypertension (HTN) and cardiovascular disease (CVD). Selective SGLT2 inhibitor dapagliflozin (DAPA) reduces hyperglycemia by promoting renal glucose excretion and is associated with osmotic diuresis and caloric loss that provide additional benefits. Our analysis assessed the effect of DAPA vs placebo (PBO) on blood pressure (BP) and body weight (BW) in patients with T2D and established CVD treated for 52 weeks in 2 clinical trials (Study 18, NCT01031680, N-922; Study 19, NCT01042977, N-965).

Methods: Patients with glycated hemoglobin ≥7% and ≤10% were randomized to double-blind PBO or DAPA 10 mg/d, added to pre-existing anti-hyperglycemic (including insulin), antihypertensive (ACEI/ARBs, diuretics), antipatelet, and lipid-lowering drugs. A medical history of HTN was an inclusion criterion for Study 18 and was present in 93% of Study 19 patients. Adjusted mean changes from baseline to week 52 were analyzed by longitudinal repeated measures.

Results: Compared with PBO, DAPA reduced systolic BP and BW (Table). Small decreases in diastolic BP were also observed. Hematocrit increased, and urine albumin/creatinine decreased with DAPA. There were small decreases in eGFR across treatment groups, indicating that volume-related adverse events was low and inconsistent across studies (Study 18, DAPA 2.8% vs PBO 0.4%; Study 19, DAPA 1.5% vs PBO 2.7%). Urinary tract infections in 1 study (Study 18, 5.9% vs 5.8%; Study 19, 11.0% vs 5.8%) and genital tract infections in 1 study (Study 18, DAPA 2.8% vs PBO 0.4%; Study 19, DAPA 1.5% vs PBO 2.7%). Urinary tract infections in 1 study (Study 18, 5.9% vs 5.8%; Study 19, 11.0% vs 5.8%) and genital tract infections in both studies (Study 18, 6.1% vs 0.9%; Study 19, 7.5% vs 0.4%) were more common with DAPA vs PBO.

Conclusions: In patients with T2D and CVD, DAPA added to usual care reduced BW. BP was also reduced, potentially through a diuretic-like mechanism, without compromising renal function.

Funding: Pharmaceutical Company Support - Supported by AstraZeneca and Bristol-Myers Squibb

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

Underline represents presenting author/disclosure.
TH-PO447
Effect of Atorvastatin on Renal NO Availability and Tubular Function in Patients with Stage II-III Chronic Kidney Disease and Type 2 Diabetes Frank H. Mose,1,2 Thomas Larsen,1,2 JannI Maigaard Jensen,1,2 Jesper N. Bech,1 Erling B. Pedersen,1,2 1Dept of Medical Research, Holstebro Hospital, Holstebro, Denmark; 2Univ of Aarhus, Aarhus, Denmark.
Background: Statins have beneficial effects on cardiovascular morbidity and mortality independently of reduction of plasma cholesterol.
Methods: In patients with type 2 diabetes and nephropathy, chronic kidney disease stage II-III, we tested the hypothesis that atorvastatin increased systemic and renal nitric oxide (NO) availability using L-NMMA as an inhibitor of NO production. We performed a randomized, placebo-controlled, crossover study, using atorvastatin/placebo treatment for five days with a standardized diet and fluid intake. We measured brachial BP (BP), central BP (cBP), GFR, urinary output (OU), free water clearance (C_{\text{f}}), fractional excretion of sodium (FE_{\text{Na}}), urinary excretion of albumin (UAER and UACR), AQP2 (u-AQP2) and ENaC (u-ENaC) and plasma concentrations of vasoactive hormones: renin, angiotensin II, aldosterone, arginine vasopressin, endothelin-1 and brain natriuretic peptide.

Results: During inhibition of nitric oxide synthesis, atorvastatin and placebo changed the effect variables significantly to the same extent, i.e. an increase in BP, cBP and cGFR, and a decrease in GFR, OU, C_{\text{f}}, FE_{\text{Na}}, u-AQP2 and u-ENaC. In addition, renin and angiotensin II was reduced, aldosterone increased, and vasopressin, endothelin-1 and brain natriuretic hormone were unchanged.

Conclusions: During inhibition of nitric oxide synthesis, atorvastatin and placebo induced the same response in brachial and central blood pressure, GFR, renal tubular function and vasoactive hormones. Thus, atorvastatin did not change nitric oxide availability in the diabetic nephropathy.
Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO448
Proteinuria Reduction with Probucol and Telmisartan in Patients with Type 2 Diabetic Nephropathy Xiang-Mei Chen, Hanyu Zhu, Guangyuan Cai, Ying Zheng. Dept of Nephrology, State Key Laboratory of Kidney Disease, General Hospital of Chinese People’s Liberation Army, Beijing, China.

Background: Combination therapy with telmisartan and probucol in the treatment of diabetic nephropathy has not been proved with sufficient clinical evidence. This study examined the clinical efficacy of telmisartan and probucol in proteinuria reduction of type 2 diabetic nephropathy.

Methods: A total of 160 type 2 diabetic nephropathy patients with proteinuria (0.5-2.0 g/24h) were enrolled in a randomized, double-blind, placebo-controlled, multicenter study. The patients were randomly divided into two groups. Telmisartan group (n=80) was administered with telmisartan (80 mg/day) and probucol placebo (1000 mg/day for 24 weeks, and then reduced to 500 mg/day for next 24 weeks). Probucol group (n=80) was administered with telmisartan (80mg/day) and probucol (1000 mg/day for 24 weeks, and then reduced to 500 mg/day for next 24 weeks). All patients were followed throughout the 48-week period, and the percentage change of urinary protein from baseline to 48 weeks was assessed.

Results: The baseline characteristics of the two groups were similar, as well as the BP and HbA1c profile over the study period. There was a significant reduction (27.0%) in urinary protein level in probucol group compared to baseline. However, urinary protein level was increased in the telmisartan group (1.45%). For patient with lower urinary protein (<1.0g/24h at baseline), the reduction in urinary protein level from baseline is significantly greater in probucol group than in telmisartan group (36.54% vs. 8.55%, P=0.013). For the patients with higher urinary protein (>1.0g/24h at baseline), there was a significantly reduction of 15.38% in urinary protein level in probucol group from baseline. However, urinary protein was increased in telmisartan group, with an average increase of 10.96% (P=0.011 for the comparison with probucol group).

Conclusions: The combination therapy of telmisartan and probucol lowers urinary protein more effectively than telmisartan alone.
Funding: Government Support - Non-U.S.

TH-PO449
In Type 1 Diabetic Patients with Albuminuria Insulin Pump Treatment Is Associated with Reduced Arterial Stiffness Signe Rosenlund,1 Simone Thelild,1,2 Tine Hansen,1 Peter Rossing,1,2,3 1Steno Diabetes Center, Denmark; 2Copenhagen University Hospital, Copenhagen, Denmark; 3Aarhus Univ.

Background: Insulin pump treatment is often associated with reduced glucose variability and in improvements in glycemic control, which could reduce development of vascular complications. We investigated the relationship between arterial stiffness, evaluated by pulse wave velocity (PWV), and treatment with insulin pump in patients with type 1 diabetes, and examined if this association was dependent of glucose control.

Methods: Cross-sectional study, from 2009-2011, including 639 Caucasian patients with type 1 diabetes. PWV measurements (Sphygmocor, AtCorMedical, Australia) were available in 59 patients with insulin pump (35 with albuminuria ≥30mg/d and 590 (28%) with albuminuria ≥30mg/d treated with multiple daily insulin injections (MDI) ≥2 injections). ANCOVA compared groups and adjusted multiple linear regression analyses investigated the association between insulin pump treatment and arterial stiffness.

Results: In the albuminuric group, PWV was significantly lower in patients with insulin pump (9.3±3.2 vs. 11.3±3.4 mmHg; p=0.001). This difference remained significant (p=0.002) after adjustment for gender, diabetes duration, eGFR, albuminuria, total-chr, smoking, office MBP. For all patients, PWV was also lower in the insulin pump group (9.3±2.8 vs. 10.4±3.3 m/s, adj. p=0.002). In multiple regression analysis, pump treatment was significantly associated with lower PWV, while HbA1c was not associated with PWV in neither patients treated with MDI or insulin pump.

Conclusions: Insulin pump treatment was independently associated with reduced arterial stiffness, while HbA1c was not. Although glucose variability was not assessed, our results suggest that glucose variability and not HbA1c, level may modify arterial stiffness. This needs confirmation in randomised prospective studies.

TH-PO450
Risk Stratification with P-Nt-proBNP and Coronary Calcium Score Predicts All-Cause Mortality in Microalbuminuric Type 2 Diabetic Patients Henrik van Scholten,1 Henrik Reinhardt,1 Peter Godske Jorgensen,2 Simone Thelild,1 Peter R. Hansen,2 Niels Winiberg,1 Andreas Kjaer,1 Hans-Henrik Parving,1 Jan Skov Jensen,2 Peter Carl Jacobsen,4 Peter Rossing.1 1Steno Diabetes Center, Denmark; 2Geontfole Hospital; 3Frederiksberg Hospital; 4Rigshospitalet.

Background: The burden of CAD is significantly increased in type 2 diabetes and associated with mortality. An effective screening tool for subclinical CAD is needed to predict and prevent cardiovascular mortality in these patients.

Methods: NT-proBNP, coronary calcium score (CCS) and echocardiography (echo) were performed in 200 asymptomatic type 2 diabetic patients with elevated UAER (>30mg/24h) and without prior history of CAD. NT-proBNP >45.2 ng/l and/or CCS ≥400 stratified patients as high risk for CAD and were further examined for significant CAD by hMPA and/or CT-angiography and/or CAG. During inhibition of nitric oxide synthesis, atorvastatin and placebo changed the effect variables significantly to the same extent, i.e. an increase in BP, cBP and cGFR, and a decrease in GFR, OU, C_{\text{f}}, FE_{\text{Na}}, u-AQP2 and u-ENaC. In addition, renin and angiotensin II was reduced, aldosterone increased, and vasopressin, endothelin-1 and brain natriuretic hormone were unchanged.

Conclusions: During inhibition of nitric oxide synthesis, atorvastatin and placebo induced the same response in brachial and central blood pressure, GFR, renal tubular function and vasoactive hormones. Thus, atorvastatin did not change nitric oxide availability in the diabetic nephropathy.
Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO451
Lowering of Albuminuria Reduces Cardio-Renal Events: Insights from ALTITUDE Siddo Jan Lambers Heerspink,1 Fredrik I. Persson,2 Toshiharu Ninomiya,1 Barry M. Brenner,3 Nish Chaturvedi,1 Scott D. Solomon,2 Marc A. Pfeffer,1 Hans-Henrik Parving,4 Dick de Zeeuw.2,3 1Clinical Pharmacology, UMC Groningen, Netherlands; 2ALTIMETE Steering Committee.

Background: Direct renin inhibition with aliskiren on top of ACEi/ARB therapy decreases albuminuria but did not decrease renal or cardiovascular (CV) events in the ALTITUDE (The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) trial. Could the overall reduction in albuminuria (14%) have been too small to afford protection? We investigated post-hoc whether in ALTITUDE albuminuria predicts renal/CV outcome and whether the degree of albuminuria reduction is related to renal/CV risk reduction.

Methods: In a randomized controlled double blind trial, 8561 subjects with type 2 diabetes and CKD, CV disease, or both were assigned to aliskiren 300 mg daily or placebo on top of ACEi or ARB therapy. Renal and CV events were collected during a median follow-up of 2.8 years.

Results: After adjusting for multiple risk markers, patients with high albuminuria (≥1000 mg/g creatinine; N=1903) at baseline showed a 9-fold renal (p<0.001) and 2-fold CV (p<0.001) risk increase compared to the low albuminuric group (<100 mg/g; N=2678). The change in albuminuria in the first 6 months of aliskiren therapy varied widely (IQR -49 to +42%). Subjects with larger reductions in albuminuria in the first 6 months (>30%; N=2738) showed a risk reduction of 58% for renal (95% CI: 69 to 45%; p=0.01) and 22% for CV (95% CI: 35 to 5%; p=0.01) events compared to subjects with an albuminuria increase between 0 and 30% (N=1251). Similar results were obtained when the aliskiren or placebo groups were separately analyzed. Residual albuminuria at month 6 showed an almost identical association with renal/CV outcome as baseline albuminuria.

Conclusions: Change in albuminuria is associated with a proportional effect on renal and CV outcome: the greater the reduction in albuminuria the greater the risk reduction. Baseline as well as residual albuminuria is directly related to renal and CV risk: the higher the albuminuria the more risk. These 58% imply that albuminuria could be monitored and targeted to the lowest achievable level in an attempt to reduce renal and CV risk.
Funding: Pharmaceutical Company Support - The ALTITUDE trial was sponsored by Novartis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
TH-PO452
No Increase in Bone Fractures with Empagliflozin (EMPA) in a Pooled Analysis of More Than 11,000 Patients with Type 2 Diabetes (T2DM)
Christoph Wanner,1 Robert D. Toto,2 John Gerich,3 Thomas Hach,4 Afshin Salsali,5 Gabriel Kim,6 Stefan Hantel,7 Hans-Juergen Woerle,8 Uli Christian Broedl,9
1 Univ of Wurzburg, Germany; 2 Univ of Texas Southwestern Medical Center, Dallas; 3 Univ of Rochester School of Medicine, Rochester, NY; 4Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; 5Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

Background: The SGLT2 inhibitor EMPA is in development for the treatment of T2DM. SGLT2 inhibitors may alter the renal reabsorption of calcium and phosphate, and may potentially have effects on bone metabolism.

Methods: Using pooled data from Phase I, II and III trials, adverse events (AEs) consistent with bone fracture were evaluated through a search of investigator-reported AEs in patients with T2DM treated with placebo (PBO; n=3522), EMPA 10 mg (n=3630) or EMPA 25 mg (n=4602) in sub-groups of gender, age (<50, ≥50–<65, ≥65–<75, ≥75 yrs), BMI (<25, ≥25–<30, ≥30–35, ≥35 kg/m2) and eGFR (<90, ≥90–<90, ≥90–60, <90 mL/min/1.73m2), Mean (SD) baseline age was 59.6 (10.0) yrs, BMI 30.0 (5.5) kg/m2, eGFR 80.1 (22.1) mL/min/1.73m2 and 63% of patients were male.

Results: The percentage of patients with fractures was similar with PBO (55/3522 [1.6%]) and EMPA 10 mg (59/3630 [1.6%]), but slightly lower with EMPA 25 mg (51/4602 [1.1%]). A greater proportion of female than male patients reported fractures in all treatment groups (35.9% vs. 27.8%), with 1.2–2.5% males: 1.0–1.3% cases with comparable rates between PBO and EMPA. The percentage of patients with fractures was generally similar between PBO and EMPA in subgroups defined by age, BMI or eGFR. No changes in serum calcium or phosphate were observed. Small changes from baseline were observed in iPTH (mean [SD] changes: -3.0 [15.7], 0.4 [15.0], -2.1 [31.1] nM/L in PBO, EMPA 10 mg, EMPA 25 mg, respectively), 25-OH vitamin D (mean [SD] changes 2.6 [4.00], 3.1 [34.8], 8.4 [36.2] nM/L, respectively), and N-telopeptide (NTx) creatinine ratio (mean [SD] changes -2 [17], 3 [19], 6 [23] nM/mM Cre, respectively).

Conclusions: In a pooled analysis of data from >11000 patients with T2DM, EMPA was not associated with an increased frequency of bone fractures versus PBO.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim

TH-PO453
Is Peritoneal Dialysis Associated with New-Onset Diabetes Mellitus? Chih-Chiang Chien,1 Dept of Nephrology, Chi-Mei Medical Center, Taiwan.

Background: Few published studies have focused on post-dialysis normalization-onset DM. This study investigates whether there is an association between dialysis modality and new-onset DM.

Methods: In the Taiwan National Health Insurance Research Database, we examined records of ESRD patients who initiated dialysis between 1999 and 2005. Patients were followed until death, transplant, dialysis withdrawal, or 31 December 2008. Predictors of new-onset DM were calculated using Cox models.

Results: A total of 51,487 incident dialysis patients were examined in this study, including 25,321 patients with pre-existing DM, 3,346 with new-onset DM and 22,820 without DM at any time. Patients’ age (mean ± SD) was 61.8 ± 11.5, 61.6 ± 13.7 and 56.5 ± 16.6 years in the pre-existing, new-onset DM and without DM groups, respectively. The cumulative incidence rate of new-onset DM was 4% at one year and 21% at nine years. Being female, in pre-existing, new-onset DM and without DM groups, respectively. The cumulative incidence rate of new-onset DM was 4% at one year and 21% at nine years. Being female, being older, and having baseline comorbidities were independent risk factors for new-onset DM in dialysis patients. Dialysis modality was not a risk factor for new-onset DM (HD to PD hazard ratio of new-onset DM = 0.94 (95% CI: 0.83-1.06). The mean duration between new-onset DM diagnosis and death was 6.10 ± 3.01 years. Pre-existing DM was associated with 80% greater death risk (HR: 1.81, 95% CI: 1.75-1.87), whereas the new-onset DM was associated with 10% increased death risk (HR: 1.10, 95% CI: 1.03-1.17).

Conclusions: Whereas diabetes mellitus does not appear to associate with new-onset DM, both pre-existing and new-onset DM are related to higher long-term mortality in maintenance dialysis patients.

TH-PO454
Diabetic Foot Ulcers and Mortality in Chronic Hemodialysis Patients Edward K. Lascen, Weiling Wang, Shu-Fang Lin, Franklin W. Maddux, Jeffrey L. Hymes.

Fresenius Medical Care, North America, Waltham, MA.

Background: Ulcers are associated with poor outcome in diabetic hemodialysis (HD) patients. We evaluated the development of foot ulcers detected by a national monthly foot check program at Fresenius Medical Care, North America facilities.

Methods: All adult diabetic HD patients with ≥1 foot check documented electronically during 7/1/09-6/30/12 in 329 facilities with ECube clinical systems were included. Foot ulcer status and deaths were followed until 12/31/12. Patients developing ulcers on follow-up were “cases”, others only “at-risk”. As of the 1st foot check date, age, gender, race, and incident patient status (vintage ≤120 days) were recorded. Logistic regression defined odds ratio (OR) for death between cases and patients-at-risk.

Results: 764 (5.4%) of 14,103 patients had foot ulcers at 1st recorded exam. Among-urea-free patients, 1,769 (13.3%) developed ulcers (cases). The mean age was 63.5±12.6 years, with more males (58.4% vs. 52.8%) and whites (71.0% vs. 63.0%) in cases (all p<0.0001). Cases had longer median follow-up time at 462 vs. 352 days. The nested median time to first ulcer was ~5 months (Table), the nested median time to death from the 1st foot ulcer was ~3.5-4.0 months. Unadjusted OR of death was 1.45 compared to patients-at-risk, and remained OR=1.51 after adjusting for case-mix (both p<0.0001).

Mortality risk was not significantly different in incident patients.

TH-PO455
Monthly Variation in Glycemic Indices in Patients Maintained with Dialysis Neal Mittman,1 Lin Ma,2 Mark E. Williams,3 Julia I. Brennan,4 Chinu M. Jani,4 Curtis D. Johnson,5 Franklin W. Maddux,6 Eduardo K. Lascen,2 1Long Island College Hospital, Brooklyn, NY; 2Fresenius Medical Care, North America, Waltham, MA; 3Joslin Diabetes Center, Boston, MA; 4Spectra Laboratories, Rockleigh, NJ.

Background: Glycemic control is conventionally monitored utilizing quarterly measurement of glycosylated hemoglobin (A1c). Because A1c may not be an ideal marker for dialysis patients, other glycemic indices have been sought. Furthermore, little is known about the comparative variability of these indices which reflect different durations of glycemia.

Methods: Simultaneous measurement of pre-dialysis serum fructosamine (SF), glycated albumin (GA), A1c and casual glucose (BG), from residual blood (of routine monthly draws) was obtained from a national sample of 1977 DM and 1454 nondiabetic (NDM) dialysis patients from 26 FMCNA facilities. Mean intra-patient variability was compared by coefficient of variation (CV) for January-March 2013. SF was albumin-corrected (AIFB) and GA was expressed as percent glycated (%GA) as recommended.

Results: BG exhibited the highest intra-patient CV in dialetics on PD, followed by DM HD, while NDM HD and PD pts had lesser CV. A1c and AIFB were the most stable for all groups. GA exhibited greater variability than SF or A1c. PD pts (both DM and NDM) had greater CV with GA than HD pts. CV with GA was lower when expressed as %GA, the method recommended by the manufacturer.

Conclusions: Monthly intra-patient variability is modest for A1c, SF, AIFB, and %GA, a necessary requirement for a periodic monitoring tool. A1c reflects a longer period of glycemia (2-3 months) and should be the most stable relative to protein-based indices (2-3 weeks of glycemia). These concurrent tests provide baseline information as we prospectively evaluate their utility and association with outcomes.

TH-PO456
Correlates of Glycosylated Hemoglobin Level in Diabetic Patients Maintained with Dialysis Neal Mittman,1 Lin Ma,2 Mark E. Williams,3 Julia I. Brennan,4 Chinu M. Jani,4 Curtis D. Johnson,3 Franklin W. Maddux,5 Eduardo K. Lascen,2 1Long Island College Hospital, Brooklyn, NY; 2Fresenius Medical Care, North America, Waltham, MA; 3Joslin Diabetes Center, Boston, MA; 4Spectra Laboratories, Rockleigh, NJ.

Background: Serial measures of glucose and Hemoglobin A1c is used to monitor glycemic control in diabetic dialysis patients (pts) and in the general population. We explored the distribution of A1c in a national sample of 1979 DM patients from 26 FMCNA facilities across the US.

Funding: JNCI, Medtronic.
Methods: Residual blood specimens were used to obtain mean monthly chemistries for the period January-March 2013. Ps were stratified by Alc as <5.5% (n=553), 5.5-7.0% (n=661), and >7.0% (n=565). Demographic and biochemical correlates of glycemia by Alc category were evaluated.

Results: As expected, serum glucose increased by Alc group accompanied by a decreasing percentage of pts with casual glucose <120mg%. Higher Alc was associated with younger age, shorter dialysis vintage and peritoneal dialysis modality (all p<0.001). There were no differences by gender, race, ethnicity, HD catheter usage, cardiovascular comorbidities (CVA, CHF, PAD, AMI), mean eKt/v and albumin between groups. Interestingly, pts with Alc=5.5% had lower mean Hgb while receiving higher mean EPO doses to maintain these Hgb levels. WBC count increased in the opposite direction of ESA dose, with no differences in neutrophil to lymphocyte ratios between groups.

Conclusions: While Alc tracks with glucose levels, it may be further affected by high ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.

TH-PO457

Glucose Level Impacts Cardiac Outcomes Incident Diabetic Patients Diabetics Undergoing Hemodialysis in Countries in which the Entity of

Methods: Patients with diabetes mellitus (DM) were contacted by the study team and made aware of the role of carbohydrates change into blood sugar, has not been announced to citizens. In Europe and the presence of chronic kidney disease. However, there has been much debate whether levels (A1C) for patients with diabetes mellitus (DM) should be <7.0% irrespective of A1c may likewise induce ESA resistance. Factors unrelated to glycemic control need to be turnover that leads to lower A1c, it is also possible that existing factors predisposing to low ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.

TH-PO457

Glucose Level Impacts Cardiac Outcomes Incident Diabetic Patients Diabetics Undergoing Hemodialysis in Countries in which the Entity of

Methods: Patients with diabetes mellitus (DM) were contacted by the study team and made aware of the role of carbohydrates change into blood sugar, has not been announced to citizens. In Europe and the presence of chronic kidney disease. However, there has been much debate whether levels (A1C) for patients with diabetes mellitus (DM) should be <7.0% irrespective of A1c may likewise induce ESA resistance. Factors unrelated to glycemic control need to be turnover that leads to lower A1c, it is also possible that existing factors predisposing to low ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.

TH-PO457

Glucose Level Impacts Cardiac Outcomes Incident Diabetic Patients Diabetics Undergoing Hemodialysis in Countries in which the Entity of

Methods: Patients with diabetes mellitus (DM) were contacted by the study team and made aware of the role of carbohydrates change into blood sugar, has not been announced to citizens. In Europe and the presence of chronic kidney disease. However, there has been much debate whether levels (A1C) for patients with diabetes mellitus (DM) should be <7.0% irrespective of A1c may likewise induce ESA resistance. Factors unrelated to glycemic control need to be turnover that leads to lower A1c, it is also possible that existing factors predisposing to low ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.

TH-PO457

Glucose Level Impacts Cardiac Outcomes Incident Diabetic Patients Diabetics Undergoing Hemodialysis in Countries in which the Entity of

Methods: Patients with diabetes mellitus (DM) were contacted by the study team and made aware of the role of carbohydrates change into blood sugar, has not been announced to citizens. In Europe and the presence of chronic kidney disease. However, there has been much debate whether levels (A1C) for patients with diabetes mellitus (DM) should be <7.0% irrespective of A1c may likewise induce ESA resistance. Factors unrelated to glycemic control need to be turnover that leads to lower A1c, it is also possible that existing factors predisposing to low ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.

TH-PO457

Glucose Level Impacts Cardiac Outcomes Incident Diabetic Patients Diabetics Undergoing Hemodialysis in Countries in which the Entity of

Methods: Patients with diabetes mellitus (DM) were contacted by the study team and made aware of the role of carbohydrates change into blood sugar, has not been announced to citizens. In Europe and the presence of chronic kidney disease. However, there has been much debate whether levels (A1C) for patients with diabetes mellitus (DM) should be <7.0% irrespective of A1c may likewise induce ESA resistance. Factors unrelated to glycemic control need to be turnover that leads to lower A1c, it is also possible that existing factors predisposing to low ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.

TH-PO457

Glucose Level Impacts Cardiac Outcomes Incident Diabetic Patients Diabetics Undergoing Hemodialysis in Countries in which the Entity of

Methods: Patients with diabetes mellitus (DM) were contacted by the study team and made aware of the role of carbohydrates change into blood sugar, has not been announced to citizens. In Europe and the presence of chronic kidney disease. However, there has been much debate whether levels (A1C) for patients with diabetes mellitus (DM) should be <7.0% irrespective of A1c may likewise induce ESA resistance. Factors unrelated to glycemic control need to be turnover that leads to lower A1c, it is also possible that existing factors predisposing to low ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.

TH-PO457

Glucose Level Impacts Cardiac Outcomes Incident Diabetic Patients Diabetics Undergoing Hemodialysis in Countries in which the Entity of

Methods: Patients with diabetes mellitus (DM) were contacted by the study team and made aware of the role of carbohydrates change into blood sugar, has not been announced to citizens. In Europe and the presence of chronic kidney disease. However, there has been much debate whether levels (A1C) for patients with diabetes mellitus (DM) should be <7.0% irrespective of A1c may likewise induce ESA resistance. Factors unrelated to glycemic control need to be turnover that leads to lower A1c, it is also possible that existing factors predisposing to low ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.

TH-PO457

Glucose Level Impacts Cardiac Outcomes Incident Diabetic Patients Diabetics Undergoing Hemodialysis in Countries in which the Entity of

Methods: Patients with diabetes mellitus (DM) were contacted by the study team and made aware of the role of carbohydrates change into blood sugar, has not been announced to citizens. In Europe and the presence of chronic kidney disease. However, there has been much debate whether levels (A1C) for patients with diabetes mellitus (DM) should be <7.0% irrespective of A1c may likewise induce ESA resistance. Factors unrelated to glycemic control need to be turnover that leads to lower A1c, it is also possible that existing factors predisposing to low ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.

TH-PO457

Glucose Level Impacts Cardiac Outcomes Incident Diabetic Patients Diabetics Undergoing Hemodialysis in Countries in which the Entity of

Methods: Patients with diabetes mellitus (DM) were contacted by the study team and made aware of the role of carbohydrates change into blood sugar, has not been announced to citizens. In Europe and the presence of chronic kidney disease. However, there has been much debate whether levels (A1C) for patients with diabetes mellitus (DM) should be <7.0% irrespective of A1c may likewise induce ESA resistance. Factors unrelated to glycemic control need to be turnover that leads to lower A1c, it is also possible that existing factors predisposing to low ESA dose requirements. Although a high ESA dose may be accompanied by a high red cell turnover that leads to lower Alc, it is also possible that existing factors predisposing to low Alc may likewise induce ESA resistance. Factors unrelated to glycemic control need to be considered in interpreting Alc values in patients on dialysis.
Influence of Normal and Bifurcated Cephalic Arch Anatomy and Hemodynamics on Cephalic Arch Stenosis Onset

**Method:** Twelve subjects were referred for hemodialysis for permanent vascular access. Venograms, Doppler, and whole blood viscosity were obtained using computational fluid dynamic modeling (CFD). The resulting geometry changes in the cephalic arch are shown via CFD simulations, a postulated failure scenario for the BCF is as follows. Increased blood pressure in the vein is responsible for the acute arch angle decrease at 3 months after fistula creation. The resulting geometry changes in the cephalic arch are shown via CFD simulations to contribute to the non-physiological hemodynamics and clinical consequences only 3 months after fistula creation.

**Conclusion:** Based on the measured acute arch angle reductions and corresponding CFD simulations, a postulated failure scenario for the BCF is as follows. Increased blood pressure in the vein is responsible for the acute arch angle decrease at 3 months after fistula creation. The resulting geometry changes in the cephalic arch are shown via CFD simulations to contribute to the non-physiological hemodynamics and clinical consequences only 3 months after fistula creation.

**Funding:** NIDDK Support, Other NIH Support - This study was funded by RO1DK090769

**TH-PO463**

Small Artery Elasticity Index (SAE) Strongly Correlates with Arterial Micro-Calcification and Increased Arterial Media Thickness in Patients Undergoing Arteriovenous Fistula (AVF) Creation

**Background:** The high maturation failure rate of AVFs is a major unsolved problem, and preoperative methods of accurately predicting failure are urgently needed. We have previously shown that SAE correlates with AVF maturation failure, and have hypothesized that this failure is due to impaired dilatation of the inflow artery and outflow vein. In this study, we hypothesized that low SAE correlates with changes in arterial histopathology that indicate calcification and increased arterial media thickness.

**Methods:** Eighteen patients underwent measurement of SAE (ml/mmHg x100) preoperatively on the day of AVF creation. SAE was measured with the HDI/PulseWave CR-2000 System; arterial pulse pressure was measured as an indicator of arterial stiffness. Arterial samples were obtained at the arterial anastomosis during AVF creation. Arterial samples were obtained at the arteriovenous anastomosis during AVF creation.

**Results:** Three arteries were excluded from analysis due to processing problems. Multiple regression analysis in the remaining 15 patients indicates that the dependent variable SAE correlated with the independent variables micro-calcification score, arterial media thickness, and pulse pressure (all P < 0.02). The correlation of SAE with these 3 variables explained two-thirds of patient-to-patient variation in SAE (R² = 0.677). Pre-operative measurement of SAE appears to be a strong indicator of inflow artery calcification, media thickness, and stiffness in patients undergoing AVF creation. This result suggests that SAE may be a useful tool in planning AVF creation.

**Conclusion:** SAE is strongly correlated with arterial stiffening, media thickness, and calcification. These findings support our hypothesis that failure of BCF arises from altered hemodynamics in the CA after fistula creation.

**Funding:** RO1DK090769

**TH-PO464**

Thresholds for Significant Increase in Dialysis Venous Pressure (VP): Criteria That Help Decide Whether to Refer for Intervention

Eduard R. Fatakhov, 1 John Jason White, 1 Anatole Besarab, 2 William D. Paulson, 1

**Background:** Vascular access failure is a major cause of morbidity and mortality in hemodialysis. Access failure is usually caused by stenosis, which causes thrombosis and access abandonment. An increase in static VP is an important method of detecting stenosis so that it can be corrected before thrombosis. However, criteria for determining when an increase in VP is statistically significant have not been established.

**Methods:** Fifty-five patients who were dialyzed with synthetic grafts or arteriovenous fistulas had 9 static VP measurements within 2 wk. VP was adjusted for mean arterial pressure (VP/ MAP), Thirty-six differences between 2 VP/MAP measurements were computed from each patient’s 9 measurements. The standard deviation of all these differences was taken to indicate background variation in VP/MAP that was not influenced by increases in stiffness. After confirming VP’s were normally distributed, we used the student t distribution to determine thresholds for a significant increase in VP.

**Results:** The standard deviation for the difference between 2 VP/MAP measurements was 0.160. We computed thresholds for a significant increase in VP/MAP for a range of P values (figure). At P < 0.05, the increase must be >0.257 to be significant, whereas at P >0.20, the increase must be >0.14. If avoiding unnecessary procedures is a priority, then a low P value is optimal, whereas if detecting an increase in stiffness is a priority, then a larger P value is optimal.

**Conclusion:** SAE is strongly correlated with arterial stiffening, media thickness, and calcification. These findings support our hypothesis that failure of BCF arises from altered hemodynamics in the CA after fistula creation.

**Funding:** RO1DK090769
Management of Dysfunctional Vascular Access by Repeated Surgery or Angioplasty. Results on a Series of 264 Procedures at 24 Months

Paola De Rango, Basso Parente, Beatrice Fiorucci, Luca Farchioni, Gianbattista Parlani, Giuseppe Giordano. Vascular and Endovascular Surgery; Hospital S.M. Misericordia; Univ of Perugia, Perugia, Italy.

Background: Dysfunctional vascular access is a common problem that remains unsolved for patients with end stage renal disease (ESRD) requiring dialysis. Object of this study was to evaluate 24 months outcomes of angioplasty compared to repeated open surgery in patients with dysfunctional vascular access.

Methods: Consecutive dysfunctional vascular accesses repaired during 2006-2013 were reviewed. Endovascular repair was performed with angioplasty alone and selective stent. Repeated open surgery was performed with multiple techniques. Patients were followed for 24 months. Primary outcome was functional patency at 6, 12 and 24 months assessed by Kaplan Meier with log rank test. Secondary outcomes included complications, reinterventions and costs. Costs were derived from procedure hospital fees according to regional codes.

Results: A total of 264 dysfunctional vascular accesses (163 males; mean age 71.7y) were treated during the study period. 96 underwent angioplasty and 168 open reintervention. Kaplan Meier estimates of primary patency at 6, 12, and 24 months were 75.4%, 68.5% and 46.2% in the angioplasty group and 92.6%, 80.7% and 66.4% in the open group (P<0.0001). Access related complications occurred in 5.2% patients in the angioplasty group and 6.8% patients in the open group. A total of 82 reinterventions were required during follow-up ranging from 1 to 5 per patient; rates were 60% in the angioplasty group and 40% in the open group. Patients after angioplasty required a mean 0.6±1.1 and those after open surgery a mean 0.4±0.97 reinterventions after the first procedure. Mean costs per patient (including first procedure and additional reinterventions) ranged from €6000 to €7012.9 in the angioplasty group and from €7114 to €7200 in the open surgical group.

Conclusions: Angioplasty can be used as an alternative procedure for the maintenance of vascular access with 46.2% patency rate at 24 months. Costs may be contained when no routine stent is applied.

TH-PO467

Fistula Patency Rate after Venous Neointimal Hyperplasia Stripping / Fistula Reconstruction in Patients with Late Autologous Arteriovenous Fistula Stenosis Fangping Lu, Xiuen Li. Nephrology, First Hospital of Tsinghua Univ, Beijing, China; Nephrology, Peking Union Medical College Hospital, Beijing, China.

Background: Although autologous arteriovenous fistula (AVF) is still the best permanent hemodialysis access, but mature AVF can occur venous neointimal hyperplasia (VNH), which lead to venous stenosis with or without thrombosis, that is the primary cause of vascular access failure. Peri-anastomotic stenosis is the main place. At present treatment of VNH is very limited. We adopt a surgical method (stripping VNH and fistula reconstruction) to repair AVF. Here we report the effect of venous neointimal hyperplasia (VNH) stripping / fistula reconstruction on the patency rate in patients with late autologous arteriovenous fistula (AVF) stenosis.

Methods: We retrospectively collected clinical data of the hemodialysis patients receiving AVF operation in our hospital from January 2007 to December 2011. There were a total of 305 patients, including 76 cases of VNH stripping / fistula reconstruction (see Fig.). We observed the fistula patency rate at 3, 6, 12 months after operation, and compared with 128 non-VNH stripping / fistula reconstruction patients and 101 newly AVF patients during the same period.

Results: We found that VNH stripping / fistula reconstruction had a good fistula patency rate (93.4%, 89.5%, 84.2% at 3, 6, 12 month respectively).

Conclusions: VNH stripping / fistula reconstruction operation was an effective method to relieve late stenosis of AVF and improve utilization rate of fistula.

TH-PO468


Background: Native arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis. AVF Stenosis and/or accessory vein (AV) are the most common causes of early fistula failure. While treatment of stenosis is better defined, there are no clear criteria for obliteration of AV. The purpose of this study was to establish scientific criteria for the management of AV.

Methods: Various Computational Fluid Dynamics (CFD) simulations were performed to analyze blood flow in AVF. The flow was assumed to be incompressible, laminar, Newtonian and transient. 2D model geometries were constructed by ANSYS Design Modeler. The meshing of all AVF models was carried out in ICEM CFD mesh. A total of 305 patients, including 76 cases of VNH stripping / fistula reconstruction (see Fig.). We observed the fistula patency rate at 3, 6, 12 months after operation, and compared with 128 non-VNH stripping / fistula reconstruction patients and 101 newly AVF patients during the same period.

Results: We found that VNH stripping / fistula reconstruction had a good fistula patency rate (93.4%, 89.5%, 84.2% at 3, 6, 12 month respectively).

Conclusions: VNH stripping / fistula reconstruction operation was an effective method to relieve late stenosis of AVF and improve utilization rate of fistula.
Rapid Dilation of Porcine Peripheral Vein with Rotary Blood Pump System

Nicholas Franano,1 Howard M. Lorce,2 Mark R. Cunningham,3 Dale M. Groth,4 Lesley A. Szenay,1 Robert D. Ainsworth,4 Barrett S. Hutto,4 James Lee,4 Steve P. Woodard,3 Geoff D. Tansley.5

1Novita Therapeutics LLC, Olathe, KS; 2Flow Forward Medical Systems LLC, Los Gatos, CA; 3Surpass Inc., Osceola, WI; 4CIRTEC Medical Systems LLC, Los Gatos, CA; 5School of Engineering, Griffith Univ, Gold Coast, QLD, Australia.

Background: The arteriovenous fistula (AVF) is the preferred form of vascular access for hemodialysis. The Arteriovenous Fistula Eligibility (AFE) System™ is designed to dilate peripheral veins prior to AVF surgery by increasing vein wall shear stress (WSS) and stimulating vascular remodeling, thereby increasing AVF eligibility and improving AVF maturation.

Methods: The pre-clinical prototype device comprises a small extracorporeal centrifugal blood pump, cuffed and heparin-coated inflow and outflow conduits, and a benchtop power unit. In a 28 kg anticoagulated pig, the device was implanted in a left external jugular vein to left saphenous vein (SV) configuration and the SV was treated for 9 days with a WSS dose of 4 Pa.

Results: AV diameter was the major determinant of flow while location and angle were insignificant. AV of at least 60% diameter of the main AVF was significant. If 2 AV’s were present, effect was additive. AV presence caused wall shear stress disturbances, while early branching of AV was also important. This information was combined with known clinical facts to establish the criteria (Table 1).

Table 1: HAQ criteria for AV obliteration
1. 60% or greater diameter of the main AVF
2. 50% in diameter and divides into branches of same size.
3. 50% diameter and divides into branches of same size.
4. AV likely to interfere with cannulation on physical examination.

Conclusions: Our study provides the first standardized and objective criteria for AV obliteration. This needs to be validated and tested in randomized clinical trials.
TH-PO471
Arterial Micro-Calciﬁcation Is Associated with Coronary Artery Calcium Score in Hemodialysis Patients
Su Jin Choi, Young Soo Kim, Sunae Yoon, Young ok Kim, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Uijeongbu-City, Kyunggi-do, Korea.

Background: We have reported that arterial micro-calciﬁcation (AMC) of vascular access has a negative impact on access patency and cardiovascular mortality in hemodialysis (HD) patients. Reasons behind increased cardiovascular mortality in AMC are not fully understood. We therefore, hypothesized that aortic stiffness is a major contributing factor. We compared coronary artery calciﬁcation (CAC) is quite common in HD patients and it is known as predictor of future cardiovascular events and all cause mortality in HD patients. The aim of this study was to explore the relationship between AMC and CAC in HD patients.

Methods: Sixty-four HD patients who received vascular access operation were included in this study. The AMC was diagnosed by pathologic examination of arterial specimen by von Kossa stain, which was acquired during the vascular access surgery.

Results: The AMC was detected in 35 (41.7%) patients. There were no signiﬁcant differences between patients with and without AMC with respect to clinical characteristics except that AMC patients had diabetes compared with 16 (32.7%) of 49 patients without AMC (p=0.001).

Results: We assessed CAC, as low (<100), in 28 patients, and high (≥100), in 36 patients. We compared CACS, as low (<100), in 28 patients, and high (≥100), in 36 patients. We compared CACS between the patients with and without AMC.

Results: Mean age was 65.8 ± 12.5 years and the male gender was 37 (57.8%). The incidence of AMC was 62.5% (n=40). The mean CACS was 439.3 ± 91.1 (0-5674.3), and the median value was 128.4. Patients with the positive AMC group showed a higher CAC than those without AMC (77.5% vs 28.9%, p=0.000). By binary logistic regression, high CAC was independently associated with positive AMC (OR 8.894, 95% CI 1.174-46.154, p=0.008).

Conclusions: The present study suggests that AMC is closely associated with CAC in HD patients.

TH-PO472
Resistance to Erythropoiesis-Stimulating Agents May Be Associated with Arterial Micro-Calciﬁcation in Hemodialysis Patients
Su Jin Choi, Hyung Sung Won, Young Soo Kim, Sunae Yoon, Young ok Kim, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea.

Background: Vascular calciﬁcation, which is independent risk factor of cardiovascular mortality and anemia are very common in hemodialysis (HD) patients. Some uremic milieu such as inﬂammation, oxidative stress, and mineral bone disturbance may contribute to these conditions. The aim of this study was to evaluate the relationship between arterial micro-calciﬁcation (AMC) and erythropoiesis-stimulating agent (ESA) hypo-responsiveness in HD patients.

Methods: 84 patients received with ESAs for anemia without iron deﬁciency were evaluated. We assessed ESA hypo-responsiveness of patients using ESA hypo-responsiveness index (EHRI), deﬁned as the weekly ESA dose per kilogram of body weight divided by the hemoglobin level. The AMC was diagnosed by pathologic examination of arterial specimen by von Kossa stain, which was acquired during the vascular access surgery.

Methods: Results: AMC was detected in 35 (41.7%) patients. There were no signiﬁcant differences between patients with and without AMC with respect to clinical characteristics except that AMC patients had diabetes compared with 16 (32.7%) of 49 patients without AMC (p=0.001).

Results: The AMC was detected in 35 (41.7%) patients. There were no signiﬁcant differences between patients with and without AMC with respect to clinical characteristics except that AMC patients had diabetes compared with 16 (32.7%) of 49 patients without AMC (p=0.001).

Results: We assessed CAC, as low (<100), in 28 patients, and high (≥100), in 36 patients. We compared CACS, as low (<100), in 28 patients, and high (≥100), in 36 patients. We compared CACS between the patients with and without AMC.

Results: Mean age was 65.8 ± 12.5 years and the male gender was 37 (57.8%). The incidence of AMC was 62.5% (n=40). The mean CACS was 439.3 ± 91.1 (0-5674.3), and the median value was 128.4. Patients with the positive AMC group showed a higher CAC than those without AMC (77.5% vs 28.9%, p=0.000). By binary logistic regression, high CAC was independently associated with positive AMC (OR 8.894, 95% CI 1.174-46.154, p=0.008).

Conclusions: The present study suggests that AMC is closely associated with CAC in HD patients.

TH-PO473
Biocompatibility of Decellularized Bovine Artery and Expanded Polytetrafluorethylene Arteriovenous Grafs in a Sheep Model
Marcos Alexandre Vieira,1 João Gabriel Roderjan,2 Eduardo Discher Vieira,3 Francisco D.A. Costa,1 Miguel C. Riella.1 1Laboratory of the Center for Cardiovascular Grafs of Tissue Engineering and Cell Culture, Catholic Univ of Paraná, Brazil; 2Nephrology, Pró Rim Foundation, Brazil.

Background: Early dysfunction is a major problem in expanded polytetrafluorethylene arteriovenous grafts (ePTFE) grafts utilized for hemodialysis vascular access. The objective of this study was to evaluate the histological and functional results of decellularized heterogeneous grafts in a stable pig model.

Methods: TH-PO473 was implanted in 11 sheep between the carotid artery and the jugular vein and in 10 sheep with a internal thoracic bovine artery (DBA), representing the histologic findings of re-endothelialization, cell growth, migration, and tissue replacement. It is possible that improvement of the graft-graft interface could decrease the rate of thrombosis in the DBA graft. The larger internal graft diameter in the DBA group may be related to a mechanism of stenotensibility, similar to what occurs in an arteriovenous fistula. The results suggest a better biological behavior associated with DBA in a sheep model.

Funding: Private Foundation Support

TH-PO474
In Vivo Tissue Engineered Blood Vessel as Vascular Graft in a Porcine Model
Carolien Rothuijzen,1 Febrayni Damenik,2 Michel Visser,4 Tom Lavrijsen,1 ChunYu Wong,1 Martin Cox,1 Ton J. Rabelink,1 Lorenzo Moroni,2 Joris I. Rotmans.1

1Dept of Nephrology, Leiden Univ Medical Center, Netherlands; 2Dept of Tissue Regeneration, Univ Twente, Netherlands; 3Xeltis BV, Netherlands; 4Dept of Surgery, Leiden Univ Medical Center.

Background: ePTFE grafts are still commonly used as arteriovenous (AV) graft for hemodialysis vascular access, despite their risk of infection and thrombosis. Tailor made tissue-engineered blood vessels (TEBVs) that resemble a native vessel may be an alternative. We developed an autologous TEBV generated in the body itself and evaluated its efficacy as vascular graft in a porcine model. Our in vivo tissue engineering method utilizes the foreign body response directed to implanted synthetic material. Implantation of a cylindrical shaped polymer rod evokes an inflammatory response culminating in the encapsulation of the rod by a tube shaped ﬁbrous vascular tissue capsule. After excision of the rod and grafting the tissue capsule in the vasculature, it can further differentiate into an adequate vascular access conduit.

Methods: Per pig, 4 polymer rods were implanted subcutaneously. After 4 weeks, rods with tissue capsules formed around it were harvested and analysed by histology and mechanical tests. Per pig, 1 tissue capsule was implanted as AV-graft in the carotid artery and jugular vein for 4 weeks and analyzed on wall remodeling.

Results: Before grafting, tissue capsules were mainly composed of circumferentially aligned myoﬁbroblasts and few leucocytes. Extracellular matrix consisted mainly of glycosaminoglycans and circular aligned collagen. Tissue capsules exhibited burst pressures of 2000 mmHg and suture strengths of 3N, both exceeding the mechanical properties of native vessels. After 4 weeks of grafting, tissue capsule wall was remodelled, with a 2-fold increase in collagen and 4.3-fold increase in myoﬁbroblast content, while the leucocyte content was reduced to 1%.

Conclusions: Using an in vivo tissue engineering approach, a completely biological, autologous TEBV was created with sufﬁcient mechanical strength to enable AV-grafting. Currently we are evaluating patency of these TEBV as vascular graft.

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

TH-PO475
Novel Antithrombotic Fusion Protein to Inhibit Arteriovenous Graft Stenosis
Christi M. Terry,1 Huan Li,2 Ilya S. Zhuplatov,3 Tze-Chen Wun,4 Alfred K. Cheung.1 1Univ of UT, SLC, UT; 2EVAS Therapeutics, Ballwin, MO; 3VITALCS, SLC, UT.

Background: Coagulation generates activated platelets, thrombin, fibrin and mural thrombi that induce cell proliferation, migration, and matrix deposition that lead to neointimal hyperplasia (NH) and stenosis of arteriovenous grafts (AVG). Yet current antipatelectant and anticoagulant drugs, that yield systemic anti-coagulation, do not substantially prevent AVG stenosis when administered in clinically safe doses. A novel antithrombotic protein has been developed to locally inhibit thrombosis: A6L15 consists of an annexin V domain that targets the protein to thrombogenic cell membranes, fused to a Kunitz protease inhibitor domain that inhibits the tissue factor/VIIa complex. A6L15 has potential for safely inhibiting thrombus-induced NH formation and its administration safety was examined in a pig model of AVG stenosis.

Methods: Pigs received an i.v. bolus of A6L15 protein (300 μg). A segment of the carotid artery and the ipsilateral jugular vein were isolated by clamping and irrigated with 5, 20 or 100 μg/mL of A6L15 for 5 min. The lumen of a polytetrafluoroethylene graft was ﬁlled with A6L15 at the same concentration as the native vessels, then placed between the artery and vein segments. Control pigs had AVG placed but received systemic heparin (n=4) or no anticoagulants (n=1).

Results: No bleeding episodes were observed in any animal at any time during the 4-week follow-up. The AVG of the untreated pig clotted at the time of surgery, while the AVG of the 19 pigs treated with high-dose A6L15 clotted at 4 wks. ACT and aPTT at 4 wks were unchanged with either A6L15 or heparin, compared to pre-operative values. In contrast, PT was marginally prolonged after heparin treatment (10.8±0.5 s vs. 10.3±0.3 s; p=0.05) but not after the highest dose A6L15 treatment (11.0±0.5 vs. 10.6±0.4 s; p=0.22; n=9). Less ﬁbrin was noted around the AVG in the 6L15-treated pigs, compared to controls.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting/disclosure.
TH-PO476

Differences in Coagulation Protein Concentrations, Platelet Function, and Viscoelasticity among Clot-Forming, and Non-Clot-Forming Hemodialysis Patients with Arteriovenous Grafts

Background: Arteriovenous Graft thrombosis is a frequent cause of graft failure. We evaluated thrombogenic factors in 20 HD patients with AVGs. The goal was to determine whether significant differences in protein concentrations, platelet function and viscoelasticity factors exist among dialysis patients requiring frequent AVG clot procedures versus those who do not.

Methods: 20 HD patients were enrolled: 10 frequent clotters (>3 declots in the previous year) and 10 were non-clotters. Patients on anti-platelets or chronic anticoagulation were excluded. Coagulation protein concentrations including tissue factor (TF), tissue factor pathway inhibitor (TFPI), prothrombin fragment 1+2 (F1+2), von Willebrand’s factor (vWF), and fibrinogen were assayed. The time to clot onset was measured by Force Onset Time (FOT) and the Reaction time (R). K represents the time from clot initiation until final clot firmness. Platelet contractile force (PCF) measured the force produced by platelets during clot retraction, while clot rigidity was measured as clot elastic modulus (CEM). FOT, CEM and PCF were measured by Hemodyne; R and K were measured by TEG.

Results: There were no significant differences in coagulation protein concentrations and platelet function; however most viscoelasticity factors were statistically significantly different in clotters compared to non-clotters.

Conclusions: Our study suggests that HD patients with recurrent AVG thrombotic events form more rapid clots with higher tensile strength compared to HD patients without recurrent graft thrombosis. Identifying effective therapies in modulating these properties that confer higher tensile strength and viscoelasticity as observed among clot-formers may be worth investigating.

TH-PO477

Buttonhole versus Rope-Ladder Cannulation for Hemodialysis – A Systemic Review

Background: The buttonhole (BH) technique has commonly been a method of native arteriovenous (AV) fistula creation during an 18 month period, pre-operative ultrasound vessel measurements were compared with direct intra-operative measurements, and clinical outcomes recorded.

Results: In 141 patients (aged 18-85, 71.9% male), 146 fistulae were formed, comprising 18 radiocephalic, 111 brachiocephalic and 17 brachio-basilic.

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

211A
Pre-operative measurements were closely correlated with intra-operative findings for both arteries (R=0.44, p<0.001) and veins (R=0.35, p<0.001) but biased towards over-estimation for both.

Arterial assessment was reasonably reliable with arteries being within 0.5mm of expected size in 33.6%, and smaller than expected in 40.6%. For vein diameter the pre-operative measurement was less reliable, with veins being within 0.5mm of expected size in 31.6%, and smaller than expected in 57.1%. Gross over-estimation of vein size was common with 25.6% being more than 1.5mm smaller than expected.

The measurements taken intra-operatively appeared to be better predictors of outcome, with primary failure occurring in only 5.7% of cases with optimal vessels at surgery (both artery and vein over 2mm) versus 13.3% of cases where vessels were deemed optimal pre-operatively (p=0.10). If vessel measurements had been more accurately known up to this point, primary failure occurring in only 5.7% of cases with optimal vessels at surgery (both arteries (R=0.44, p<0.001) and veins (R=0.35, p<0.001) but biased towards over-estimation of vein size.

Conclusion: Pre-operative ultrasound provides reasonable prediction of vessel sizes prior to fistula surgery, but size over-estimation is common, particularly with veins. Measured intra-operatively, both artery and vein size are important predictors of outcome – further refinement of venous assessment could therefore improve access planning.

Funding: Clinical Revenue Support

TH-PO481
Haemodialysis Access: Patient Reasoning and Fistula Refusal
Dami Ashby, Lina Johansson, Neill D. Duncan, Jeremy Crane. Imperial College Kidney and Transplant Centre, Imperial College London, London, United Kingdom.

Background: Compared to other forms of access, arteriovenous fistulae are associated with improved outcomes in haemodialysis patients. Guidelines and incentives have been developed to increase fistula prevalence but some patients are reluctant to undergo fistula formation.

Methods: Patient reasoning, knowledge and influences were explored using questionnaires and brief structured interviews, in a group of prevalent haemodialysis patients declining fistula access.

Results: Fifty-eight patients (aged 34-87, 58% male) currently dialysing on a tunneled line were identified. All completed questionnaires and 16 patients went on to give structured interviews.

Most reasons for declining fistula formation were common to a number of patients, including pain during dialysis (cited by 71%), appearance (67%), pain at home (57%), permanence (24%) and fear of bleeding (21%). The risk of surgical failure was often cited (e.g. “my veins are really difficult”) but other individual-specific reasons were also often given (e.g. “I work in a prison”; “I wouldn’t be able to use cuticles”) which were considered by the patient to outweigh other considerations. All patients understood what a fistula is and were able to describe key features. Most patients reported being told that a fistula is a safer form of access, but in structured interviews, all patients clearly thought that this is not the case.

Other patients were more influential than professionals in decision making (cited by 87% and 26% respectively, p<0.001). Some patients expressed mistrust of professional advice (e.g. “it was told very one-sidedly”) often associated with perceived pressure (e.g. “they tried to convince me”; “because its more cost-effective”), and all patients felt strongly that access is a personal choice.

Conclusions: Patient-specific components to reasoning are not uncommon - many have individual and rational reasons which outweigh generic advice. Decision-making is more influenced by other patients than by professionals, with negative observations leaving a lasting impression. Better understanding of patient reasoning could improve concordance between patient and professional and facilitate informed choice.

Funding: Clinical Revenue Support

TH-PO482
Ultrasound-Guided Percutaneous Thrombolysis in Patients with Thrombosed Hemodialysis Grafts
Sara M. Vigano,1 Giuliana Loizzo,2 Giuseppe Bacchini,1 Francesco Locatelli,3 1Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy; 2Nephrology, Dialysis and Transplantation, Univ of Bari, Bari, Italy.

Background: The purpose of this study is to assess the safety and efficacy of the Arrow-Treterolata percutaneous thrombolysis device (PTD) using ultrasound-guided technique in the treatment of thrombosed vascular access grafts in dialysis patients and to evaluate the immediate and long term outcome in this cohort of patients.

Methods: Fifty-nine patients with graft occlusion underwent mechanical thrombolysis with PTD during 107 months. To maintain the patency during the procedure we used saline solution (0.9%) with 5000 U1 of Solide Heparin. All patients had large clot burden. Technical success, complications, primary and secondary patency rates were noted. Kaplan-Meier analyses were performed.

Results: The mean follow-up period was 29.2 months. Whereas patients with a graft vascular access are subjected to a regular Doppler follow-up, the technical success rate was 100%, while the clinical success rate was 91.7%.

Conclusions: Ultrasound-guided percutaneous mechanical thrombolysis with the Arrow-Treterolata device is a safety and less invasive method for the treatment of thrombosed grafts; it potentially allows to remove clots with minimal risk of wall damage requiring the administration of small amounts of thrombolytics.Moreover it is an out-patients procedure,that not imply patients’ hospitalization and it is performed in a sterile room. Furthermore patients are not exposed to radiation and to iodinated contrast agents. Thus this procedure could be a valid alternative to the surgical thrombectomy.

Funding: Clinical Revenue Support

TH-PO483
Uremia Induces a Proliferative Response through SERCA2a and Related Genes Dysregulation: A Novel Theory for Arterio-Venous Fistula Failure
Bertrand N. Mukete,1 Georges Khoury,1 Suchita J. Mehta,2 Lathauari Hadri,3 Jasvirver Singh,1 Jared M. Radbel,1 Chadi Suifi,1 Elie El-Charabaty,1 Frank M. Rosel,1 Marianne Smith,1 Roger Hajjar,2 Suzanne E. El Sayegh. 1Staten Island Univ Hosp, NY, 2Mount Sinai School of Medicine, NY.

Background: Sucedendoplastic reticular calcium ATPase-2a (SERCA2a) has been shown to be reduced in proliferating vascular smooth muscle cells while SERCA2b is upregulated. Arterio-venous fistula (AVF) closure is a major cause of morbidity in patients with end stage renal disease (ESRD). The molecular basis of AVF closure has not been fully elucidated and we hypothesize that the expression of SERCA2a and related genes are affected in subjects with ESRD.

Methods: In this case control study, we enrolled 18 patients, nine with ESRD going for AVF insertion and nine with normal renal function (NRF) going for coronary artery bypass surgery. Brachial and saphenous veins from ESRD and NRF patients respectively were isolated. Gene expression for SERCA2a, SERCA2b, phospholamban (PLN), endothelial nitric oxide synthase (eNOS) and CD31 were measured using real time quantitative polymerase chain reaction. Hematxol stain/cosin staining was used to analyze the integrity of the venous and immunohistochemistry (IHM) was used to visualize and quantify genes of interest. Two-tailed t-test was used to calculate the difference between means and 95% confidence interval (CI) between the two groups.

Results: The difference in mean and 95% CI for gene expression in NRF versus ESRD was +1.9 (0.74 to 3.1), p < 0.01 for SERCA2a, -1.3 (-2.5 to -0.16), p = 0.03 for SERCA2b, +1.3 (0.59 to 2.0), p < 0.01 for PLN, -4.4 (-9.6 to 0.83), p = 0.09 for eNOS and -1.1 (-3.8 to 1.5), p = 0.37 for CD31. Protein expression was confirmed using IFM.

Conclusions: SERCA2a was significantly decreased while SERCA2b was increased in the brachial vein of ESRD subjects when compared to corresponding genes in the saphenous veins of subjects with NRF. The level of eNOS expression was statistically unchanged in both groups. Our findings suggest a pro-proliferative response of ESRD based on SERCA2 expression, which may exacerbate or accelerate AVF shunt failure in ESRD subjects. Funding: Other U.S. Government Support

TH-PO484
Bone Morphogenetic Protein-7 (BMP-7) Inhibits Oxidative Stress-Induced Smooth Muscle Cells
Jasvinder Singh,1 Jared M. Radbel,1 Chadi Saifan,1 Elie El-Charabaty,1 Frank M. Rosel,1 Marianne Smith,1 Roger Hajjar,2 Suzanne E. El Sayegh. 1Staten Island Univ Hosp, NY, 2Mount Sinai School of Medicine, NY.

Background: Oxidative stress and activation of chemokines including MCP-1 are known to be downstream mechanisms responsible for the neointimal hyperplasia after creation of hemodialysis vascular access.

Methods: After stimulating the human umbilical vein endothelial cells with H2O2, cell viability, MCP-1 mRNA expression (by quantitative real-time PCR), MAPK activity and transcription factors activities of smooth muscle had been measured. Oxidative stress was analyzed by confocal microscopy using 2’-7’-dichlorofluorescein diacetate (DCF-DA) and by measuring 8-isoprostane in cell culture medium.

Results: Cell viability was over 90% when the cells were incubated with 0.5 mM of H2O2 for 4 hr. 0.5 mM H2O2 stimulated MCP-1 mRNA expression in a dose- and time-dependent manner. 1 mM H2O2 showed maximum inhibition of MCP-1 expression and viability. The significant expression of MAPK and transcription factors activity was observed. The gene expression for SERCA2a, SERCA2b, phospholamban (PLN), endothelial nitric oxide synthase (eNOS) and CD31 were measured using real time quantitative polymerase chain reaction. Hematxol stain/cosin staining was used to analyze the integrity of the venous and immunohistochemistry (IHM) was used to visualize and quantify genes of interest. Two-tailed t-test was used to calculate the difference between means and 95% confidence interval (CI) between the two groups.

Results: The difference in mean and 95% CI for gene expression in NRF versus ESRD was +1.9 (0.74 to 3.1), p < 0.01 for SERCA2a, -1.3 (-2.5 to -0.16), p = 0.03 for SERCA2b, +1.3 (0.59 to 2.0), p < 0.01 for PLN, -4.4 (-9.6 to 0.83), p = 0.09 for eNOS and -1.1 (-3.8 to 1.5), p = 0.37 for CD31. Protein expression was confirmed using IFM.

Conclusions: SERCA2a was significantly decreased while SERCA2b was increased in the brachial vein of ESRD subjects when compared to corresponding genes in the saphenous veins of subjects with NRF. The level of eNOS expression was statistically unchanged in both groups. Our findings suggest a pro-proliferative response of ESRD based on SERCA2 expression, which may exacerbate or accelerate AVF shunt failure in ESRD subjects. Funding: Other U.S. Government Support
dependent manner with a peak at 4 hr. H2O2 stimulated phosphorylation of p38 and JNK, and induced MCP-1 mRNA expression in a

dose-dependent manner. BMP-7 significantly inhibited H2O2-induced intracellular ROS production and 8-isoprostane levels in cell culture medium. BMP-7 significantly inhibited H2O2-induced phosphorylation of JNK, c-Jun and c-Fos, but did not inhibit H2O2-induced phosphorylation of p38 and p65.

Conclusions: These data suggest that oxidative stress directly stimulates MCP-1 expression in vascular endothelial cells and BMP-7 inhibits it through the anti-oxidant and inhibition of JNK-AP-1 pathway. This study provides a new insight into the potential of BMP-7 as an anti-oxidant to prevent neointimal hyperplasia in vascular access.

TH-PO487
Natural History of Venous Morphologic Changes in Dialysis Access Stenosis

Timmy C. Lee,1 Maheshika Sirimali Somarathna,1 Begofía Campos,2 Lois J. Arend,1 Pabir Roy-Chaudhury,1 1Dept of Internal Medicine, Univ of Cincinnati, Cincinnati, OH; 2Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL

Background: The natural history of arteriovenous fistula (AVF) non-maturation is likely influenced by vascular insults to the vein prior to and after AVF creation and involves different responses to vascular injury from uremia independently, and uremia in combination with hemodynamics. The objective of this study was to perform a morphometric analysis from vein specimens from subjects without chronic kidney disease (CKD), collected at time of new surgery, and from failing stenotic AVFs.

Methods: Vein samples from 11 non-kidney disease subjects from deceased donors, 29 CKD subjects at time of new access creation, and 20 subjects with stenotic AVF were collected and morphometric analysis performed.

Results: The mean values of average/intimal/media thickness and maximal intimal/media thickness were 0.61±0.38, 0.73±0.43, 0.53±0.40 for vein specimens from subjects without chronic kidney disease (CKD), collected at time of new surgery, and from failing stenotic AVFs.

Conclusions: Our results show significantly progressive increases in neointimal hyperplasia from non-CKD to stenotic vein specimens (see figure). These changes suggest that vascular injuries from uremia and hemodynamics may play a key role in these progressive vascular changes and natural history of vascular access dysfunction.

Funding: Clinical Revenue Support

TH-PO488

Clinicalpathologic Correlations of Explanted Fistulas and Synthetic Grafts
Laura Minhui Kim, Pooja Gupta, Rohan John, Jagdish Butany, Charmaine E. Lok. 1Toronto General Hospital, Toronto, Canada

Background: In hemodialysis patients, both fistulas (AVF) and grafts are associated with complications which may require their excision. In contrast, kidney transplanted patients may have arteriovenous accesses that are no longer required and may be excised if they become problematic. We aimed to describe the histopathologic changes associated with excised fistulas and grafts to determine if there is any association with their clinical reason for removal.

Methods: All explanted AVF and grafts were collected from 2001-2012 from the Surgical Pathology database of Toronto General Hospital, and detailed histopathologic evaluation performed. Differences in pathologic findings versus access type were compared by Chi-Square (SAS, v9.2).

Results: Among 110 explanted specimens, there were 64 AVF and 46 grafts. Patients with AVF were on average 47 years old with 69% males; and those with grafts were 59 years old with 39% males. Patients with grafts were more likely to be hypertensive and have coronary artery disease. Glomerulonephritis was the most common cause of ESRD in both. Successful transplant with problematic (e.g. aneurysmal or symptomatic) access was the most common reason for fistula removal whereas aneurysm and infection were the most likely reasons for grafts. There was significantly more adventitial chronic inflammation (p<0.0001), medial acute inflammation (p=0.01), medial chronic inflammation (p=0.03) and intimal acute inflammation (p=0.004) in explanted grafts compared to fistulas. The media of synthetic grafts was also more prone to calcification (<0.0001). Neointimal proliferation was commonly seen in both fistulas and synthetic grafts (95% and 93% of specimens in each group).

Conclusions: Histopathologically, synthetic grafts were more commonly inflamed, likely corresponding to infection as a more common reason for graft removal compared to AVF. Significant vessel inflammation existed in AVF that would have otherwise been functional if not for transplantation, indicating that inflammation itself cannot be a sole pathologic criteria distinguishing between infection and other causes of inflammation. Gram staining and developing a classification system may be helpful in this regard.

Funding: Clinical Revenue Support

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

Underline represents presenting author/disclosure.

213A
TH-PO489

Effect of Arteriovenous Hemodialysis Shunt Location on Cardiac Events in Patients Having Coronary Artery Bypass Graft Using an Internal Thoracic Artery

Leonid Feldman, 1 Shai Effrati, 1 Ilia Beberashvili, 2 Zhan Averbukh, 1

Background: The possibility of developing coronary steal in patients having coronary artery bypass graft (CABG) using internal thoracic artery (ITA) and ipsilateral extremity arteriovenous (AV) hemodialysis shunt has been reported. The impact of this phenomenon on clinical outcomes is uncertain. The aim of this study was to investigate an association between the AV dialysis shunt location regarding the side of the ITA/CABG and clinical outcomes.

Methods: This is a retrospective cohort study based on data recorded in the patient files. Inclusion criteria were defined as ages between 18 and 85, availability of clinical data and presence of a patent upper extremity AV shunt (native fistula or synthetic graft) as a vascular access to dialysis. Patients with a catheter or with lower extremity AV shunt as dialysis access and patients having CABG without using an ITA were excluded from the study. The eligible patients were divided into 2 groups: those with ipsilateral and those with contralateral location of ITA/CABG and AV shunt. The outcomes were: death from any cause, cardiac death and a first cardiac event.

Results: In a group of 112 chronic hemodialysis patients having CABG, 32 had an ipsilateral and 25 had a contralateral location of ITA/CABG and an upper extremity AV shunt. Mean follow-up period was 39.0±24.7 months. Significantly more cardiac events occurred in the group with an ipsilateral compared to a contralateral location of coronary ITA/CABGs and dialysis AV shunts (hazard ratio, 2.16 [95% CI, 1.11 to 4.19], p=0.023). There was no difference between the groups in all cause mortality risk (hazard ratio, 1.005 [95% CI, 0.43 to 2.37], p=0.990) and in the risk of cardiac death (hazard ratio, 2.43 [95% CI, 0.64 to 9.17], p=0.191).

Conclusions: The ipsilateral location of a CABG with the use of ITA and upper extremity AV dialysis shunt may be associated with increased risk of cardiac events. Placing an upper extremity AV hemodialysis shunt in patient with functioning ITA/CABG would be better performed on a contralateral side.

TH-PO490

Influence of Hemodialysis on the Cerebrovascular Supply – Role of Arteriovenous Fistula (Pilot Study)

Ivan Rychlik, 1 Tomas Zahradnicek, 1 Tomas Peisker, 2

Background: Part of patients on maintenance hemodialysis (HD) therapy complains of neurological symptoms like vertigo, headache, during HD. No data are available concerning influence of blood flow of the arteriovenous fistula (AVF) on vertebrobasilar (VB) vascular supply. We tested whether blood flow AVF flow rate had negative impact on cerebrovascular supply in VB arteries during HD session.

Methods: Pts were defined as stable on HD >1y, with native brachio- or radiocephalic AVF, normotensive, normovolemic according to Fresenius Body Composition Monitor. Using dopplersonography (dUSG), following parameters were measured: i) peak-systolic velocity (PSV), end-diastolic velocity (EDV), calculated mean flow velocity (MFV) before and during HD session in vertebrobasilar segments, ii) blood flow. Furthermore, AVF blood flow was measured by Fresenius blood temperature monitor (BTM). We compared the blood flow in VB supply before and during HD session in connection with AVF blood flow.

Results: In mean (mean±SD) age 75y (53-71), 112% (40%) females, 25% (diabetics, 50% CHD) were included. During follow-up period, re-vascularization was performed in 124 patients (59.3%). Graft use, oral anticoagulant administration, higher ESA/Hb, and lower ABI were associated with patency rates. Based on the median value of ESA/Hb, all the patients were divided into 2 groups: the High and Low ESA/Hb group. Kaplan-Meier analysis showed High ESA/Hb was significantly associated with VA failure event (p=0.0146).

Cox regression analysis revealed that not only AV graft (hazard ratio 2.267, p=0.0013) but also High ESA/Hb (hazard ratio 1.773, p=0.0303) were related to VA failure event. Meier analysis showed High ESA/Hb was significantly more with VB clinical symptoms was disclosed in 3 pts (37%) and dUSG vascular pathology (50% stenosis or occlusion) on VB arteries was proven in 2 of them. The influence of inappropriate hyperviscosity, intradialytic hypotension, ion-dysbalances, etc., during dialysis sessions were excluded.

Conclusions: According to our results, cerebral hyperfusion due to the pre-existing vascular pathology on VB arteries seems to be impacted by hemodynamic effect of AVF blood flow. A dUSG-screening of during-dialy sis-six-symptomatic pts could be useful to prevent cerebral ischemic impairment.

(30 supported by P VERY 34)

TH-PO491

Frequent Pre-Dialysis Nephrology Care and Later Dialysis Initiation Are Associated with Arteriovenous Access Use at Dialysis Start: A DOPPS Study

Bryan Becker, 1 Yun Li, 2 Ronald L. Pisoni, 3 Christi Priya Dhayalanand, 2 Christian Combe, 4 Joel Port, 5 David C. Mendelsohn, 6 Hidemi Kawanishi, 6 Friedrich K. Port, 7, 8 Panduranga R. Rao, 3 Bruce M. Robinson, 1, 7, *Arbor Research, 3, 7, 8, Michigan; 2, 8, Chulalongkorn University, 7, 8, Ho Chi Minh City, Vietnam; 3, 8, University of Toronto, 7, 8, University of British Columbia, 7, 8, King Faisal Specialist Hospital & Research Center, 7, 8, University of Toronto, 7, 8, University of British Columbia, 7, 8, University of Toronto, 7, 8, University of British Columbia, 7, 8, University of Toronto, 7, 8, University of British Columbia, 7, 8, University of Toronto, 7, 8, University of British Columbia, 7, 8, University of Toronto, 7, 8, University of British Columbia.

Background: Patients on dialysis receive care at different sites and times, and the use of AV access is variable. This study sought to determine the association between pre-dialysis nephrology care and dialysis initiation. Specifically, it was hypothesized that AV access use at study entry would be associated with more frequent pre-dialysis care and later dialysis start.

Methods: Data were from phase 4 of the DOPPS (Dialysis Outcomes and Practice Patterns Study, 2009-2011). Among patients on dialysis <120 days at enrollment and with data on eGFR at dialysis start and frequency of pre-dialysis care (n=853), logistic regression was used to estimate odds of an AV access at dialysis start, accounting for facility clustering and listed covariates. AV access at DOPPS enrollment was used when access at dialysis start was missing.

Results: 28% of US patients used an AV access at HD start, compared to 51% in Europe and 87% in Japan. In the adjusted model, patients who saw a nephrologist more often in the year before dialysis were more likely to have an AV access (Table). Patients with a lower eGFR at start of dialysis were also more likely to have an AV access.

Conclusions: AV access use at start of dialysis is much lower in US than Europe or Japan. Emphasis on frequent pre-dialysis nephrology care and avoiding unnecessary early dialysis starts in order to an AV access before starting dialysis may improve outcomes during the dialysis transition period.

Funding: Pharmaceutical Company Support - The DOPPS is supported by research grants from Amgen (founding sponsor, since 1996), Kyowa Hakko Kirin (since 1999, in Japan), AbVie (since 2009), Sanofi (since 2009), Baxter Healthcare (since 2011), and Vifor Fresenius Medical Care Renal Pharma (since 2012), with additional country-specific support provided in Canada by Amgen-Canada, Janssen, BHC Medical, Takeda and Kidney Foundation of Canada, and in Germany by Hexal and WiNe Institute. Support from the DOPPS sponsors is provided without restrictions on publications.

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

Underline represents presenting author/disclosure.

214A
TH-PO492

Local Anesthesia in Arteriovenous Fistula Placement: Patient Perception of Pain and Early Patency Outcomes

Erick R. Mishler, Amanda M. Valliant, Alexander S. Yevzlin. 1 Arizona Kidney Disease and Hypertension Centers, Phoenix, AZ; 2Univ of Wisconsin Hospitals and Clinics, Madison, WI.

Background: US end stage renal disease (ESRD) vascular access outcomes, though improving, continue to lag behind those of Europe. As a result of this persistent trend, US Nephrologists have recently started to create arteriovenous (AV) access. This retrospective study examined patient perceptions representing for AV placement and development of several aspects of fistula creation using monitored anesthesia care (MAC) rather than brachial plexus nerve blockade, including adequacy of analgesia and early post-operative access patency as well as intraoperative complications.

Methods: Patients undergoing AV fistula placement using only MAC from September 2011 to January 2012 were surveyed post-operatively and asked to rate their intraprocedural pain on a scale of 0 to 10 from that in the preceding 2 weeks on study. In patients who received study drug, no supplemental iron was needed by subgroups of 40 (77%) in the SFP group and of 31 (60%) in the placebo group (p=0.09). At EoT, the prescribed ESA dose was reduced from baseline by 5% in the SFP subgroup and increased by 33% in the placebo subgroup, a difference of 38% (p=0.008). In the SFP subgroup, reticulocyte hemoglobin (CHR) remained stable, but declined in the placebo subgroup by a mean of 1.61 pg (p=0.008) at EoT.

Conclusions: SFP, delivered via dialyse, requires 35% less ESA and 48% less IV iron than the placebo group, while maintaining hemoglobin concentrations. SFP reduced ESA requirements by 38% among patients who did not require IV iron, while maintaining availability for erythropoiesis, as evaluated by Chr. SFP is a promising means of providing iron to CKD-HD patients.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

TH-PO495

Initial Change of Iron Metabolic Flux prior to Differentiation of Erythroid Progenitors after Epoetin Beta Pegol (C.E.R.A.) Treatment


Background: Epoetin beta pegol (C.E.R.A.) is a novel long-acting erythropoiesis stimulating agent. C.E.R.A. has been reported to promote mobilization of iron storage tissue by the accelerated maturation of immature erythroblast which has ability to absorb Fe (1.1-2.1). For emergency department care, the HR was 1.5 (1.1-1.9); among HD patients without same-day IV iron exposure, the HR was 3.6 (1.9-6.9). For all-cause hospitalization, the HR was 1.4 (1.1-1.9); among HD patients without same-day IV iron exposure, the HR was 3.3 (1.9-5.7).

Conclusions: These results indicate that erythropoietic activity is essential for suppression of hepcidin after C.E.R.A. treatment. Suppression of serum hepcidin levels and transient decrease in serum iron levels in early phase after C.E.R.A. treatment, prior to differentiation of erythroid progenitors suggest that sensing initial change of iron metabolic flux leads to suppression of hepcidin after C.E.R.A. treatment. It is possible that this flux occurs by the accelerated maturation of immature erythroblast which has ability to absorb iron after C.E.R.A. treatment, but further investigation is needed.

TH-PO496

Relative Safety of Peginesatide versus Epoetin Alfa

Eric D. Weinhandl,1 David T. Gilbertson,2 Robert N. Foley,12 Allan J. Collins.1,2 USRDs Coordinating Center, MMRF, Minneapolis, MN; 3Univ of Minnesota, Minneapolis, MN.

Background: Omontys (peginesatide) was recalled in February 2013, after reports of serious hypersensitivity reactions and deaths. We used Medicare Quarterly Standard Analytical Files (QSAs) to compare adverse event rates in patients who received a first dose of peginesatide (PEG) between July 1 and November 30, 2012, and matched controls who received a dose of epoetin alfa (EPO) during the same era.

Methods: PEG and EPO exposure were ascertained from outpatient facility claims. Patients with recent exposure to ferumoxytol or iron dextran or residing in states without PEG use during the study era were excluded. For each PEG user, we identified 2 matched controls with identical dialysis provider affiliation, dialytic modality, and same-day IV iron exposure; and similar propensity score (PS) of PEG initiation. The PS was a function of comorbidity, specific disease (CVD), all-cause hospitalization, and emergency department care.

Results: We identified 8,693 PEG users (number of composite events, 29) and 17,386 matched controls (21). The hazard ratio (HR) of the composite event for PEG versus EPO was 2.8 (95% confidence interval, 1.6-4.8), among hemodialysis (HD) patients without same-day IV iron exposure, the HR was 3.6 (1.9-6.9). For all-cause hospitalization, the HR was 1.4 (1.1-1.9); among HD patients without same-day IV iron exposure, the HR was 1.5 (1.2-1.7). For emergency department care, the HR was 1.1 (0.9-1.4); among HD patients without same-day IV iron exposure, the HR was 1.3 (1.0-1.7).

Conclusions: Relative to traditional dialysate fluid iron exposure to peginesatide was associated with increased risk of death or hospitalization due to cardiovascular disease; increased risk persisted in patients without concurrent intravenous iron use. These data illustrate the potential utility of Medicare QSAs for timely pharmacovigilance.

Funding: NIDDK Support

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

Underline represents presenting author/disclosure.
A Randomized Controlled Trial of Costs Associated with Anemia Therapy in Hemodialysis Patients Treated with Intravenous Darboepoetin alfa versus Intravenous Epoetin alfa

Andrea L. Woodland,1 Sean W. Murphy,2 Brendan J. Barrett,3 Bryant M. Curtis,4 Pharmacy Dept, Eastern Health, St. John’s, Canada; 4Dept of Medicine, Memorial Univ, St. John’s, Canada.

Background: Anemia of Chronic Kidney Disease is associated with adverse outcomes and a reduced quality of life. Erythropoiesis stimulating agents (ESAs) have improved anemia management and two agents are available in Canada, epoetin alfa (EPO) and darboepoetin alfa (DA). EPO and DA are considered to be equally effective in achieving target hemoglobin in dialysis patients but it is not clear if there is a cost difference. There have been few head-to-head comparisons of the two; most published data is from observational switch studies.

Methods: An open label randomized controlled trial of intravenous (IV) DA versus EPO was conducted in 50 hemodialysis patients. A dose stabilization run-in phase was followed by a 12 month active phase. ESAs and iron were dosed using an algorithm to maintain hemoglobin(Hb) within 100-120g/L. The primary outcome was ESA cost (Canadian $) per patient over 12 months. Secondary outcomes included deviation from target ranges in anemia indices, iron dose and cost, time and number of dose changes required for dose stabilization, number of dose changes in the active phase and the dose conversion ratio.

Results: The median cost over 12 months was $4179 (IQR $2416-5955) for EPO and $2303 (IQR $1178-4219) for DA with a difference of $1876 (p=0.017). The median weekly iron dose was 40.4mg for EPO and 41.7mg for DA (p=0.992). There were no significant differences in Hb: 108.0g/L EPO and 109.8g/L DA (p=0.336); serum ferritin: 848μg/L EPO and 720μg/L DA (p=0.202); TSAT: 26.7% EPO and 26.8% DA (p=0.472). The number of dose changes and the time to hemoglobin stability were similar for both groups. The dose conversion ratio was 280.1:95% CI 197-362:1 at the end of the run-in phase, 360:95% CI 262-457:1 at the 3 month point of the active phase and 382:1 (95% CI 235-529:1) at the 6 month point of the active phase.

Conclusions: In this study of hemodialysis patients with comparable anemia management IV darboepoetin cost $1876 less per year per patient than IV epoetin.

Optimal Hemoglobin Target Might Be Different between Elderly Hemodialysis Patients and Non-Elderly Patients

Norio Hanafusa,1,4 Takanoji Nomura,2 Takeshi Hasegawa,3,4 Masaomi Nangaku.1,4

Background: Elderly population is growing in their numbers among hemodialysis population. However, there is no evidence about the relationship between hemoglobin (Hb) level and survival by age. We investigated the effect of age on the relationship between Hb and survival in Japan DOPPS (JDDOPS) cohort.

Methods: We included the entire JDDOPS phase 3 and 4 population in the study. The population was divided at the age of 70 years old to make the elderly and the non-elderly population. We used Cox’s proportional hazard model to investigate survival with Hb values incorporated as time dependent variable. Interaction between Hb and age was investigated. Inverse propensity treatment weight (IPTW) method was used to adjust propensity for erythropoietin use.

Results: The study population included 3,359 patients with 568 deaths during median follow up of 2.66 years. Interaction between age groups and Hb values was significant (p<0.001). Non-elderly population experienced poorer survival for Hb <9g/dl compared to elderly population (HR 4.90: 95% CI 3.46 – 6.95 vs HR 1.79: 95% CI 1.30 – 2.38, p=0.001 for interaction; with Hb >9 –10g/dl made as reference group) Hb values between 9 and 10 g/dl among non-elderly population and Hb ≥ 12 g/dl among elderly population were both related to poorer survival after IPTW adjustment (HR 1.37: 95% CI 1.06 – 1.77; HR 1.40: 95%CI 1.04 – 1.88, respectively), although the interaction did not reach its significance (p=0.09, 0.364).

Conclusions: Older population might be tolerant for lower Hb values, while higher Hb levels might relate to poorer prognosis among the population. Therefore, optimal Hb ranges might be different for the elderly population compared to the non-elderly population. These results render evidences to the detailed consideration about anemia management by patients’ characteristics and about its individualization.

Is Heparin-25 Production Increased in Patients with Chronic Kidney Disease?

Adam Rumjon, Iain C. Macdougall. Dept of Renal Medicine, King’s College Hospital, London, United Kingdom.

Background: Heparin-25 (hep-25) plays a critical role in iron metabolism, and the levels of this peptide are greatly increased in end-stage renal disease. It remains unclear whether this is due to reduced clearance, or increased production. The aim of this study was to explore hep-25 production in vivo in haemodialysis patients.

Methods: Inclusion criteria for this study were: HD for >3 months, Hb >10 g/dl, CRP <20 mg/L, HD via an AV/PTFE graft, stable IV iron/EPO dose for >1 month, and no hospitalisations for >1 month. A pre-dialysis blood sample (10ml) was separated by Ficoll Hypaque centrifugation. Serum hep-25 levels were measured using liquid chromatography mass spectrometry. Peripheral blood mononuclear cells (PBMCs) were processed immediately (5-6 x10⁶ cells/ml), qRT-PCR was performed using the Applied Biosystems 7900HT Fast Real-Time system. Amplification reactions were performed (triplicate) using Taqman HAMP and GAPDH primers.

Results: To date, 7 patients (5 males, 2 females) have been studied. Median IV iron dose was 100mg/week, and median EPO dose was 46.2 [IQR 18.9-114.6] μg/kg/wk. Serum hep-25 levels were significantly elevated in the HD population (14.9±2.7 vs 4.9±0.8, p<0.021). Interestingly, HAMP mRNA levels were significantly lower than in healthy controls (mean fold-change 0.667±0.06 in HD compared to controls (p=0.026)).

Conclusions: Despite higher circulating levels of hep-25, significantly lower transcription of HAMP mRNA was unexpectedly observed in HD patients. This counter-intuitive result, which has not been described previously, requires confirmation in a larger cohort of patients. Elucidation of this effect is also required; it is possible that negative feedback mechanisms may be in operation in HD patients to reduce hep-25 levels.
Results: Compared with Hb levels in normal rats, levels in Nx rats gradually and significantly decreased as kidney disease progressed. In contrast, C.E.R.A. significantly inhibited the decrease in HD levels (Hb: Nx, 12.5±0.5 g/dL; C.E.R.A., 14.7±0.6 [p<0.05]). Normal, 15.6±0.3; n=7–9), and increased Ret numbers to around normal range. Whereas iron availability was lowered in Nx rats regarding the significant elevation of plasma Hep-25 and ferritin levels as CKD progressed, C.E.R.A. treatment improved these parameters to within normal range (Hep-25: Nx, 17.1±1.9 ng/ml; C.E.R.A., 9.8±1.6 [p<0.05]). Normal, 9.0±1.5; Ferritin: Nx, 609.8±118.8 ng/mL; C.E.R.A., 322.3±140.1 [p<0.05]. Normal, 298.7±74.3) with improving CKD-associated anemia. There was no significant change in plasma IL-6 levels among these groups.

Conclusions: C.E.R.A. protected against gradually decreasing Hb levels in anemia model rats possibly by correcting iron availability in addition to erythropoiesis as reported.

TH-PO502
Anemia Management Trends in Hospital-Based Dialysis Centers: 2010-2013
George N. Cortisidis,1 Anjali Acharya,1 Chun-Lan Chang,2 Jerrold W. Hill,2 Gregory A. Maglinte,3 Anjali B. Saxena,1 Mark Stephens,2 Richard A. Lafayette.1
'NYC Hospital Corp; 2IMS Health; 3Amenix; 4Stanford; 5PHA.

Background: In response to changes in the prescribing information of erythropoietin stimulating agents (ESAs) and dialysis reimbursement, anemia management practices in dialysis have changed in the past three years. Hospital-based dialysis centers (HBDCs) differ from free-standing dialysis centers and may warrant special analysis. This study describes trends and regional variation in anemia management practices in HBDCs from January 2010 to March 2013.

Methods: Electronic medical records of 5404 hemodialysis patients in 50 US-based HBDCs were analyzed retrospectively. Patients were at least 18 years old and had at least one hemoglobin (Hb) measurement and one ESA dose between January 2010 and March 2013. Descriptive statistics were collected monthly for Hb and iron biomarkers (serum ferritin and transferrin saturation), and every 4 weeks for darbepoetin alfa, epoetin alfa and IV iron doses.

Results: Mean/standard deviation) monthly Hb declined from 11.4(1.2) to 10.7(1.2) g/dL, the percent of patients with mean monthly Hb <10 g/dL rose from 11.3% to 24.4%, and the percent of patients with mean monthly Hb >12 g/dL declined from 30.1% to 11.2%. Most patients received darbepoetin alfa. The darbepoetin alfa median (interquartile range) cumulative 4-week dose declined 41% from 170(100,340) to 100(50,200) mcg, and the cumulative median 4-week IV iron dose increased 50% from 250 to 375 mg. Regional differences were observed in ESA and iron dosing levels, while average Hb differed only slightly by region. Mean darbepoetin alfa doses were 5% lower while IV iron doses were 51% higher in HBDCs in the South and West than in the Northeast/Midwest.

Conclusions: Consistent with reported national trends, HBDCs have modified anemia management practices since 2010, with continuing declines in ESA doses, higher doses of IV iron and falling Hb. The relatively small variation in regional ESA utilization, but relatively large variation in IV iron doses, did not have an observable impact on the Hb level achieved, which may be due to demographic differences or other factors not observed in this study.

Funding: Pharmaceutical Company Support - Amgen Inc.

TH-PO503
Correlation of Plasma Ascorbic Acid Level with Erythropoietin Resistance
William D. Siroweit,1 Yuguang Liu,2 Swomya Bal,3 Krystal Hunter,4 Amanda Logan,1 Lawrence S. Weisberg,1 Garry J. Handelman.1
1Cooper Medical School of Rowan Univ; 2Univ of Massachusetts.

Background: In end stage renal disease (ESRD), one cause of erythropoietin (EPO) resistance is functional iron deficiency. Iron stores are normal, but erythropoiesis is less effective due to decreased iron delivery to the bone marrow. Ascorbic acid (AA) may improve iron availability. The relation of plasma AA level with EPO resistance in a contemporary, prevalent hemodialysis (HD) population is not known. We hypothesize that plasma AA level correlates inversely with EPO resistance.

Methods: Prevalent HD patients in 2011 were recruited for enrollment. Inclusion criteria were age >18 years and vintage ≥3 months. Plasma samples collected in the outpatient setting were preserved with metaphosphoric acid and placed on dry ice or stored at -80° F until assayed for AA by HPLC. Hematologic data on a subset of 179 HD patients with ferritin >100 ng/ml was obtained. Individual EPO dose was calculated as mean weekly dose over a 3-month period. Pearson correlation was used to assess the relationship between plasma AA level and EPO resistance (units/week/Hb), transferrin saturation (TSAT%), and ferritin.

Results: Over the entire plasma AA range (1.78-409.3 μM), AA did not correlate with EPO resistance. However, in 148 patients with plasma AA levels in the physiologic range (0-100 μM), plasma AA inversely correlated with EPO resistance (r= -0.21, p= 0.01), directly correlated with TSAT (r= 0.162, p= 0.05), and did not correlate with ferritin.

Conclusions: AA at physiologic plasma levels is associated with less EPO resistance and increased TSAT. In patients with low plasma AA levels, supplemental AA may treat functional iron deficiency and EPO resistance by increasing iron availability. These results support proceeding with a randomized controlled trial.

Funding: Private Foundation Support

TH-PO504
Implementation of Anemia Protocol and Changes in Quality of Life for Chronic Hemodialysis Patients
Eduardo K. Lacson, Nien-Chen Li, Cindy Allegretti, Norma J. Osthusn, Franklin W. Maddux, Jeffrey L. Hymes. Fresenius Medical Care, North America, Waltham, MA.

Background: A national Medical Advisory Board endorsed anemia management protocol for hemodialysis (HD) patients, consistent with the FDA black box warning on erythropoietin (ESA) use, was incrementally adopted at FMCNA beginning April 2011. We evaluated the impact on Kidney Disease Quality of Life-36 (KDQOL) scores from the first 50 participating facilities.

Methods: All 11,307 HD chronic patients with paired KDQOL scores (PCS, MCS, Symptom Problems, Burden, and Effects domains) up to 12 months before and within 3-15 months after protocol implementation were evaluated. The last available hemoglobin (Hgb) and ESA dose/treatment prior to the KDQOL surveys were recorded. Subgroups with large changes in hemoglobin (drop of >1 g/dL) and ESA dose/treatment (drop of >5,000 units) were also evaluated.

Results: The cohort: mean age 61.4 ±14.2 years; 54.6% male; 54.4% white (42.2% black) and 53.3% diabetics. The median time from KDQOL to initiating the anemia protocol was 3.3 months (range <1 to 11.9), and from then to the 2nd KDQOL was 9 months (range 3.0 to 14.9, last survey: 4/26/13). Mean scores for PCS (37.7 to 37.6) and Symptoms (79.4 to 79.6) were unchanged while MCS (51.0 to 51.2), Burden (53.3 to 54.6), and Effects (73.9 to 74.9) increased (p<0.05). Mean/median Hgb pre-baseline KDQOL were both 11.2 g/dL and pre-2nd KDQOL was both 11.2 g/dL (p<0.001). Patients with >1 g/dL drop in Hgb (N=2497, 28.8%, fit-up mean Hgb 10.3) had a drop in PCS (-0.7), Symptoms (-0.7), and increase in Burden (+1.3), a >5,000 units decline in ESA dose (N=1934, 22.1%) increased PCS (+0.45), Burden (+1.7), and Effects (+1.9) with all p<0.05. The clinical relevance of these statistically significant score changes is unknown.

Conclusions: Implementation of an anemia protocol that was consistent with FDA guidelines significantly decreased our HD patients’ mean Hgb and ESA dose over 3-15 months. Overall, there was no decline in KDQOL scores in the same patients treated using the protocol over time.

Funding: None

TH-PO505
Predicting Hemoglobin Response to Erythropoietin, Effect of Dose and Hemoglobin Concentration
Michael E. Brier, Jenny Feng, Adam E. Gaweda.
Univ of Louisville.

Background: Several factors moderate the response to exogenous erythropoietin (EPO) in hemodialysis dependent end-stage renal failure patients. The determination of starting doses and dosage adjustment schedules were based on data obtained when subjects exhibited a different dose response curve than they do currently. We performed a linear mixed model regression analysis of hemoglobin (Hb) response in individual patients for the years 2004 to 2012 to test the hypothesis that Hb response is a function of the change in 4 months of prior EPO, current Hb, and current EPO dose.

Methods: The data consisted of 5580 EPO and Hb combinations from 153 patients. We calculated the mean weekly EPO dose per month, the change in EPO dose from the prior month, change in Hb from the prior month, and the target Hb for the year in which the data were collected. Hb target ranged from about 12.5 in 2004 to 10.5 in 2012 and was estimated as the mean achieved Hb for all Hb measurements for the year. We divided EPO dose into 5 groups < 3000, 3001-6000, 6001-9000, 9001-15,000, and > 15,000. The independent variable was the change in Hb and we investigated the following factors: Dose, difference in current Hb from target, past 3 months change in Hb, past 4 months change in EPO, and current Hb.

Results: The results of the statistical analysis are shown in the following table which represent the change in Hb concentration in response to a increase in dose of 1,000 units.
Hb Dose (1/1000) 0-3,000 3,001 to 6,000 6,001 to 9,000 9,001 to 15,000 15,001 to

The current change in Hb is influenced by up to 4 months of past EPO doses, the prior 3-5 days in Hb over the last 3 months, current Hb, Dose, and difference between the current Hb and the target Hb.

Conclusions: In the range of observed Hb concentrations (10.5 to 12.5 g/dL), the response to a change in EPO dose demonstrates a negative relationship as Hb increases, the response decreases. Also, as dose increases response is decreased by as much 70%. One must take into account up to 4 months prior EPO and Hb in order to predict the response to a EPO dose change.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO506
Therapeutic Effects of Renal Anemia Treated with Two Different Erythropoiesis Stimulating Agents: Darbepoetin Alpha and Continuous Erythropoietin Receptor Activator in Predialysis Patients with Chronic Renal Failure. Takashi Yokoyama.

Methods: 36 predialysis patients were observed for six months. They were divided into two groups according to Erythropoiesis Stimulating Agents (ESAs): Group A (n=19, aged 75 ± 4.74 years old) was treated with DA and Group B (n=17, 68.41 ± 12.75 years old) with C.E.R.A. Peracutaneous administration of DA (10–180 µ) or C.E.R.A. (75–250 µ) at 21–35 day intervals was performed in order to maintain the target hemoglobin (Hb) level between 10.0 and 13.0 g/dL. The weekly average values of Hb, FRN, high sensitive C-reactive protein (hsCRP), albumin (Alb) and estimated GFR (eGFR) were compared at the same intervals and the serial changes of these clinical markers in both groups were observed.

Results: 1) At the baseline, no marked differences were observed between the two groups according to Hb (A: 9.28±1.17 g/dL vs B: 8.37±0.50), eGFR (17.16±7.66 mL/min/1.73m2 vs 17.50±10.30), Alb (3.79±0.52 g/dL vs 3.64±0.61) and hsCR (0.16±0.37 mg/dL vs 0.13±0.17). 2) Hb levels from the second day measured to the sixth day measured in the two groups were as follows : second day (A: 9.97±1.05 g/dL vs B: 9.64±0.53), third (10.36±1.20 vs 10.27±0.86), fourth (10.16±1.36 vs 10.79±1.28), fifth (10.15±1.34 vs 10.46±1.34) and sixth (10.39±1.13 vs 10.13±0.85). No marked differences were found between the two groups during the six months. Administration volumes of ESAS for the two groups were as follows: baseline (A: 68.3±33.3 µg vs B: 141.2±19.6), third month (82.0±50.1 vs 152.9±27.8), six month (104.0±35.8 vs 171.4±56.7). The average rate between DA and C.E.R.A. over the six months was 1.74. 3) No marked differences were detected in FRN, hsCRP, Alb and eGFR during this period.

Conclusions: The evidences of smaller amounts of administration volume at 21–35 day intervals and equal therapeutic effects of renal anemia demonstrate DA's superiority to C.E.R.A. in predialysis treatment of anemia.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

TH-PO507
Hemoglobin Variability of Japanese Hemodialysis Patients with Long Acting Erythropoiesis Stimulating Agent Treatment. Yasuhiro Ito.

Methods: 591 HD patients were enrolled. ESA therapy switched from epoetin beta (EPO) to C.E.R.A., and they were followed up for 6 months. According to Hb levels during this period, patients were classified into 6 category groups reported by Ebben; constant target (T, Hb levels of every month within target), constant high (H, Hb levels constantly over target), constant low (L, Hb levels constantly under target), high amplitude (HA, Hb levels over, under and within target), low amplitude high (LAH, Hb levels over and within target), and low amplitude low (LAL, Hb levels under and within target). We checked patients’ hospitalizations and deaths for next 6 months, and examined the influence of every category for these events. We compared these data with our previous data under EPO treatment.

Results: Mean Hb level before usage of C.E.R.A. was 10.9±0.85 g/dL. Hb levels of every month showed from 10.6±0.92 g/dL to 11.0±0.92 g/dL during 6 months. Rates of every Hb category under C.E.R.A. treatment were 17% (T), 0% (H), 1% (L), 17% (HA), 20% (LAH) and 45% (LAL), and those under epoetin beta treatment were 14.9% (T), 1.1% (H), 5.6% (L), 16.5% (HA), 14.1% (LAH) and 47.9% (LAL). Hospitalization rate were 4.4% (T), 22.2% (L), 14.9% (HA), 11.4% (LAH) and 9.0% (LAL). Hb variability and its effects for prognosis were similar with C.E.R.A. and EPO.

Conclusions: C.E.R.A. was useful for renal anemia treatment of Japanese patients. Hb variability of C.E.R.A. and its effect for prognosis was similar with that of EPO.
Effect of Reduced CoQ10 on Anti-Oxidative Status in Hemodialysis Patients

Shigeru Owada,1 Teruhiko Maeba,1 Aki Hirayama,2 Atsushi Ueda,3 Sohji Nagase,4* 1Diabetes Center, Asao Clinic, Kawasaki, Kanagawa, Japan; 2Center for Integrative Medicine, Tsukuba Univ of Technology, Tsukuba, Ibaraki, Japan; 3Nephrology, Tsukuba Univ Hospital Hitachi Medical Education and Research Center, Hitachi, Ibaraki, Japan; 4Internal Medicine, Nagase Clinic, Moriya, Ibaraki, Japan.

Background: Reduced CoQ10 (CoQH) has a principal role of mitochondrial function and is an antioxidant properties. Serum CoQH level is lower in dialysis patients. Then we investigated the effects of CoQH supplementation on antioxidative capacities in hemodialysis patients (HD).

Methods: 200mg of CoQH (day was administered by orally to 30 HD patients (67±8 years) for 3 months after written consent obtained. 1. Serum CoQH concentration, 2. soluble lectin-like oxidized low-density lipoprotein receptor-1 (s-LOX-1) and LOX-1 ligand containing Apo B (LAB) were measured and calculate LOX-index (s-LOX-1 x LAB) as a predictive marker for CVD (Clinical Chemistry, 2010, 56:350). 3. Ratio of triglyceride content and negative charge value of LDL (LDL-CMF), 4. hydroxyl radical scavenging activity (OHSA) were measured.

Results: Each parameter of 3 months after taking CoQH were as follows: 1. Total and reduced CoQ10 (µg/ml) levels were significantly increased (CoQ10; 0.61±0.19 to 3.36±1.70, CoQH; 0.57±0.18 to 3.20±1.43). 2. LOX-index was significantly decreased (3225±2010 to 2190±1488). 3. Tg ratio in LDL was not different (0.33±0.07 to 0.31±0.07), but LDL-CMF was significantly decreased (2.8±1.5 to 1.1±0.4). 4. Serum OHSA (mM GSH equivalent) was significantly increased (7.5±1.5 to 8.4±1.7).

Conclusions: We investigated the relationship between LOX-index and lipoprotein profile and effects of CoQH on the anti-oxidative activities expression in HD patients. Before supplementation of CoQH, serum total CoQ10 and CoQH levels were significantly lower compared to normal subjects and these were increased after supplementation. LOX-index and LDL-CMF were decreased and OHSA was increased. These results suggest that oxidative stress in HD patients was improved by CoQH supplementation.

Mechanisms Linking Atherosclerosis and End-Stage Renal Disease: Alterations in Lymphocyte Activation Molecules in Dialysis Patients with Atherosclerosis

Miguel Hueso,1 Mariona Mestres,2 Estanis Navarro,2 Juan Torras,1 Inés Rama,1 Alberto M. Martinez-Castelao,1 Jose M. Grino,3 Nephrology, Hospital Bellvitge, L’Hospitalet, Barcelona, Spain; 3Immunology, Hospital Bellvitge, L’Hospitalet, Barcelona, Spain; 3Laboratori d’Oncologia Molecular, IDIBELL, L’Hospitalet, Barcelona, Spain.

Background: The mechanisms linking Chronic Kidney Disease (CKD) and atherosclerosis (ATS) are not well known. T lymphocytes display a key role in ATS and L-selectin is important in lymphocyte-endothelial cell interaction. Thus, the aim of this study is to investigate if patients on dialysis with atherosclerosis displayed alterations in the expression of L-selectin or of other lymphocyte activation molecules.

Methods: Study of cases (dialysis patient with ATS) and controls (dialysis patient without ATS) based in dialysis patients waiting for their first kidney transplantation. Atherosclerosis was diagnosed by angiography or arteriography. Whole blood samples were obtained before dialysis and were co-stained with the following mAbs: anti-CD26 (L-selectin), anti-CD44F(ab’), anti-CD59, anti-HLADR and anti-CD34F(ab’), with lymphocytes markers CD3F(ab’), CD4F(ab’), CD59F(ab’), prior to be studied by citometry.

Results: 64 dialysis patients (26 with ATS and 38 without ATS) were studied. Patients with ATS displayed a higher proportion of CD44 lymphocytes (801±360 cells/mm³ in patients without ATS vs 1073±548 cells/mm³ in ATS; p=0.032), CD59F(ab’’) (323±172 cells/mm³ in patients without ATS vs 455±254 cells/mm³ in ATS; p=0.026), CD25F(ab’’) (339±196 cells/mm³ in patients without ATS vs 603±336 cells/mm³ in ATS; p=0.008), CD3F(ab’)25 HLADR (33±18 cell/mm³ in patients without ATS vs 48±33 cell/mm³ in ATS; p=0.035), CD3F(ab’)25 HLADR (9±10 cell/mm³ in patients with ATS vs 24±16 cell/mm³ in ATS; p=0.030) and less Mean Fluorescence Intensity (MFI) of L-selectin expressed by lymphocytes (T18±73 in patients without ATS vs 84±39 in ATS; p=0.027).

Conclusions: Dialysis patients with ATS displayed a down-regulation of L-selectin and HLADR activation of lymphocytes in ATS. These results suggest the presence of a chronic inflammatory background that is lacking in dialysis patients not suffering ATS.

Funding: Government Support - Non-U.S.
**Methods:** Blood samples were from controls, HD and CKD. Plasma and monocytes were studied ex vivo or after culture with normal and uremic serum in the presence of M-CSF and dexamethasone. Ga6s, Axl and Mer were evaluated by real-time PCR, ELISA and FACs.

**Results:** Monocytes from HD had decreased gene expression of Mer and Axl and increased expression of TNF-α and IL-1β. Mer expression was significantly decreased in circulating CD14+CD16+ monocytes from HD, a specific subset linked to adverse vascular events. Significantly increased levels of soluble receptors Axl and Mer were found in CKD and HD plasma, consistent with ongoing monocyte/macrophage activation. Furthermore, Ga6s levels, known to be increased in systemic inflammation, were significantly elevated in CKD and HD and associated with increased sMer and sAxl levels. Addition of uremic sera to monocytes cultured with M-CSF and dexamethasone, suppressed the expression of Mer, CD163 and CD206, receptors associated with M2 polarization.

**Conclusions:** TAM receptors have known immunoregulatory function and decrease proinflammatory cytokine secretion. We showed increased TAM ligand and circulating soluble TAM receptor in the plasma and decreased TAM receptor expression on monocytes from HD and CKD patients. These data support the hypothesis that there is a deficiency of TAM receptor mediated regulation of inflammation in patients with chronic renal failure.

**Funding:** Private Foundation Support

**TH-PO515**

**Modifications of Levels of 1, 25(OH)D Vitamin due to Administration of a Single, Large Oral Dose of 25-Hydroxycholecalcif erol in Hemodialysis Patients**

*Jose Luis Merino,1 Jose Luis Teruel,2 Milagros Fernandez-Lucas,2 Blanca Bueno,2 Juan Jose Villafruela,3 Antonio Gomis,2 Vicente Paraiso,1 Carlos Quereda1*

**Background:** Low levels of Vitamin D have been associated with increased cardiovascular risk, and mortality. The deficiency is common in patients with chronic kidney disease and dialysis. We have evaluated the modifications of serum levels of Vitamin D and mineral metabolism markers after the administration of a high single dose, oral dose of 25-OH-Cholecalciferol (3 mg, Hidroforte®). Methods: Chronic hemodialysis patients with 25(OH)D < 30ng/ml were included. A higher level of 1,25(OH)2D has been observed due to an isolated dose of 3 mg of 25-OH-Cholecalciferol (3 mg, Hidroforte®). Results: Only two cases showed serum calcium > 10.5 mg/dl. There were no differences between both groups neither in phosphorous level nor in number of samples with serum phosphorous > 5.5 mg/dl. Conclusions: A higher levels of 1,25(OH)VitD were observed in the treated group and was maintained for 16 weeks. The levels of 1,25 and 25(OH)D were even bigger in the treated group than in the controlled one. This fact was associated with a significant decrease in both TH levels and the 8 post-treatment. We found no differences between both groups neither in phosphorous level nor in number of samples with serum phosphorous > 5.5 mg/dl. A higher level of 1,25(OH)VitD was observed due to an isolated dose of 3 mg of 25-OH-Cholecalciferol, this dose keeps enough levels of 25(OH)VitD with a CV mortality or hospitalization and all-cause mortality. The relationships between TSAT events/100 patient-years, P < 0.001) and all-cause mortality rates (5.38 vs. 2.31 events/100 (OR, 2.04), and troponin-T protein

**TH-PO516**

**The Impact of Transferrin Saturation on the Clinical Outcome in Incident Dialysis Patients**

*Hyung Mo Koo,1 Fa Mee Doh,1 Hye-Young Kang,2 Hyung Jung Oh,3 Shin-Wook Kang.4 1Dept of Internal Medicine, Yonsei Unive College of Medicine; 2Severance Biomedical Science Institute, Brain Korea 21, 3Yonsei Univ, Seoul, Korea.*

**Background:** Transferrin saturation (TSAT) is a marker reflecting the availability of iron for erythropoiesis and is closely associated with hemoglobin (Hb) levels. Although anemia is an independent risk factor for cardiovascular (CV) events and mortality in patients with end-stage renal disease (ESRD), the impact of TSAT on the clinical outcome has never been elucidated in dialysis patients.

**Methods:** A total of 879 anemic incident dialysis patients were recruited from 36 dialysis centers of the Clinical Research Center for ESRD in Korea and were divided into 3 groups according to baseline TSAT of ≤20%, 20-40%, and >40%. Cox regression analysis was performed to determine the independent prognostic values of TSAT for a composite of CV mortality or hospitalization and all-cause mortality. The relationships between TSAT and echocardiographic findings and inflammatory/cardiac biomarkers were also evaluated using logistic regression analysis.

**Results:** There were no differences in Hb levels and the proportion of patients on erythropoiesis-stimulating agents or iron supplements between the 3 groups. During a mean follow-up duration of 19.3 mo, 51 (5.8%) patients died. CV composite (11.71 vs. 5.55 events/100 patient-years, P < 0.001) and all-cause mortality rates (5.38 vs. 2.31 events/100 patient-years, P = 0.004) were significantly higher in patients with TSAT ≤20% compared to those with TSA≥20% (reference). TSAT ≤20% and >20% were both significantly associated with increased risk for death. **Conclusion:** TSAT ≤20% was an independent predictor of CV death and B lymphopenia is associated with higher risk of death. The incidence of infection and CVD hospitalization was 24% and 14%, respectively. Both cases, B lymphopenia was linked with higher risk of hospitalization (CVD and infection causes. These findings suggest quantitative immunological change could be new markers of morbidity and mortality in HD patients.

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

**Underline represents presenting author/disclosure."
Cinacalcet Treatment Decreases Serum Free Testosterone Concentration in Male Hemodialysed Patients with Chronic Kidney Disease and Secondary Hyperparathyroidism

Andrzej Wieczek, Piotr Kuczerka, Marcin Adamczak. Dept of Nephrology, Endocrinology and Metabolic Diseases, Medical Univ of Silesia, Katowice, Poland.

Background: Calcium Receptor is expressed, among others in testis. Cinacalcet is used in the treatment of secondary hyperparathyroidism (sHPT) in hemodialysed patients with chronic kidney disease (HDP). In most of male HDP, serum free testosterone concentrations are low. The aim of this study was to assess the influence of six-month treatment with cinacalcet on the serum free testosterone concentration.

Methods: In 40 male HDP with sHPT (PTH>300 pg/ml), enrolled in this prospective, open-label, single arm study, plasma PTH and serum free testosterone concentrations were measured before the first dose of cinacalcet and then after 3 and 6 months of treatment. Wilcoxon matched pairs test and Spearman test were performed. Results are shown as means with 95% confidence interval.

Results: In the 35 patients who completed the study cinacalcet treatment caused significant decrease of serum PTH from 1109 pg/ml (805-1407 pg/ml) at the baseline, to 781 pg/ml (475-1086 pg/ml) after 3 months of treatment (p=0.002), and to 605 pg/ml (298-912 pg/ml; p<0.0001) after 6 months of treatment and also led to decrease of serum free testosterone concentration from 6.99 pg/ml (5.61-8.30 pg/ml) to 5.87 pg/ml (4.99-6.95 pg/ml; p<0.003) and to 5.94 pg/ml (4.95-6.95 pg/ml; p=0.03), respectively. There were no significant correlation between changes of serum free testosterone concentration and changes of plasma PTH concentration and cinacalcet dose, respectively.

Conclusions: Treatment with cinacalcet decreases serum free testosterone concentration in male HDP with sHPT. 2. Such a decrease is not related to the changes of plasma PTH concentration.

Funding: Government Support - Non-U.S.

TH-PO523

Gastrointestinal Microbiota and Inflammation in Dialysis Patients

Teena Cherian, Madhumathi Rao. Medicine/Nephrology, Tufts Medical Center, Boston, MA.

Background: Alterations in gastrointestinal (GI) microbiota could potentially mediate inflammation in dialysis patients. We examined the relationship between GI microbiota, markers of bacterial translocation and immune activation among hemodialysis (HD), and peritoneal dialysis (PD) patients and healthy controls (HC).

Methods: Blood and stool samples were collected from 22 HD and 13 PD patients and 9 age-matched HC. Recent antibiotic use, dialysis catheter, GI pathology or surgery were excluded. Stool microbiota was studied by pyrosequencing the 16S rRNA genes. Serum concentrations of Interleukin-6 (IL-6), C-reactive protein (CRP), soluble CD14 and LPS binding protein were measured; bacterial translocation from the GI tract was measured using quantitative PCR of the 16S rDNA genes in spent dialysate and plasma.

Results: Table 1 compares clinical and laboratory parameters among HD, PD and CRP, IL-6, sCD14 and LPS binding protein concentrations were significantly higher among dialysis patients. Profiles of GI microbiota showed differences in diversity and equitability indices and the numbers of operational taxonomic units in dialysis patients and in the Firmicutes and Bacteroidetes phyla compared to healthy controls. Finally spent dialysate tested positive for LPS in 6 of 22 HD patients suggesting bacterial translocation during dialysis.

Conclusions: Dialysis patients show measurable alterations in GI microbiota in the setting of elevated immune activation markers. This could predispose to colonization by pathogens, impair barrier function and immune response in GI epithelium.
**TH-PO524**

The Relation between Serum Hepcidin-25 (HPC) Level and Other Iron Metabolism Markers during Intravenous Iron Administration in Hemodialysis (HD) Patients

Noriko Saito,1 Shigeru Miyazaki,2 Kazuhide Saito,1 Hiroki Takimoto,1 Masakazu Shimotani,2 Yutaka Tsutaba,4 Kozo Ikarakashi,1 Tetsuo Miyamoto,1 Mika Matsumoto,2 Hiroshi Tanaka,3 Tetsu Kato,4 Takayasu Ohtake,4 Shuzo Kobayashi,2

Background: Hepcidin is a crucial player of iron metabolism. Iron-overload and inflammation stimulate hepatic production, whereas anemia, iron depletion inhibit hepatic production. It is not elucidated that the sequential changes of the relation between HPC level and other iron parameters during intravenous iron administration in HD patients.

Methods: 21 HD patients with low serum ferritin level (23±16 ng/ml) were administered saccharated ferric oxide (Fe 40mg) intravenously for 11 consecutive HD sessions. We evaluated the following markers at 0 to 16 weeks after starting the therapy: HPC, GDF15, soluble transferrin receptor (sTfR) and standard hematological parameters including high sensitive CRP (hs-CRP). Serum HPC level was determined by L-MS/MS. GDF 15 and sTfR levels were measured by ELISA. Serum samples of normal volunteers (N) were served as controls.

Results: HD patients with low serum ferritin level showed lower Fe(μg/ml) and HPC(ng/ml), higher GDF15(ng/ml), sTfR(μmol/ml) and hs-CRP(μg/ml) than N (43±8 vs 45.8±5.2, 5.9±9.4 vs 4 vs 11.1±1.9* , 7.4±1.2 vs 6.0±2.3*, 30.8±11.7 vs 16.3±5.6*, 1454±2100 vs 237±290**, respectively). HPC level was increased at 4W(30.9±13.3) and then decreased to 0W at 10W(5.9±3.3). HB (g/dl) increased from 8.8±1:1 at 0W to 10.9±1.0 ** at 10W. In stepwise multiple regression analyses, UIBC and Fe were independently associated with HPC before the therapy, and at 4W, ferritin, GDF15 and hs-CRP were significant variables influencing HPC level which were the same as seen in N. At 6W and thereafter, ferritin was the only significant predictor of HPC. *P<0.05, **P<0.01.

Conclusions: Predictors of HPC level were quite different before and after intravenous iron administration. HPC level were significantly influenced by ferritin concentration after iron administration therapy in HD patients.

**TH-PO525**

Plasma Pentraxin-3 Levels Are Associated with Risk of Nutritional Status in Hemodialysis Patients

Tetsuo Miyamoto,1 Mika Matsumoto,2 Hiroshi Tanaka,3 Tetsu Kato,4 Takayasu Ohtake,4 Shuzo Kobayashi,2

Background: Pentraxin-3 (PTX3) is a pattern recognition receptor which modulates immunoinflammatory biomarkers which are closely and specifically linked to nutritional status. Inflammation stimulate HPC production, whereas anemia, iron depletion inhibit HPC production. The purpose of this study was to evaluate the predictive value of PTX3 in nutritional status of patients with hemodialysis patients. We investigated the factors of for undergoing stable hemodialysis by examining the relationship of nutritional intake and changes of body nutritional status of patients with hemodialysis patients.

Methods: Transferring analysis was performed to assess the role of nutritional risk (NR) as predictor of mortality and cardiovascular morbidity in HD. NR was evaluated using the NRS2002 screening method (Clin Nutr 2003, 22:321-336). The study population (n=12) was divided according to NR score into 4 categories: 0 (normal nutritional status), 1 (mild), 2 (moderate) and 3 (severe) impairment. Clinical and biochemical parameters, CRP and the variability in the low frequency range of systolic blood pressure (LF SBP) and of interbeat intervals (LF IBI) rate, representative of autonomic function, were also analyzed in all patients. Primary (death) and secondary (fatal and non-fatal cardiovascular events) outcome were recorded during a follow-up period of 60 months (range 0-96W).

Results: Plasma albumin, LSF SBP and LFI IBI progressively decreased from NR1 to NR3, while CRP increased in NR2 and NR3. Kaplan-Meier analysis of primary outcome (3 y mortality) showed gradually decreasing survival rates for patients with increasing NR score from NR1 to NR3 (p=0.004, 0.001 and 0.001). Cox regression analysis with age, clinical and biochemical data, CRP and autonomic markers in the model identified NR score and age as powerful predictors of all cause mortality. The probability of the secondary outcome was markedly increased in NR2 and NR3 as compared to NR0 and NR1. Ischemic heart disease and intradialytic hemodynamic instability were significant predictors of cardiovascular events (p=0.015 and 0.001).

Conclusions: In HD, even mild nutritional impairment is associated with autonomic dysfunction and increased mortality. Moderate and severe nutritional impairment are associated with both increased cardiac and cardiovascular markers, especially in patients with cardiac disease. Malnutrition in concert with autonomic dysfunction and inflammation are associated with increased mortality and morbidity in elderly HD patients.

**TH-PO527**

The Longitudinal Change of Corrected Mid-Arm Muscle Area Predicts Mortality in Hemodialysis Patients

Sumi Hidaka,1 Kunihiro Ishioka,2 Hidekazu Moriya,1 Takayasu Ohtake,2 Shuzo Kobayashi,2 Department of Nephrology, Immunology and Vascular Medicine, Shonan Kamakura General Hospital, Kamakura, Japan.

Background: Protein-energy wasting is associated with increased morbidity and mortality in maintenance hemodialysis (HD) patients. Therefore, nutritional status needs to be regularly assessed to detect malnutrition earlier. The aim of this study was to investigate the predictive value of anthropometric parameters on mortality.

Methods: This study included a cohort of 52 maintenance HD patients (36 men, mean age 63.3±4.2 years). Anthropometric measurements were made in 2001, 2003, and 2005 and patients were followed up until 2012. Anthropometric measurements included body mass index (BMI), mid-arm circumference (MAC), triceps skinfold (TSF), mid-arm muscle circumference (MAMC) and corrected mid-arm muscle area (cMAMA). We investigated the predictors for all-cause death using Kaplan-Meier analysis and Cox proportional hazards analysis.

Results: During the mean follow-up of 117.8 months, 27 patients died. The deceased group had a significantly higher age at the enrolment in the study (p=0.001), but there was no significant difference in HD duration between the surviving and the deceased groups. Basal serum albumin level in deceased group was lower and serum β2-microglobulin level was higher than those in the surviving group (p=0.012 and p=0.042, respectively). Basal BMI, AC, and cMAMA did not differ significantly between the two groups, but the 4-year changes (△) of each value were significantly increased in the surviving group. Kaplan-Meier analysis revealed that the patients with decreased △cMAMA (N=15) had a significantly lower survival rate compared with those with increased △cMAMA (N=37, p=0.003). Multivariate Cox proportional hazards analyses demonstrated that the △cMAMA was a significant predictor of all-cause mortality after adjustments for confounding factors, such as age, serum albumin, serum β2-microglobulin, and △BMI. An increase in △cMAMA of 1 cm² reduced mortality by 6.9%.

Conclusions: These results demonstrate that the decrease in △cMAMA is a significant predictor for mortality in HD patients. The interventions to increase △cMAMA are well worth trials.

**TH-PO528**

Relationship of Nutritional Intake and Body Composition for Undergoing Stable Hemodialysis

Yukie Kitajima,1 Taeko Takahashi,3 Yuzuru Sato,2 Tokyo Healthcare Univ, Tokyo, Japan; 3Sato Junkunkai Hospital, Matsuyama, Japan.

Background: It is important to maintain activities of daily living (ADL) in elderly dialysis patients. Further, cardiovascular disease (CVD) is a major cause of morbidity and mortality. Assessment of body composition is necessary for evaluating the nutritional status of patients with hemodialysis patients. We investigated the factors of for undergoing stable hemodialysis by examining the relationship of nutritional intake and changes of body composition, especially grip strength for six years in hemodialysis patients.

Methods: The studied cases were 40 stable out-patients who were undergoing hemodialysis between 2007 and 2013. Grip strength measurement was measured before dialysis. Body composition was measured after completion of dialysis on the last day of the week. Patients were divided into two groups according to rate of grip strength; those

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
with rate of change (decrease) of grip strength ≥ 15% (Group A) and with < 15% (Group B). The method of evaluating for nutritional intakingse the meal recording method.

Results: Average decrease in grip strength of hemodialysis patients was lower than average value of a healthy person (60.5%), their grip strength was significantly reduced for six years (<17.0%). Grip strength correlated with lean body mass (r=0.552, p<0.002). In nutritional intake, their energy intake (p<0.05) were significantly higher, protein catabolic rate (PCR) did not change and fat free mass (FFM) and fat mass (FM) increased significantly (p<0.01) in Group B. In comparison, N, fat and total protein intake (p<0.01) were significantly higher, % grip strength (46.8%, p<0.001) and Alb (3.5mg/dL, p<0.002) of Group A were significantly lower than % grip strength (73.2%) and Alb (3.9mg/dL) of Group B. Group A was hospitalized with CVD and fracture (p<0.01) than Group B.

Conclusions: For six years, the more rate of decrease of grip strength is large, the more patient’s malnutrition and amount of muscles decreases, hospitalization including CVD and fracture increase. However, it is necessary for hemodialysis patients to maintain energy intake and activity for stable survival and ADL. Therefore, to prevent the decrease in muscle mass, to intake enough energy is important factor for undergoing stable hemodialysis.

Funding: Government Support - Non-U.S.

TH-P0529
The Effects of Parenteral Amino Acid Therapy on Protein Carbamylation in End Stage Kidney Disease: Sahrin Kalam,1 Anders H. Berg,2 Caitlin A. Trotter,3 Hector Tamez,1 Julia Beth Wenger,1 Joseph James Deferio,4 S. Ananth Karumanchi,5 Ravi I. Thadhani.1
1Nephrology Div, Massachusetts General Hospital, Boston, MA; 2Div of Clinical Chemistry, Beth Israel Deaconess Medical Center, Boston, MA; 3Nephrology Div and Center for Vascular Biology Research, Beth Israel Deaconess Medical Center, Boston, MA.

Background: Carbamylation is a spontaneous chemical modification of proteins and amino acids by reactive cyanate, a byproduct of urea. Protein carbamylation is associated with complications if targeted to reducing protein carbamylation.

Methods: To determine the effects of increasing amino acid concentrations in vitro and in animals can attenuate baseline and 6 weeks were compared.

Results: 125cc infusions and 3 subjects receiving 250cc infusions; 18 infusions total per subject).

Respective percent changes in C-Alb at the end of the 6 week study period were: -23.6%, -17.0% +12.9%, -4.8%, and -4.6%. Notably, the only subject 9.0, 7.8, 5.1, 6.2, and 8.0. Respective percent changes in C-Alb, mmol C-Alb/mol albumin) for the 5 subjects were

Conclusions: The increase in energy after the lectures presented reinforces the need for intervention programs in sectors of hemodialysis as a prevention of clinical complications and consequent improvement in quality of life.

Funding: Private Foundation Support

TH-P0530
Effects of Branched-Chain Amino Acid on Elderly Dialysis Patients Suffering from Malnutrition: Taeko Takahashi,1 Yuzuru Sato,1 Yuki Kitajima,2 Ayako Naka,1 Yoshiko Miyazaki.1
1Grupo CHR; 2Universidade Estadual de Campinas, Campinas, Sao Paulo, Brazil.

Background: The present study investigated whether elderly dialysis patients suffering from malnutrition accompanied by decrease in both body protein and skeletal muscle experienced improvement in nutrition as a result of ingesting branched-chain amino acid (BCAA).

Methods: 29 hemodialysis patients (13 males, 16 females, average age 78.5 ± 7.0 years, average dialysis duration 6.7 ± 4.8 years, diabetes mellitus 48.3%) were chosen from a total of 61 people subjected to dietary management in our hospital and nursing home. Patients receiving tube feeding or with ALB of ≤3.5 g/dl were excluded. The patients consumed protein-calorie-kilo food (4,000 mg containing BCAA). Results of amino acid as well as ALB, CRP, BUN analyses and appetite survey conducted for 3 months before and after BCAA ingestion were compared.

Conclusions: The results: The average daily amount of food containing BCAA was 3,318.8 mg. BUN significantly increased in Group B (p<0.05 for 50.7 ± 16.8 g and comparison of median values for essential amino acids showed that the following 6 of 9 items increased significantly: valine from 183.6 ± 47.6 to 246.7 ± 76.3 mmol/mL, methionine from 23.0 ± 4.7 to 25.9 ± 7.7 mmol/mL, isoleucine from 63.5 ± 21.4 to 86.2 ± 43.5 mmol/mL, leucine from 97.1 ± 28.8 to 153.7 ± 78.4 mmol/mL, phenylalanine from 65.0 ± 14.6 to 71.5 ± 14.5 mmol/mL, and histidine from 83.2 ± 14.2 to 89.1 ± 15.4 mmol/mL. In addition, BCAA levels increased significantly from 346.8 ± 93.4 to 499.8 ± 188.0 mmol/mL, and the Fisher ratio increased significantly from 3.96 ± 4.7 to 4.04 ± 1.6 mmol/mL. No significant changes were observed for TP, Alb, CRP levels or the appetite survey.

Funding: Private Foundation Support

TH-P0532
Nutritional Education: New Tool for Guidance of Hemodialysis Patients with Focus on Humidity, Phosphorus and Potassium: Camila Machado de Barros,1 Bruna Benedetti,1 Julia Salgado Azeg,2 Maria Flavia Sgavioi,2 Edelli Simioni Abreu,2 Rosana Farah,2 Bárbara Margareth Menardi Biavo,1 Jacqueline Santos,1 Carmen B. Tzanno-Martins.1
1Nutrition, Grupo CHR, São Paulo, Brazil; 2Nutrition, Universidade Presbiteriana Mackenzie, São Paulo, Brazil.

Background: The objective of this study was to determine humidity, phosphorus and potassium of foods (fruits, leaf vegetables and non-leaf vegetables) in order to evaluate the best foods to be consumed by CKD patients and develop educational material for them.

Methods: We prepared an educational material to be presented to patients. Three comparative tables were created, one for each of three food groups: fruits, leaf vegetables and non-leaf vegetables. The food selection was made according to the nutritional guidelines for patients with CKD. The survey data for the elaboration of the project was carried out by three different sources: TACO - Brazilian Table of Food Composition (UNICAMP, 2006); UNIFESP Nutritional Table; and Food Composition Table of the United States Department of Agriculture (USDA, 2007).

Results: We’ve confirmed that fruits considered ‘dry’ obviously contain less water in its composition (69% moisture). However, phosphorus (30 mg / 100 g) and potassium (312 mg / 100 g) levels are considered normal, as they have great increase of its percentage. The three fruits with higher humidity content were pyriform orange (Citrus aurantium pyriforme) (89.6%), Key lime (Citrus aurantifolia) (87.4%) and strawberry (91.5%). And the ones with the lowest rates, excluding ‘dry’ fruits, were avocado (85.3%), tangerine (81.0%) and guava (80.8%). It was found that all plant foods should be cooked, because they have large amount of potassium. Although we have examined the phosphorus content in these foods, it is known that these are not the usual sources for this mineral, but they can influence phosphorus’ increase in the patient’s body when consumed in large quantities.

Conclusions: It was evident the lack of literature related to the amount of water contained in food. Therefore, it is necessary to develop more studies in order to analyze the influence of foods in daily intake of liquid by CKD patient.

Funding: Private Foundation Support

TH-P0533
Effects of Carnitine on Oxidative Stress and Inflammatory Responses to Intravenous Iron Administration to Patients with CKD: Zayed Arnawy,1 Amr Abd Elkadd,1 Adel Rafik Jabbour,1 Bishara Shafik Bisharat,1 Abdalla Bowirrat,1 Hashem J. Bishara,1 Zaid Abassi.2
1Nazareth Hospital-EMMS, Galilee Faculty of Medicine - Bar Ilan Univ, Zafed, Israel; 2Physiology, Faculty of Medicine, Technion, Israel.

Background: Anemia is a common problem in CKD patients. It is attributed to decreased erythropoietin (EPO) and iron stores. Therefore, therapy includes EPO and iron replenishment. However, the latter induces oxidative stress. Randomized studies suggested that L-carnitine supplementation might have positive effects on the response to EPO in long term HD patients. Unfortunately, there is no evidence whether this approach is also beneficial in earlier-stage of CKD.

Methods: This study included 26 anemic CKD patients (stages 2-4) that were given a weekly IVIR (Sodium ferric gluconate, 125 mg/100 ml) for 8 weeks, and during weeks 5-8

Key: TH - Thursday; FR - Friday; SA - Saturday; OR-Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author/disclosure.
also received carnitine (20mg/kg, IV) prior to IVIR administration. Weekly blood samples were drawn before and after each IVIR for advanced oxidative protein products (AOOP), neutrophil gelatinase-associated lipocalin (NGAL), in addition to routine complete blood count and biochemical analyses. Results: IVIR for 4 weeks did not increase hemoglobin levels, yet worsened the oxidative burden as was evident by elevated plasma AOOP from 229.1±27.3 to 318.1±39.3 μg/L at 6 weeks (p<0.01) and 367±41.4 μmol/L at 4 weeks. Plasma NGAL levels were not significantly affected by IVIR (265.4±48.6 vs. 265.1±44.7 and 205.7±39.4 μmol/L at 1 and 4 weeks, respectively). Simultaneous administration of carnitine with IVIR resulted in a mild hemoglobin increase. Interestingly, carnitine therapy abolished the IVIR-induced oxidative stress, where AOOP levels were 237±31.85 and 271±82.38 μmol/L at 1 and 4 weeks, respectively, p<NS). Furthermore, carnitine therapy decreased NGAL levels to 201.3±36.63 (p=0.02), and 239±48.55 ng/ml (p<0.05). No changes in CRP, Scr, BUN, albumin or WBC were observed following IVIR alone or combined with carnitine.

Conclusions: This study demonstrates that IVIR in CKD patients provokes oxidative stress, as evident by elevation of AOOP. The antioxidative effects of carnitine, suggests a role for carnitine therapy also in earlier-stage CKD patients.

Funding: Government Support - Non-U.S.

TH-POS34

The Plasma Concentration of Free Carnitine Should Be Increased above Normal in Order to Reduce the Darbepeoetin Alfa Dose in HD Patients Administered Levocarnitine

Masaki Aono, Yuzuru Sato, Sato Junkanskikakusa, Matuyama, Ehime, Japan.

Background: Plasma concentration of free carnitine decreases significantly in hemodialysis patients, and the free carnitine deficiency impairs response to Darbepeoetin Alfa (DA) renal anemia therapy on HD. Levocarnitine can be administered to improve DA-resistance anemia, but the adequate dose for improvement has not been yet determined.

Methods: Over a three-month period, a daily dose of levocarnitine (1800mg/day) was administered orally to 134 patients on HD who were diagnosed with carnitine deficiency (plasma concentration of free carnitine <30μmol/L). At the end of the three months, the patients were divided into 3 groups according to the concentration of plasma free carnitine (FC) as follows: group 1: FC<30μmol/L, N=22, group 2: 30<FC<72, N=13, group 3: FC>72, N=99. DA dosage and the erythropoietin resistance index (ERI: DA dose (μg/week)/Hb (g/dL)/body weight (Kg) x 100) were compared among the patients in the three groups before and after the treatment.

Results: In group 2, the plasma concentration of free carnitine increased from a mean of 18±5.6 μmol/L to 45.8±11.3 μmol/L after administration of levocarnitine (paired t-test P=0.05) and decreased significantly from 23.4±3.1 to 25.0±4.6 mol/L in group 1, the dosage of DA and ERI decreased significantly only in group 3 (DA: from 23.3±1.8 to 23.1±3.54 μg/week, p<0.001, ERI: 7.4±3.2 to 5.3±5.3, P=0.01), but remained unchanged in the other two groups (in group 1, DA: from 23.3±1.8 to 23.1±3.54, P=0.43, ERI: from 4.3±3.9 to 3.9±2.8, P=0.46; in group 2, DA: from 11.4±1.1 to 10.2±1.17, P=0.08, ERI: from 3.4±4.7 to 2.0±2.9, P=0.36).

Conclusions: This study suggested that levocarnitine can reduce the dose of DA and improve the resistance to DA in renal anemia patients on HD. But it appears to be necessary to increase the level of plasma carnitine above normal to obtain a sufficient effect of carnitine in HD patients. The monitoring of plasma concentration of free carnitine is important to assess the effect of levocarnitine to improve erythropoietin resistance.

TH-POS35

Predictors of Habitual Physical Activity in Hemodialysis Patients

Sivakumar Sridharan,1 Jocelyn Berdepardo,1 Kirsten L. Rennie,1 Neil Ashman,2 Andrew Davenport,2 Michael K. Almond,3 Anindya Banerjee,6 Enric Vilar,1,2 Andrew Davenport,4 Michael K. Almond, 5 Anindya Banerjee,6 Enric Vilar,1,2

Background: Physical activity is a potential intervention to improve quality of life and extend life expectancy in long-term hemodialysis patient. It is vital to understand factors in physical activity. The Plasma Concentration of Free Carnitine Should Be Increased above Normal in Order to Reduce the Darbepeoetin Alfa Dose in HD Patients Administered Levocarnitine

Satoshi Aono, Yuzuru Sato, Sato Junkansikanaka, Matuyama, Ehime, Japan.

Methods: Each study subject was administered the validated Recent Physical Activity Questionnaire (RPAQ). RPAQ enquires about time spent on activities at home, at work and during various recreational activities in the preceding 4 weeks. We assigned MET (metabolic equivalent of task) values for each activity. Resting energy expenditure (REE) was estimated using a novel predictive equation validated in renal failure. Total energy expenditure (TEE) was estimated from MET and REE. TEE estimation assumed 8 hours sleep and that the remaining unreported hours from RPAQ were spent in light activity. Energy Expenditure from physical activity (PAEE) was calculated as TEE – REE.

Results: 1500 HD patients (910 males) completed the RPAQ. Mean age was 62.6(15.5) years. There were 682 Whites, 418 Asians and 400 Blacks. 790 patients were on Hemodialinfilation(HDF). Mean REE was 1554 kcal/day, mean TEE 1840 kcal/day and mean PAEE 295 kcal/day. Male patients, those aged < 65 and those who were employed had significantly higher REE, PAEE and TEE (p<0.001). No significant difference was noted in the mean PAEE among various ethnic groups. PAEE was significantly less in those with heart disease, diabetes and arthritis and higher in those receiving HDF. In multivariate regression analysis, the independent predictors of PAEE were age, sex, employment status (p<0.001 for all), TEE therapy (p<0.001) and dialysis vintage (p<0.02) with these factors accounting for 50% of the variance in PAEE.

Conclusions: Mean daily MET values of the study subjects indicate a sedentary lifestyle for most HD patients. Age, sex, employment status, HDF therapy and dialysis vintage are the principal determinants of energy expenditure from physical activity in HD patients.

TH-POS36

Effects of Kibow Probiotic Supplementation Renadyl™ on Uremic Toxins in Hemodialysis Patients

Subhash J. Saggi,1 Mary C. Mallappallil,1 Usha N. Vyas,2 Griet Lrl Glorieux,3 Peter L. Liang,1 Pari Ranganathan,2 Bohdan Pechenyak,2 Gary R. Briel,1 Lorraine L.A. Thomas,1 Raymond C. Vanholder,1 Natarajan Ranganathan,2 Eli A. Friedman.1

Background: Before our primary studies in patients with CKD 3-4 (n=31) given Renadyl™, a safe proprietary probiotic dietary supplement that metabolizes nitrogenous wastes in the bowel, at a dose of 90-270 B CFU per day, over a 4 month period showed that BUN, creatinine and K+ levels declined.

Methods: We now conducted a prospective double blind cross over trial with placebo and Renadyl™ in 26 stable CKD patients on hemodialysis. Dosage administered was 180 B CFU per day, given in 3 divided doses. Our primary aim was a 20% reduction in BUN levels over an 8 week period. Patients' dialysis prescriptions were unchanged. Our secondary aim was to see if there would be changes in WBC count. C-reactive protein (CRP), total and/or free serum concentrations of indoxyl sulfate, indole acetate, p-cresyl sulfate, hippuric acid, serum pentosidine, 3-carboxy-4-methyl-5-propyl-2-furan-propionic acid (CMPF), uric acid and beta-2 microglobulin. Solutes were measured by HPLC and ELISA. QoL changes were assessed by a modified SF-36 questionnaire. Patient adherence was assessed by pill count and stool culture to confirm probiotic growth during study and absence during placebo period. Data were analyzed using ANOVA for a crossover study with a mixed model methodology in SAS to account for treatment, period and sequence effects.

Results: Administration of probiotics was safe and showed a decline in a 4 week period (6.02x106/μl to 5.5x106/μl, p=0.05) and total indoxyl glucuronide (0.76mg/dL to 0.65mg/dL, p=0.05) and a trend towards reduction in CRP (13.7±2mg/dL to 11.5±1mg/dL, p=0.07).

Conclusions: Administration of Kibow Probiotic Renadyl™ in ESRD patients is safe and showed a protective effect by the trend to reduce markers of inflammation. Further investigation in a larger population or at a higher dose might yield mechanistic insights into the probiotic effects on the inflammatory cascade of uremia.

Funding: Pharmaceutical Company Support - Kibow Biotech, Inc.

TH-POS37

Effect of Convection Therapy on Advance Glycation End Products

Arun Nongnuch,1 Andrew Davenport.2

Background: Cardiovascular disease (CVD) is a major cause of death in the dialysis population. Advance Glycation End Products (AGEs) have been strongly associated with CVD. AGEs are formed by the Maillard reaction and are predominantly renally excreted. Levels of both serum AGEs and AGES deposited in tissues are increased in dialysis patients. Previous studies have shown that tissue AGEs had greater association with CVD than serum AGEs, and tissue AGE deposition can be measured by skin autofluorescence (sAF).

Methods: We measured tissue AGEs using skin autofluorescence (sAF) (DiagnOptics, Groningen, Netherlands) on the non-fluflsta arm of 332 chronic hemodialysis patients, 169 on HD and 163 on HDF.

Results: The results are shown in the table (figure).

Conclusions: The addition of convective clearance with HDF appears to reduce the accumulation of tissue AGEs, by improving middle molecule clearances. Prospective studies are required to determine whether HDF reduces the risk of cardiovascular death in long term hemodialysis patient.

Funding: Private Foundation Support
TH-P0538

Treatment by High Cut-Off Hemodialysis Leads to Higher Hemoglobin and Decreased Heparin in HD Patients

Background: Multiple inflammatory stimuli are linked to clinical signs and symptoms and CV mortality in HD patients. Inflamed HD patients also show impaired responses to erythropoiesis-stimulating agents (ESAs).

Aim of this pilot study was to investigate if HD treatment with a membrane having a high molecular permeability in a broad MW range improves ESA responsiveness (ESA resistance index, ERI) and decreases in CV mortality in HD patients. Inflammation in HD patients is not well studied in incident hemodialysis (iHD) patients in their first 3 months and anhedonia during the previous two weeks. Scores range from 0-6; a positive DA score (PHQ2). The PHQ2 consists of two questions that determine presence of depressed mood (PHQ-2). The PHQ2 was positive in 23.3% of patients. Logistic regression identified male iHD patients as having significantly impaired responses to ESA treatment.

Methods: 24 ESRD patients (6, 65±16 years, 70±11 kg) on 3x week high-flux HD/HDF (≥ 3 months) with adequate iron status (TSAT >20%, ferritin >100 ng/mL) were randomized into a study group (Theralite high cut-off membrane (Gambro) alternating with routine high-flux HD/HDF) or control group (routine HD/HDF) and treated for 12 weeks. ESA dose was adapted, to guidelines to maintain Hb levels in between 10-12 g/dL. Heparin, k- and x-FLCs, ESA dose, Hb and albumin were analyzed. (NCT01526798)

Results: 5 patients dropped out during the study period. One patient was excluded due to unusual high ferritin. In both groups a reduction of ERI has been observed. Only in the study group a significant increase in Hb levels and a decrease of heparcin values to a significant lower level was detectable during the study period (fig. 1). An albumin drop was detectable in the study group and values stabilized after ~2 weeks at the lower level. Intradialytic RRs of x and 3.5 FLcs were higher in the study group compared to controls.

Conclusions: High cut-off dialysis allows a significant better removal of large urmic toxins (3, 5 FLcs) and improves ESA responsiveness (indicated by rise in Hb and fall in heparcin). Larger studies are needed to confirm if regular treatment with high permeability membranes leads to an improvement in anemia of chronic inflammation in HD patients.

Funding: Pharmaceutical Company Support - Gambro Lundia AB

TH-P0539

Depressive Affect in Incident Hemodialysis Patients: Prevalence and Risk Factors

Background: Depression is common among patients with end-stage renal disease, yet is not well studied in incident hemodialysis (iHD) patients in their first month of chronic outpatient dialysis. This study investigated the prevalence of and risk factors for depressive affect (DA) in the FMCNA RightStart Program.

Methods: From a random sample of 108 dialysis centers, 429 iHD patients in their first month of dialysis at FMCNA during January-March 2013 were contacted by telephone for up to three tries for depression screening utilizing the Patient Health Questionnaire 2 (PHQ2). The PHQ2 consists of two questions that determine presence of depressed mood and anhedonia during the previous two weeks. Scores range from 0-6; a positive DA score was defined as ≥ 3. Clinical and lab parameters were collected up to the first 120 days of dialysis and associations between DA were assessed using multivariate logistic regression.

Results: Of 429 patients, 172 (40.1%) were successfully screened with the PHQ2, 192 (44.8%) could not be reached, 6 (1.4%) refused and 59 (13.8%) did not have a valid telephone number. Responders were: 41.3% females; mean age of 65±14.6 years; 64.5% had diabetes; and 67.4% utilized dialysis catheters. The PHQ2 was positive in 23.3% of patients. Logistic regression identified male iHD patients had significantly lower risk of DA (OR=0.32, p=0.02), while higher log of creatinine (Cr) trended towards greater risk for DA (OR=5.48, p=0.08). There were no associations between DA and age, diabetes, access type, ethnicity, race, body mass index, residual renal function, number of comorbidities, albumin, interdialytic weight gain, or urea reduction ratio.

Conclusions: The prevalence of DA by PHQ2 was 23.3% in this iHD patient cohort, consistent with prior reports in the literature. A decreased risk for DA was observed in males. Creaintine levels may play a role as a determinant of DA, but further studies are required to better understand these associations.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-P0540

Reduced Renal Fibrosis after Unilateral Ureteral Obstruction in Mice

Lacking a Subunit of N-Type Calcium Channels

Background: Renal tubules are innervated by sympathetic nerves in which N-type Ca2+ channels are densely distributed. It has been reported that sympathetic nerve activity is increased in patients with chronic renal diseases. We recently reported the increased expression of N-type Ca2+ channel in the kidneys after unilateral ureteral obstruction (UUO) and the reduction of renal fibrosis by L/N-type Ca2+ channel blocker in rats (JAP Renal Physiol 304: F665-73, 2013). However, the role of N-type Ca2+ channel in renal fibrosis is not totally understood.

Methods: To address this issue, we induced UO in male mice lacking the αn subunit of N-type Ca2+ channel (Cav2.2) and wild type (WT) littermates and analyzed several renal fibrotic parameters in this study.

Results: In C57BL/6N mice, the expression of Cav2.2 was absent in normal, contralateral, and sham-operated kidney, while Cav2.2 became detectable in the interstitium of the kidney after UUO. In UUO kidneys, Cav2.2 was expressed in the interstitial cells positive for α-SMA, a marker for myofibroblasts, but not in T-lymphocytes, Macrophages, and endotelial cells. At baseline as well as after UUO, there was no significant difference in mean blood pressure, heart rate, and renal function (serum creatinine and blood urea nitrogen levels) between WT mice and Cav2.2 mutant mice. The expression level of a-SMA in the UUO kidneys of Cav2.2 mutant mice was significantly decreased compared to that in WT mice. Cav2.2 deficiency reduced the production of fibronectin, but not type I or type III collagen in the kidney after UO. Sirius red-positive area was significantly reduced in Cav2.2 mutant kidney compared to that in WT kidney after UO (1.97% vs. 3.57%, P<0.001).

Conclusions: Our data suggest that Cav2.2 is implicated in myofibroblast activation and the production of extracellular matrix during renal fibrosis. Cav2.2 might be a novel therapeutic target for the treatment of fibrotic kidney disease.

TH-P0541

Effects of Tissue-Specific, Targeted Expression of Baculovirus p35 Pan-Caspase Inhibitor on Renal Fibrogenesis following Ureter Obstruction

Background: The caspase family of enzymes participates in cell apoptotic and proinflammatory reactions. Although caspase activation was known to be involved in renal fibrogenesis following unilateral ureter obstruction (UUO), in such an obstructive kidney there is a question to be determined.

Methods: Three lines of transgenic (tg) mice were used. p35 tg mice that bear the pan-caspase inhibitor protein p35 gene separated from a universal CAG promoter by a floxed STOP sequence were crossed with γtG.Cre and FSP.Cre tg mice that express Cre recombinase in tubular epithelial cells and fibroblasts, respectively. Two double-tg mice (γtG.Crep35 and FSP.Crep35) and wild-type mice were then challenged with UUO. Cell apoptosis was defined by in situ end labeling and the point-counting method. Fibrosis-related parameters in the kidneys were determined by histopathology and qPCR.

Results: Matrix deposition by Masson’s trichrome staining in the peritubular interstitium and mRNA levels of fibronectin (FN)-EIIA were significantly increased in the UUO kidneys of the wild-type and FSP.Crep35 tg mice, but not in those of the γtG.Crep35 mice, possibly due to tubular epithelium-specific induction of p35 gene product, compared to the native kidneys (8.1±1.9, 7.9±3.2, 3.8±1.2, vs. 0.9±0.1 [% blue area]; 9.4±3.1, 10.3±3.6, 5.7±1.5, vs. 1.0±0.5 [FN–EIIA mRNA/GAPDH mRNA]). Additionally, compared to the wild-type mice, the number of apoptotic cells and mRNA levels of NLRP3, a caspase-1-dependent, central component of inflammasome, in the UUO kidneys were significantly lower in the γtG.Crep35 mice while those were not significantly altered in the FSP.Crep35 tg mice.

Conclusions: Tissue-specific, targeted expression of p35 pan-caspase inhibitor provides evidence of the critical role of caspase activation, i.e., induction of apoptosis and inflammasome, in tubular epithelium, but not in fibroblasts, in renal fibrogenesis following ureter obstruction.

Funding: Government Support - Non-U.S.
TH-PO542

Induction of Renal Fibrosis by a Cell Cycle Regulator | Jadid Mogeysi,1,2 Adel Tarcsacalvi,1 Nag San Ht Li Seng,1 Shenyang Li,2 Didier Portilla,2 Peter M. Price.1,2

Background: Expression of a cell cycle regulatory protein, p21WAF1/CIP1, in cells after partial nephrectomy is associated with fibrotic changes and progression. The p21 protein is an inhibitor of cyclin-dependent kinases-1 and -2 (Cdk1, Cdk2), but the mechanism of how its expression contributes to fibrosis is unclear.

Methods: Cultured proximal tubule cells were transduced by adenoviruses including those expressing full-length p21, N- and C-terminal p21, and DN-Cdk2. The Cdk-inhibitory drug purvalanol was used at 9 µM. Also, several mouse models of renal fibrosis were used, either unilateral ischemia/reperfusion, ureteral obstruction, or partial nephrectomy.

Results: We reported previously that p21 KO mice were protected from renal fibrosis using 5/6 nephrectomy, UUO/release, or unilateral ischemia/reperfusion and that after AKI, proximal tubules were the major sites of p21 mRNA induction. We now show that in a p21 KO background, induction of transgenic p21 specifically in proximal tubules resulted in expression of fibrotic markers after unilateral ischemia or 14 days following UUO that was released after 3 days, showing that proximal tubular cells are a significant source of the signal for induction of fibrosis. We also show that p21 over-expression in cultured kidney cells results in increased TGF-β mRNA and release of TGF-β.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO543

Sonic Hedgehog Is an Inducible, Tubule-Derived Growth Factor for Interstitial Fibroblasts after Kidney Injury | Dong Zhou,1 Yingjian Li,1 Li Li Zhou,1 Roderick J. Tan,1 Youhua Liu,1 Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA.

Background: Tubular epithelium constitutes the major part of renal parenchyma, and is the primary target of various kidney injuries. However, how the injured tubules drive fibroblast proliferation and activation in the interstitium remains elusive. Here we show that sonic Hedgehog (Shh), an evolutionarily conserved, secreted and extracellular signaling protein, is an inducible, tubule-derived growth factor that plays an important role in promoting renal fibrosis.

Methods: Various animal models of CKD as well as human kidney biopsies were used. Shh signaling was induced by cyclopamine (CPN) in vitro and in vivo. Results: We found that Shh was specifically induced in renal tubular epithelia in various models of kidney injury induced by adriamycin (ADR), ischemia/reperfusion injury (IRI) and 5/6 nephrectomy, respectively. Shh was also markedly induced in renal tubules of human kidney biopsies from CKD patients with different etiologies. In vitro, recombinant Shh promoted rat kidney fibroblasts (NRK-49F) proliferation, as assessed by cell counting, MTT assay, and BrdU incorporation assay, which was accompanied by induction of numerous proliferation-related genes including e-cos, c-myc, proliferative cell nuclear antigen, and cyclin D1. However, Shh had no appreciable effect on the proliferation of other major kidney cells, such as podocytes, proximal tubular epithelial cells (HKC-8) and inner medullar collecting ducts (mIMCD-3). To investigate the role of Shh in fibroblast proliferation in vivo, we administered CPN, a small molecule Smo inhibitor, at 3 days after IRI. At 10 days after IRI, we found that CPN markedly inhibited fibroblast proliferation, reduced myofibroblasts population, and attenuated fibrotic lesions in vivo.

Conclusions: Collectively, these studies identify Shh as a potent tubule-derived growth factor that specifically promotes interstitial fibroblast proliferation. Our data also indicate that blockade of Shh signaling is a novel strategy for therapeutic intervention of renal fibrosis.

Funding: NIDDK Support

TH-PO544

Matrix Metalloprotease-7 Is a Biomarker and Pathogenic Mediator of Kidney Fibrosis | Dong Zhou,1 Li Li Zhou,1 Roderick J. Tan,2 Fan Fan Hou,1 Youhua Liu.1 Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA; Renal Div, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China.

Background: Matrix metalloprotease-7 (MMP-7), a secreted, zinc and calcium dependent endopeptidase that degrades a broad range of extracellular matrix (ECM) and other substrates, is a transteccial target of canonical Wnt/β-catenin signaling. We previously demonstrated that urinary MMP-7 is surrogate biomarker for renal Wnt/β-catenin activity. However, whether MMP-7 plays a role in renal fibrogenesis is completely unknown.

Methods: Urinary MMP-7 from normal subjects and CKD patients was measured by ELISA. MMP-7 knockout and wild-type control mice were subjected to UUO. Cultured human renal proximal tubular cells were treated with recombinant MMP-7.

Results: Urinary MMP-7 level was markedly increased in CKD patients, comparing to normal subjects. Similarly, increased MMP-7 was observed in renal tubules of human kidney biopsies from CKD patients. MMP-7 mRNA and protein expression were also induced in animal models of renal fibrosis such as UUO. To study the role of MMP-7 in renal fibrogenesis, MMP-7−/− mice and their WT controls were subjected to obstructive injury for 7 days. Compared with WT controls, MMP-7−/− mice displayed reduced fibrotic lesions, characterized by decreased expression of Snail1, α-smooth muscle actin, vimentin, FSP1, E-cadherin, type IV collagen. Abolition of MMP-7 in vivo also preserved E-cadherin primarily by inhibiting its extracellular shedding, with no effect on E-cadherin mRNA abundance. In vitro, MMP-7 incubation reduced E-cadherin staining in plasma membrane of proximal tubular cells (HKC-8), which resulted in increased β-catenin nuclear localization. Co-immunoprecipitation revealed a diminished E-cadherin/β-catenin complex formation, with concomitant increase of b-catenin/LEF1 binding, after MMP-7 treatment in HKC-8 cells.

Conclusions: These observations suggest that MMP-7 not only is a biomarker, but also plays a crucial role in mediating tubular injury and interstitial fibrosis by promoting E-cadherin shedding and β-catenin activation.

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

TH-PO545

Slit2 Inhibits Renal Fibrosis after Ischemia Reperfusion Injury | Darren A. Yuen,1 Yi-Wei Huang,1 Guang-Ying Liu,1 Sajedabani Patel,1 Rohan John,2 Lisa Robinson.1 Hospital for Sick Children, Canada; 2Univ Health Network, Canada.

Background: Fibrosis is a critical contributor to CKD progression for which no specific therapies exist. Acting on its cognate Robo receptors, Slit2 is a secreted protein that modulates the actin cytoskeleton of multiple cells. As fibroblast activation is dependent upon cytokine/cellular rearrangements, we hypothesized that Slit2 may exhibit anti-fibrotic activity and prevent renal fibrosis after AKI.

Methods: Renal fibroblasts were examined for Rbo1 expression using qRT-PCR, immunoblotting, and immunostaining. The effects of Slit2 alone or in combination with its decoy receptor Robo1b on TGF-β-mediated fibroblast collagen production were tested using a [3H]-proline incorporation assay. To assess the effects of Slit2 in vivo, mice undergoing left renal ischemia-reperfusion injury (IRI) received 3x weekly i.p. injections of N-Slit2 (a bioactive Slit2 fragment), C-Slit2 (an inactive Slit2 fragment) or vehicle. Thirteen days post IRI, mice underwent right nephrectomy and 24 h later, renal function and structure were analyzed.

Results: Renal fibroblasts expressed Rbo1 mRNA and protein. Slit2 dose-dependently reduced TGF-β-induced [3H]-proline incorporation, whereas Slit2 incubation with its decoy receptor blocked its anti-fibrotic activity. In the mouse model of renal IRI, administration of inactive C-Slit2 had no effect, but bioactive N-Slit2 improved serum creatinine and urea. N-Slit2 also reduced α-SMA+ activated fibroblast number and collagen deposition in the injured kidney.

Conclusions: These data demonstrate that Slit2 exerts predominantly anti-fibrotic effects by inhibiting TGF-β-induced fibroblast activation. Slit2 may represent a novel therapy targeting renal fibrosis.

Funding: Government Support - Non-U.S.

TH-PO546

Reduced Renal DDAH1 Activity Protects against Progressive Kidney Damage | James Alexander Tomlinson,1 Ben Caplin,2 Dirk Dornmann,1 Peter Allen,1 Sanjay Khadayate,1 Jill T. Norman,2 David C. Wheeler,2 James M. Leiper.1 Medical Research Council Clinical Sciences Centre, Imperial College, London, United Kingdom; 2Centre for Nephrology, UCL Medical School Royal Free, London, United Kingdom.

Background: Asymmetric dimethylarginine (ADMA) competitively inhibits nitric oxide (NO) synthesis whilst dimethylarginine dimethylaminoacylase 1 (DDAH1) metabolises ADMA; representing an alternative pathway for NO regulation. Although an association between elevated circulating ADMA and poor cardiovascular and renal outcomes has been widely reported, a causal link is unresolved. We recently published evidence of a DDAH1 gene variant that leads to lower plasma ADMA but counter-intuitively, associates with a steeper rate of eGFR decline.

Methods: The principal site of renal DDAH1 expression is within the renal proximal tubule (PT). We tested the hypothesis that reduced kidney DDAH1 activity slows the progression of kidney function decline by: (A) generating a novel PT-specific DDAH1 gene knockout (KO) mouse; (B) subjecting it to a folate model of CKD and (C) confirmed gene expression associations observed in the KO mouse within human renal allografts.

Results: (A) KO mice had elevated PT cell ADMA (60%, p<0.05), with a reduction in NO synthesis (60%, p<0.05) and no effect observed in other organs, urine, plasma or systemic BP. Urine proteomic analysis revealed an 8-fold reduction in uromodulin (UMOD; p<0.001) with PT1 deletion. (B) At 12 weeks post folate injury, WT mice had a >2-fold rise in fibrotic gene expression (Coll12a and TGFβ); p<0.05, whereas KO mice
A Simple Method for Detection of Epithelial-Mesenchymal Transition during Renal Fibrosis In Vivo

Background: Epithelial-mesenchymal transition (EMT) in renal fibrosis is generally defined by the loss of epithelial markers and the acquisition of mesenchymal phenotypes. This transition is typically characterized by the loss of polarity, cell-cell adhesion, and cell-matrix interactions, leading to the formation of fibroblasts-like cells that contribute to the deposition of extracellular matrix (ECM) and the progression of kidney fibrosis.

Methods: To address the need for a simplified method to detect EMT in kidney fibrosis, we investigated the use of bromodeoxyuridine (BrdU) labeling. Previously, we reported that renal progenitor cells are important in acute and chronic kidney disease. In the current study, we examined the role of BrdU+ cells in the progression of renal fibrosis.

Results: After unilateral ureteral obstruction (UUO), some BrdU+ tubular cells were protruded from the basement membrane of normal rat kidneys. Most proximal tubular cells became BrdU+ after 4-week labeling. BrdU+ cells were detectable in AQP1-positive proximal tubules, but not in the interstitium.

Conclusions: The number of BrdU+ cells was positively associated with labeling period. This finding suggests that BrdU+ cells can be used as a marker of EMT in renal fibrosis.

Funding: This work was supported by the National Institutes of Health (NIH) grant DK112028 to H. William Schnaper.

TH-PO547

Different Roles for the Three AKT Isoforms in TGF-β-Induced Fibrogenesis

Benaya Rozen-zvi, H. William Schnaper, Tomoko Hayashida.

PosteriouThank you for providing the document and its content. I understand that the document contains information about renal fibrosis, epithelial-mesenchymal transition, and methods for detecting EMT in renal fibrosis. The document includes background information, methods, results, and conclusions from a study investigating the role of Sphingosine Kinase 2 (SphK2) in renal fibrosis using a simple method for detection of EMT. The study found that BrdU+ cells were detectable in AQP1-positive proximal tubules, but not in the interstitium. The number of BrdU+ cells was positively associated with labeling period, suggesting that BrdU+ cells can be used as a marker of EMT in renal fibrosis.

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

Underline represents presenting author/discourse.

227A
fibrogenesis. We here tested the hypothesis that cell-specific delivery of IFNγ to platelet-derived growth factor receptor beta (PDGFRβ)-expressing myofibroblasts attenuates renal fibroblasts systemic side effects.

**Methods:** PDGFRβ expression was determined in fibrotic mouse and human kidney by specific staining. IFNγ conjugate (IFNγ-PEG-PPB) was synthesized by coupling of PDGFRβ-specific peptide (PPB) to IFNγ via a PEG linker. The biological activity & anti-fibrotic effects were analyzed in vitro. Anti-fibrotic effects of targeted (IFNγ-PEG-PPB) and free IFNγ were investigated in the unilateral ureteral obstruction (UUO) model in C57BL/6 mice at 3 & 7 days.

**Results:** PDGFRβ expression was highly upregulated in mouse & human fibrotic kidneys. PDGFRβ expression co-localized with αSMA-positive myofibroblasts. In vitro, IFNγ-PEG-PPB induced NO release in RAW cells (indicative of biological activity) & inhibited expression of collagen I, αSMA in fibrotic NIH 3T3 fibroblasts. In vivo, IFNγ-PEG-PPB specifically accumulated in the PDGFRβ-positive myofibroblasts. IFNγ-PEG-PPB treatment induced a significant reduction of renal collagen I, fibronectin and αSMA expression (both at mRNA & protein level), and was more effective than non-targeted IFNγ. In contrast to non-targeted IFNγ, IFNγ-PEG-PPB did not induce IFNγ-related side effects.

**Conclusions:** Specific targeting of IFNγ to PDGFRβ-expressing myofibroblasts attenuates renal fibrosis without causing adverse effects in an experimental for renal fibrosis in mice.

**Key: TH-PO552**

**Contribution of Hydrogen Peroxide-Inducible Clone-5 to the Regulation of Mesangial Cell Proliferation in Mesangioproliferative Glomerulonephritis**

**Ariunbold Jamba,1 Shuji Kondo,1 Maki Urushihara,1 Takashi Nagai,1 Toshiaki Habu,1,2,3**

**Methods:** Hydrogen peroxide-inducible clone-5 (Hic-5) is a transforming growth factor-β (TGF-β)-inducible focal adhesion protein homologous to paxillin. We have previously demonstrated that Hic-5 was localized in mesangial cells (MC) and its extracellular matrix (ECM) expression in mesangioproliferative GN produced by injection of Habu venom (4 mg/kg) into hemephrenic wild type (Hic-5+/+) and Hic-5 deficient (Hic-5−/−) mice. In addition, we examined how Hic-5 is involved in MC proliferation using isolated cultured MC from Hic-5+/+ and Hic-5−/− mice.

**Results:** Habu venom-induced GN in Hic-5−/− mice demonstrated glomerular cell proliferation at day 7. Surprisingly, glomerular cell number was significantly increased in Hic-5−/− GN mice compared to Hic-5+/+ GN mice (P=0.01). Ki-67 positive cells as well as expressions of fibronectin and alpha-smooth muscle actin were also increased in Hic-5−/− GN mice compared to Hic-5+/+ GN mice (P=0.01). In vitro experiments about MC proliferation by cell counting and WST-8 assay showed that Hic-5−/− MC significantly proliferated compared to Hic-5+/+ MC. Interestingly, TGF-β1 induced proliferation in Hic-5−/− MC but did not in Hic-5+/+ MC. In contrast, PDGFR-BB, another growth factor, increased both Hic-5−/− and Hic-5+/+ MC in the same degree. These data suggest that Hic-5 might be a specific downstream molecule of TGF-β1 to control MC proliferation in glomerular injury. Finally, Hic-5−/− MC showed increased level of phospho-paxillin, which has mitogenic potential. Hic-5 is the most important regulatory role of Hic-5 against paxillin signaling for MC growth.

**Conclusions:** In conclusion, Hic-5 might regulate MC proliferation under TGF-β1 stimulation in the development of mesangioproliferative GN.

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

**Key: TH-PO555**

**AMP-Kinase Activation by AICAR Inhibits Renal Fibrosis and Inhibits Transforming Growth Factor-β1 Induced Activation of Kidney Myofibroblasts**

**Kuan-hsing Chen, Huang-Hao Hsu, Ming-Yang Chang, Cheng-chih Hung.**

**Background:** Activation of interstitial myofibroblasts and excessive production of extracellular matrix proteins are final common pathways contributing to chronic kidney disease. Although the number of studies, AMPK (AMP-kinase) activation has been shown to inhibit fibrosis in vitro. Here, we examined the effect of an AMPK activator, AICAR, on inhibiting the progression of renal fibrosis in vivo and TGF-β1 activation of renal interstitial fibroblasts in vitro.

**Methods:** Urinary unilateral obstruction (UUO) model was induced in adult male BALB/c mice. Mice with UUO were given with intra-peritoneal AICAR (500 mg body weight/day) or saline daily, one day prior the UUO surgery. Both obstructed and contralateral kidneys were harvested 7 days after surgery. Kidney tissues were prepared for further pathological and molecular biological analysis. Cultured rat renal interstitial fibroblasts (NRK-49F) were stimulated with recombinant human TGF-β1 1ng/ml. Alternatively, NRK-49F cells were pre-incubated with AICAR or specific inhibitors for 30 mins before TGF-β1 treatment. Total RNA was extracted for RT-PCR or real-time PCR and total cell lysates were extracted for Western Blot analysis.

**Results:** In a mouse model of renal interstitial fibrosis induced by unilateral ureteral obstruction (UUO), administration of AICAR attenuated the extracellular matrix protein deposition following injury. AICAR suppressed the expression α-smooth muscle actin (α-SMA) and collagen and fibronectin in UUO kidney. Treatment of cultured renal interstitial fibroblasts with AICAR inhibited their activation by TGF-β1, as evidenced by dose-dependent blockade of α-SMA and collagen I expression. Moreover, the effects of AICAR in inhibition of kidney myofibroblast activation by TGF-β1 were associated with down-regulation of ERK 1/2 MAPK pathways.

**Conclusions:** Thus, our results suggest that AICAR reduces the tubulointerstitial fibrosis in UUO mice and inhibits TGF-β1 induced kidney myofibroblast activation. The AMPK activation by AICAR may hold therapeutic potential in the treatment of renal tubulointerstitial fibrosis.

**Funding:** Government Support - Non-U.S.
TH-POS56
Loss of Endothelial Nitric Oxide Augments Renal Fibrosis via Promoting Local Fibroblast Proliferation
Jinhua Lì,1 Yu Bo Yang Sun,2 Xinli Qu,1 David J. Nikolic-Paterson,2 1Dept of Anatomy and Developmental Biology, Monash University, Australia; 2Dept of Medicine, Monash Unv, Australia.

Background: Deficiency in nitric oxide synthase 3 (NOS3/ENOS) exacerbates renal injury in the remnant kidney and diabetic nephropathy. Nitric oxide (NO) is a potent vasodilator released by the endothelium that suppresses vascular smooth muscle cell growth and inhibits platelet aggregation. This study investigated whether the loss of endothelial-derived NO contributes to renal interstitial fibrosis through promoting local fibroblast proliferation.

Methods: Unilateral ureteral obstruction (UUO) and STZ-induced diabetic nephropathy were performed in wild type (WT) and NOS3-/- C57BL/6J mice. Western blotting showed a marked reduction in total NOS3 levels. Interstitial fibroblast proliferation was first seen at 48hr in WT UUO, indicating that endothelial injury proceeds interstitial fibroblast proliferation. Compared to WT mice, UUO in NOS3-/- mice had significantly increased accumulation of α-smooth muscle actin (α-SMA)-positive myofibroblasts and a higher level of myofibroblast proliferation (Ki67+α-SMA+ cells), which was associated with increased deposition of collagen I and fibrinogen. Similarly, STZ-induced diabetes resulted in greater accumulation of α-SMA+ myofibroblasts and higher levels of myofibroblast proliferation compared to WT mice. In vitro, the supernatant from mouse microvascular endothelial cells (MMECs) in which NO production was blocked by L-NAME, significantly increased the proliferation of renal fibroblasts (NRK49F) compared to normal media. Also, fibroblasts stimulated by hypoxia (5% oxygen) or PDGF-BB showed greater proliferation in the presence of L-NAME-treated supernatant. Finally, the supernatant from MMECs expressing NOS3 significantly inhibited PDGF-BB-induced proliferation of NRK49F cells. Since the half-life of NO is less than 5 seconds, this effect is likely through an indirect pathway.

Conclusions: In summary, our studies show that endothelial NO production is a powerful regulator of fibroblast proliferation and renal fibrosis.

Funding: Government Support - Non-U.S.

TH-POS57
Role of Interactions between the Silt Diaphragm and Glomerular Basement Membrane in Alport Syndrome
Diana Rubel, Jenny Kruegel, Rainer Girgenti, Gerhard A. Mueller, Oliver Gross. Nephrology & Rheumatology, Univ Medicine Goettingen, Goettingen, Germany.

Background: Heterozygous Podocin-mutations and -polymorphisms can aggravate the phenotype of heterozygous carriers of type IV collagen mutations (COL4A3/4) with an unusual early onset of renal failure. This points toward an interaction between the slit diaphragm and glomerular basement membrane (GBM), which is essential for podocytes’ structure and function. In the present study, we report about COL4A3-, integrin α2β1 (ITGA2)- and DDR1- single (sKO), double (dKO) and triple knockout (tKO) mice, respectively, and its effect on slit diaphragm proteins.

Methods: COL4A3-, ITGA2-, DDR1- and their respective dKO, as well as iKO and WT (WT) mice were investigated at different ages using real-time PCR, light and electron microscopy and immunohistochemistry.

Results: In sKO mice, the relative expression of nephrin and podocin was strongly reduced compared to WT. Their expression in COL4A3/TGTA2 or COL4A3/DDR1 iKO and tKO, was comparable to WT till 4.5 weeks of age and decreased by 7.5 weeks. These results were consistent with a longer survival, later progress of kidney fibrosis and maintenance of podocyte footprocesses. In immunohistochemistry, quantity of nephrin and podocin in 4.5 week COL4A3 was comparable to WT, but podocin accumulated in the areas of podocyte effacement in an age-dependent manner. The same accumulation was found in tKO at a later stage of disease. Nephrin increased in iKO in areas of still preserved footprocesses.

Conclusions: In conclusion, the impaired GBM in Alport-mice has an impact on podocyte function and development of fibrosis. Nephrin and podocin expression is strongly regulated by impaired GBM composition as well as altered signaling to the collagen IV receptors integrin α2β1 and DDR1. The knockout of these collagen receptors in Alport-mice results in preserved expression of nephrin and podocin proteins. Knowledge about the regulatory mechanisms of these interactions could lead to a better understanding of the podocyte behavior in pathological processes, the impact of GBM maturation on podocytes and direct to new therapeutic targets for glomerular diseases.

TH-POS58
MMP-9-Dependent Notch Signalling Contributes to Endothelial-Mesenchymal Transition in Kidney Endothelial Cells
Ye Zhao,1 Yun Zhang,1 Jialin Zhang,2 Guoping Zheng,2 David C. Harris,3 1The University of Sydney; 2Shanxi Medical University; 3First Teaching Hospital of Shanxi Medical University; Children’s Hospital at Westmead, Sydney.

Background: Endothelial-mesenchymal transition (EndoMT) has been shown to be a major source of myofibroblast formation in kidney fibrosis. Previously we showed that MMP-9 induced EndoMT in glomerular endothelial cells. This study investigated whether Notch signalling plays a role MMP-9-induced EndoMT.

Methods: Mouse renal peritubular endothelial cells (MRPECs) were isolated by magnetic microbead separation using anti-CD146 Ab. MRPECs were co-cultured with tubular epithelial cells over a polyester insert to maintain their phenotype. MMP-9 or TGF-β1 failed to induce EndoMT. EndoMT was assessed by morphological changes, immunofluorescence staining and Western blot (WB) of endothelial (CD31 and VE-cadherin) and mesenchymal markers (α-SMA and vimentin). Small name and Notch signalling were examined by RT-PCR and WB. MMP-9 expression was examined by immunohistochemistry.

Results: TGF-β1 (10 ng/ml) and recombinant MMP-9 (2 μg/ml) induced EndoMT in HREGC and MRPEC as evidenced by significant downregulation of VE-cadherin & CD31 and upregulation of α-SMA & vimentin. Recombinant MMP-9 also induced EndoMT in both HREGC’s and MRPECs with upregulation of Notch signalling evidenced by an increase of Notch intracellular domain (NICD) accompanied by a decrease of Notch 1. Inhibition of MMP-9 or Notch signalling demonstrated a dose-dependent response in preventing TGF-β1-induced α-SMA and NICD in HREGCs. MMP-9 deficiency also led to a significant reduction in MMP-9 induced NICD and α-SMA proteins in MRPECs of MMP-9 KO mice.

Conclusions: MMP-9-promoted Notch signalling plays an important role in TGF-β1-induced EndoMT in mouse renal endothelial cells.

Funding: Government Support - Non-U.S.

TH-POS59
ASK1-p38/JNK Signalling Promotes Renal Fibrosis and Apoptosis in the Obstructed Mouse Kidney
David J. Nikolic-Paterson,1 Frank Yuanfang Ma.2 1Dept of Nephrology, Monash Medical Centre, Clayton, Victoria, Australia; 2Dept of Medicine, Monash Univ, Clayton, Victoria, Australia.

Background: Apoptosis signal-regulating kinase 1 (ASK1) is a member of the large mitogen-activated protein kinase kinase (MAP3K) family. ASK1 is activated in response to oxidative stress and then can activate the downstream stress-activated protein kinases, p38 and JNK, which have been implicated in promoting renal fibrosis. The aim of this study was to determine whether ASK1 plays a role in p38/JNK signalling and interstitial fibrosis in experimental kidney disease.

Methods: Unilateral ureteral obstruction (UUO) was induced in groups of 6 wild type (WT) and ASK1 gene deficient (Ask1/-/-) mice. Mice were killed on day 7 after UUO.

Results: Western blotting of UUO kidney identified a 3-5 fold increase in the levels of phosphorylation of ASK1, p38, and JNK compared to the non-obstructed kidney. The WT UUO kidney exhibited marked accumulation of α-SM actin and increased deposition of collagen IV, up-regulation of mRNA levels for pro-fibrotic (Col I, Col IV, α-SMA, PAI-1, TGF-β1) and pro-inflammatory molecules (CCL2), and increased tubular and interstitial cell apoptosis. In contrast, increased activation of p38 and JNK signalling was prevented in Ask1/-/- UUO mice (P<0.001 vs WT UUO). Ask1/-/- UUO mice were protected from renal fibrosis on the basis of: -29% in α-SMA myofibroblasts (P<0.001 vs WT UUO); +53% in macrophage accumulation (P<0.001); +43% in collagen IV deposition (P<0.001); and; -40-51% mRNA levels of pro-fibrotic and pro-inflammatory molecules (all P<0.05). In addition, apoptosis of tubular epithelial cells and interstitial cells was significantly reduced in Ask1/-/- UUO (-37% and +41%, respectively; both P<0.05). However, Ask1/-/- UUO kidney showed no protection from tubular injury based on KIM-1 mRNA levels.

Conclusions: This study shows Ask1 as an important upstream activator of p38 and JNK signalling in the obstructed kidney, and identifies ASK1 as a potential therapeutic target in renal fibrosis.

Funding: Government Support - Non-U.S.

TH-POS60
Kruppel-Like Factor 15 Modulates Renal Interstitial Fibrosis by ERK/MAPK and JNK/MAPK Pathways Regulation
Xiao Gao, Changlin Mei, Guiquan Wu. Kidney Institute of PLA, Changzheng Hospital, Second Military Medical Univ, Shanghai, China.

Background: Renal interstitial fibrosis is a hallmark of progressive chronic kidney disease (CKD). Previous studies reported that kruppel-like factor 15 (KLF15) is an important regulator of cardiac fibrosis and could reduce the expression of extracellular matrix in mesangial cells. However, the role of this transcription factor in renal interstitial fibrosis has not been reported.

Methods: In this study, we examined KLF15 expression in the remnant kidney of 5/6 nephrectomized rats 12 or 24 weeks after operation. In vitro we examined the effect of altered KLF15 expression on the production of extracellular matrix and the pro-fibrotic factor CTGF in rat renal fibroblasts (NRK-49F), and further explored the related mechanisms.

Results: The level of KLF15 was drastically decreased in the renal interstitium of 5/6 nephrectomized rats with progressive interstitial fibrosis, especially at 24 weeks. Our in vitro evidence showed that overexpression of KLF15 repressed basal and TGF-β1-induced extracellular matrix and CTGF in NRK-49F cells. In addition, transfection of growth factor β1 (TGF-β1)-mediated activation of extracellular-regulated kinase (ERK)/ mitogen-activated protein kinase (MAPK) and Jun N-terminal kinase (JNK)/MAPK downregulated KLF15 expression and increased the level of extracellular matrix and CTGF, and all these effects were completely abolished by ERK/S inhibitor and JNK inhibitor in NRK-49F cells.

Conclusions: Our findings implicate that KLF15 plays an important role and may prove to be an antifibrotic factor in renal interstitial fibrosis through regulation of ERK/MAPK and JNK/MAPK signaling pathways.

Funding: Government Support - Non-U.S.
TH-P0561

Background: Fluid and (uremic) toxins are retained in chronic kidney disease (CKD), with their accumulation in plasma (P) and its impact extensively studied. Little attention has been paid to interstitial fluid (IF) and toxin accumulation and their potential physiological impact. We validated IF toxin accumulation using osmotic and mechanical properties in CKD patients.

Methods: Microdialysis (MD), reverse iostiosis (RI), subcutaneous canulae and microcarnes were used to sample IF in CKD patients. IF pressure was measured by the wick-in-needle technique and volume by bioimpedance. Comparisons were made with plasma and with healthy controls.

Results: IF volume was significantly expanded in CKD patients with edema (mean difference with controls 9L; p<0.0009), with plasma and intracellular volumes being similar. IF in CKD patients was a high pressure compartment; mean 4.6±1mmHg (-0.9mmHg in control, p<0.0005). A novel parameter, the edema refill time (ERT) correlated strongly with IF pressure and volume. Small uremic toxins seemed to circulate relatively freely between IF and plasma, with high IF:P correlations for urea, creatinine, urate and phosphate in “steady states” (r=0.74-0.98). Hemodialysis (HD) induced a difference in the IF and plasma decay curves, especially for phosphate where IF decay seemed to lag behind that of plasma (p=0.04). Paired metabolomic (LC/MS/MS) analysis identified at least 36 “small” uremic toxins up to 444Da with similar IF:P ratios. Proteomics revealed a clearly different large molecule expression between P and IF, with IF accumulation of several molecules including known large uremic toxins such as beta-2 microglobulin, complement factor D, IgG kappa light chain, cystatin C and retinol binding protein (IF: P normalized relative abundance 1.5-10.2).

Conclusions: Volume accumulation in CKD is mainly in IF, a high pressure compartment with mechanical properties potentially de...

TH-P0562

Background: PBI-4050 is a first-in-class novel orally active compound which displays anti-inflammatory/anti-fibrotic activities via a novel mechanism of action. PBI-4050 has demonstrated strong anti-fibrotic activities in different kidney fibrosis animal models. PBI-4050 plays a key role in inflammation/fibrosis regulation by reducing pro-fibrotic cytokines, fibrocyte differentiation, myofibroblast activation and epithelial-mesenchymal transition (EMT) resulting in improvement of organ function.

Methods: PBI-4050 was tested in the following animal models: 5/6-nephrectomized rats (end-stage renal failure), doxurubicin-induced nephrotoxicity and renal ischemia (acute kidney injury), and db/db mice (diabetic kidney disease).

Results: Treatment of PBI-4050 reduces fibrosis via the regulation of macrophages, T cells, fibrocytes/fibroblasts/myofibroblasts and epithelial cells. In a pro-fibrotic phase, PBI-4050 plays a regulation role by promoting a Type 1, anti-fibrotic cytokine production phenotype in macrophages and T cells, resulting in a reduction of the over-expression or over-production of TGF-β, MCP-1, CTGF, IL-4, IL-13 and IL-23. Interestingly, MCP-1 is also an inducer of fibrocyte precursor migration in tissue. Fibrocyte differentiation, resident fibroblast activation and EMT are the key sources of activated myofibroblasts and successive accumulation of extracellular matrix protein deposition and fibrosis. PBI-4050 inhibits fibrocyte differentiation, fibroblast activation and EMT as demonstrated by a reduction in alpha smooth muscle actin (α-SMA), collagen I and fibronectin mRNA expression. PBI-4050 also plays a role in tissue remodeling by regulating MMP and TIMP expression.

Conclusions: Taken together, these preclinical results suggest that PBI-4050 offers the potential as a novel therapy for the treatment of kidney fibrosis.

TH-P0563
The RNA-Binding Protein QUAKING Is a Potent Modulator of the Fibrogenic Response to Kidney Injury Ruben de Bruin, Eric P. Van der Veer, Hettie C. de Boer, Jacques Duijns, Erik Biessen, Ton J. Rabelink, Anton Jan Van Zonneveld. Nephrology, LUMC, Pathology, MUMC.

Background: Chronic progressive kidney diseases are characterized by tubulo-interstitial deposition of extracellular matrix, tubular atrophy and dilation. Recruitment of circulating monocytes to sites of tissue injury leads to the local generation of cytokines and growth factors that promote fibroblast activation, proliferation and production of extracellular matrix. We have identified Quaking (Kennedy) as a novel post-transcriptional regulator of both monocyte and fibroblast activation and differentiation, implicating a central position in the pathogenesis of renal fibrosis.

Results: Following FACS sorting of human CD14+CD16-, CD14+CD16+ and CD14-CD16+ monocyte subpopulations, we identified that QKI mRNA is moderately expressed in CD14+CD16+ monocytes, while QKI is potently induced in the activated CD16+ monocytes (n=3, p<0.05). Importantly, the differentiation of monocytes to macrophages by GM-CSF was coupled with a further increase in QKI expression (n=6, p<0.05). Abrogation of QKI in THP-1 and U937 monocytes using lentiviral siRNA reduced cellular adhesion in a novel perfusion assay that simulates endothelial denudation (n=3, p<0.05). In parallel, we investigated the consequences of reduced QKI protein levels in human renal fibroblasts (TK173), which yielded marked attenuation of cellular proliferation, and a perturbed capacity to acquire the myofibroblast phenotype in response to TGF-β1, as evidenced by decreased α-smooth muscle actin and collagen marker expression as compared to wild-type fibroblasts (n=3, p<0.05). Collectively, we identified that QKI serves as a double-edged sword in renal interstitial fibrosis, as it possesses the capacity to drive critical events in both myeloid and mesenchymal cells.

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

TH-P0564
Glomerular Fibrosis Revisited: Podocyte Injury Shuts Down Colla2 mRNA, Leading to Abnormal Collagen Accumulation. Masahiro Koizumi, Masafumi Matsusaka. Tokai Univ School of Medicine, Japan.

Background: Type 1 collagen (Col1a2) accumulates in sclerotic glomeruli, which often occurs as transcriptional upregulation of the Col1a2 genes. On the other hand, our microarray analysis indicated that normal mouse glomeruli abundantly express Colla2 mRNA, which is markedly decreased after podocyte injury. Normal Col is composed of two α1(I) and one α2(I) chains. It has been shown that Colla2a2 mutant mice abnormally accumulated mechanical, homostimulating and deglomerulosclerotic. We hypothesized that podocyte injury downregulates Colla2a2 mRNA, which leads to accumulation of Coll.

Methods: Glomerular Colla2a2 mRNA was quantified by RT-PCR in immunotoxin-inducible podocyte injury mice (NEP25, n=9). Colla2a2 transcriptional activity was also monitored, utilizing Colla2a2-EGFP mice (n=12).

Results: Glomerular Colla2a2 mRNA was decreased to 24% 7 days after induction of podocyte injury, while Colla1a2 mRNA did not change. In non-injured Colla2a2-EGFP mice, EGFP was intensely expressed in podocytes and mesangial cells. Unlike previous reports, immunostaining detected intense Col in normal glomeruli. We next indicated various degrees of podocyte injury in NEP25/Colla2a2-EGFP. Two weeks after high dose toxin, most glomeruli were severely injured with podocyte loss, mesangial expansion and mesangiolysis. EGFP almost disappeared in them. Col staining also declined in the lesion of mesangiolysis. Two weeks after moderate dose toxin, EGFP declined in both podocytes and mesangial cells in glomeruli containing injured podocytes, with EGFP area being 30.5±7.7%, but not in normal glomeruli (30.5±7.8%, p<0.05). Eight weeks after mild podocyte injury, FSGS was established, where EGFP disappeared in sclerotic glomeruli, in which Col was intensely stained.

Conclusions: Collectively, podocyte injury suppresses Colla2a2 mRNA in both podocytes and mesangial cells. The latter, in severe case, causes mesangiolysis. Our study also suggests that prolonged suppression of Colla2a2 may induce accumulation of MMP-resistant α1(I), homostimulating, thereby leading to the characteristic phenotype of glomerulosclerosis.

TH-P0565
A Selective JAK3 Inhibitor, CP690,550, Suppresses Bone Marrow-Derived Fibroblast Activation and Renal Fibrosis. Jinzie Yan, William E. Mitch, Yalin Wang. Dept of Medicine, Div of Nephrology, Baylor College of Medicine, Houston, TX.

Background: Renal fibrosis is the final common manifestation of chronic kidney disease resulting in progressive loss of kidney parenchyma and renal function. We have recently demonstrated that bone marrow-derived fibroblast precursors contribute significantly to the pathogenesis of renal fibrosis. However, the signaling mechanisms underlying the activation of bone marrow-derived fibroblast precursors in the kidney are not fully understood. In this study, we investigated the role of JAK3/STAT6 signaling pathway in the activation of bone marrow-derived fibroblasts using a selective JAK3 inhibitor, CP690,550.

Methods: We examined the role of JAK3/STAT6 signaling in monocyte-to-fibroblast transition in vitro and myeloid fibroblast activation and renal fibrosis induced by unilateral ureteral obstruction.

Results: In cultured mouse monocytes, pro-fibrotic cytokines IL-4 and IL-13 activated STAT6 and induced expression of fibroblast marker (α-smooth muscle actin and extracellular matrix proteins (fibronectin and type 1 collagen), which was blocked by CP690,550. Obstructive injury led to activation of STAT6 in the interstitial cells of the kidney, which was abolished by treatment with CP690,550. Furthermore, mice treated with CP690,550 accumulated fewer bone marrow-derived fibroblasts in the kidneys after the obstructive injury compared with vehicle-treated mice. Finally, treatment with CP690,550 significantly reduced myofibroblast activation and suppressed expression of fibronectin and type I collagen in response to the obstructive injury.

Conclusions: Our results demonstrate that JAK3/STAT6 signaling plays an important role in the activation of bone marrow-derived fibroblasts during the development of renal fibrosis. CP690,550 may serve as a novel therapeutic agent for the treatment of chronic kidney disease.

Funding: NIDDK Support
Background: Chronic kidney diseases (CKDs) affect millions and are leading cause of morbidity and mortality in Western world. Renal fibrosis is an uncontrolled wound-healing process defined by excessive deposition of the extracellular matrix (ECM). Recently, the determinative role of interleukin (IL)-17 has been suggested in matrix metalloproteinases (MMP) dependent ECM remodeling. However, the role of MMP12 in progressive kidney disease is still unknown.

Methods: Unilateral ureteral obstruction induced (UUO) mice model of renal fibrosis on C57Bl/6J (WT) and IL17 KO mice and HK2 proximal tubular epithelial (PTEC) and NRK-49F renal fibroblasts were used in our experiments.

Results: 5 days after the onset of UUO the number of IL17+ T cells was elevated in the kidney. Simultaneously the number of MMP12 positive PTECs increased in WT but not in IL17 KO mice. IL17 treatment of the HK2 cells resulted in a NK dependent increase in the number of MMP12+ cells. eMMP12 treatment of NRK49F cells increased the proliferation and collagen production of the fibroblasts. Specific MMP12 inhibitor treatment of WT animals decreased the level of renal αSMA and collagen1.

Conclusions: Our data suggest that PTECs are responsible for the production of MMP12 in the fibrotic kidney. According to our observations MMP12 may be a link between inflammation and the severity of renal fibrosis. Moreover, beside the previously hypothesised role of MMP12 on ECM degradation we suggest that MMP12 may directly act on renal fibrosis by inducing proliferation and ECM production of renal fibroblasts.

Funding: Government Support - Non-U.S.

TH-PO567

Proximal Tubule PPARα/β Attenuates Renal Fibrosis and Inflammation Caused by Unilateral Ureteral Obstruction (UUO) Shenvan Li,1,2 Nithya Mariappan,1,2 Judit Megyesi,1,2 Brian B. Shank,1,2 Sue Thues,1,2 Peter M. Price,1,2 Jeremy Stuart Dubfield,1,2 Didier Portilla,1,2 ‘Medicine/ Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR; 2Medicine, Central Arkansas Veterans Healthcare Systems, Little Rock, AR.

Background: Previous studies suggest that activation of proximal tubule PPARα reduces inflammation and ameliorates tissue fibrosis but the mechanisms involved are not clear.

Methods: We compared the effects of UUO on wild type and proximal tubule PPARα Tg mice and also examined the effects of increased PPARα expression using adenovirus transduction in cultured mouse proximal tubules exposed to arachidonic acid.

Results: After 5 days of UUO PPARα expression was significantly reduced in kidney tissue of wild type mice but this down-regulation was attenuated in PPARα Tg mice. When compared with wild type mice subjected to UUO, PPARα Tg mice had reduced mRNA and protein expression of proximal tubule TGFβ1, with reduced production of extracellular matrix proteins including collagen 1, fibronectin, α-SMA, and reduced tubulo-interstitial fibrosis. Western blot-mediated increased expression of microRNA 21 in kidney tissue was also reduced in PPARα Tg mice. Over-expression of PPARα in cultured proximal tubular cells by adenoviral transduction reduced arachidonic acid (AA)-mediated increased production of TGFβ, collagen4, and laminin B demonstrating PPARα protected AA-induced TBM degradation. Flow cytometry studies of dissociated whole kidneys demonstrated reduced macrophage infiltration to kidney tissue in PPARα Tg mice after UUO. Increased expression of pro-inflammatory cytokines including IL1-β, IL-6, and TNF-α in wild type mice was also significantly reduced in kidney tissue of PPARα Tg mice. In contrast, the expression of anti-inflammatory cytokines IL-10 and Arginase-1 was significantly increased in kidney tissue of PPARα Tg mice when compared with wild type mice subjected to UUO.

Conclusions: Our studies demonstrate several mechanisms by which preserved expression of proximal tubule PPARα reduces tubulo-interstitial fibrosis and inflammation associated with obstructive uropathy.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO568

Myeloid Cells-Derived Tissue-Type Plasminogen Activator Promotes Renal Fibrosis and Inflammation Ling Lin,2 Kebin Hu,1 Dept. of Medicine, Penn State Univ College of Medicine, Hershey, PA.

Background: Tissue-type plasminogen activator (tPA), a serine protease up-regulated during chronic kidney disease, has been shown to promote renal fibrosis and inflammation by activating various signaling cascades. However, the origin and the responsible cells of the activated IPA signaling remain unknown.

Methods: We created chimeric mice that lack IPA in either their myeloid cells or renal parenchyma by bone marrow transplantation between IPA wild-type (WT) and knockout (KO) mice using the following donor/recipient combinations: WT/WT, WT/KO, KO/WT and KO/KO, and subjected these mice to unilateral ureteral obstruction for 7 days, followed by evaluation of renal damages, fibrosis, and inflammation.

Results: It was found that WT/WT and WT/KO mice showed diminished level of tubulointerstitial injuries, fibrosis, and inflammation as demonstrated by HE staining. Western blot or immune fluorescence staining for α-SMA and collagen1, as well as quantitative PCR for chemokines. However, KO/WT and KO/KO mice showed lower level of damages and decreased fibrosis and inflammation than that from WT/WT and WT/Ko mice, suggesting that mice that lack of IPA in the myeloid cells were protected from fibrotic and inflammatory injuries.

Conclusions: Thus, it is plausible that myeloid cells contribute to IPA signaling in response to chronic kidney injury.

Funding: Private Foundation Support

TH-PO569

Fibrogenic Pathways Are Activated by the Macrophage Phagocytic Receptor CD36 with Apoptotic Cell Clearance Daryl M. Okamura,1 Lixia Zeng,2 Ikuyo Yamaguchi,3 Subramaniam Pennathur.4 'Dept of Pediatrics, Div of Nephrology, Seattle Childrens Research Institute, Seattle, WA; 4Dept of Internal Medicine, Div of Nephrology, Univ of Michigan, Ann Arbor, MI.

Background: The progression of chronic kidney disease is due to a maladaptive wound healing response where tubular apoptosis and macrophage activation are two important processes. The removal of apoptotic cells is an innate function of tissue macrophages (mphi), however, its role in disease progression is unclear.

Methods: The present study was designed to investigate the role of mphi CD36, a recognized receptor of apoptotic cells, by unilateral ureteral obstruction (UUO). In order to differentiate the mphi CD36-specific effects in vivo, we generated CD36 chimeric mice by bone marrow transplantation and performed UUO surgery: CD36 ko/wt (donor/recipient) with chimeric controls.

Results: CD36 expression is up-regulated with M2 activation. After UUO, CD36 mphi comprised 30-50% of the phagocytic subpopulation. Following phagocytosis of apoptotic cells, there was 65-75% reduction in TNF-α and TGF-b mRNA levels in CD36+/− compared to CD36+/+ mphi. Fibrosis severity was decreased by 41% and fibronectin and procollagen mRNA levels were decreased by 40-50% in CD36 ko/wt mice at day 14. There was a 30% decrease in NF-κB activation in CD36 ko/wt mice at day 14 after UUO compared to CD36 wt/wt mice. There was a 60-70% reduction in kidney TGF-b and TGF-α mRNA levels in CD36 ko/wt mice after UUO. Since oxidized phospholipids/lipids are the major ligands for CD36, we measured the level of apoptotic cells by TUNEL staining. We found that there was a 56% increase in TUNEL+ cells in CD36/k0/wt at day 14 despite a reduction in fibrosis severity. Furthermore, mphi isolated from UUO kidneys demonstrated that there was 40-50% reduction in lipid hydroperoxides and a 60-70% reduction in F2 isoprostane levels in CD36−/− compared to CD36+/+ mphi at day 14.

Conclusions: These data suggest that mphi CD36 is a critical regulator of fibrogenic signaling and extracellular matrix expansion during chronic kidney injury and suggests that oxidative mechanisms may play a key role in mediating these pathways.

Funding: NIDDK Support

TH-PO570

Tissue Remodeling Induced by Indoxyl Sulfate and p-Cresol Sulfate: Roles of Epidermal Growth Factor Receptor Activation Chiao-Yin Sun,1,2 Ling-Hsiung Hsueh,3 Chiau-Jong Hsu,3 Ling-Chin Wang,31,2 Chi-Chuan Ko,2,3 Ching-Chang Chang,2,31,2 Chi-Chieh Hsu,3 Shih-Chieh Hsueh,3 Chang-Shih Kuo,3 Ching-Jueh Yu,3 Ching-Chang Chang,2,31,2 Chang-Chi Su,3 Kuei-Yu Lin,3 Shing-Ching Lin,3 Yuan-Chung Liu,3 Chihsuen Lin,3 Chiao-Yin Sun,1,2 Ting-Chun Lin,3 Min-Hung Chuang,3 Chiao-Yin Sun,1,2,3

Background: Uremic toxins have determinant roles in the progression of chronic kidney disease clinically. Indoxyl sulfate (IS) and p-cresol sulfate (PCS) could cause renal fibrosis by activating RAAS. Epidermal Growth Factor (EGF) is known for its role in promoting cell cause proliferation and matrix deposition. It is hypothesized that EGFR activated by IS and PCS might cause renal tissue remodeling and fibrosis.

Methods: Cultured renal tubular cells (HK2) and B-6 mice with ½-nephrectomy were made based on the x-ray structure of extra-cellular domains of EGFR. The results showed that IS/PCS interacted with extracellular domains of EGFR near the EGF binding site by the hydrophobic force. EGFR dimerization and phosphorylation increased by IS and PCS in vitro. IS and PCS activated EGFR downstream signaling proteins (Jak1, and Stat3) in vitro. Increased cell membrane localization of EGFR was noted in vitro.

Results: Docking models for the putative interaction between IS/PCS and EGFR were made based on the x-ray structure of extra-cellular domains of EGFR. The results showed that IS/PCS interacted with extracellular domains of EGFR near the EGF binding site by the hydrophobic force. EGFR dimerization and phosphorylation increased by IS and PCS in vitro. IS and PCS activated EGFR downstream signaling proteins (Jak1, and Stat3) in vitro.

Funding: NIDDK Support
IS and PCS increased MMP2 and MMP9 expression in *vivo*, which was antagonized by N-acetylcysteine and EGF inhibitor. In *vivo* study with 1/2 nephrectomy mice showed that IS and PCS significantly increased the serum EGF concentration and renal EGF phosphorylation. IS and PCS also increased renal MMP2 and MMP9 expression *significantly in vivo*.

**Conclusions:** It was suggested that IS and PCS could activate EGF via a ligand independent and dependent pathway by direct EGF binding and increasing EGF level. The EGF activation might induce renal tissue remodeling by increasing the expression of MMPs.

**TH-PO571**

**Participation of WNT Protein in Acute Kidney Injury**

Akhiro Kuma, Tetsu Miyamoto, Ryota Serino, Narutoshi Kabashima, Masahito Tamura, Yutaka Otsuji. The Second Dept of Internal Medicine, School of Medicine, Univ of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan.

**Background:** Acute kidney injury (AKI) can recover or progress to chronic kidney disease (CKD) or end-stage renal disease. Furthermore, kidney fibrosis which is not effectively treated can lead to renal failure. WNT family proteins have been implicated in organ fibrosis. Although previous studies revealed the expression of WNT10A in fibroblasts, the mechanisms of such expression have been elusive. We focused on kidney fibrosis following interstitial fibrosis in AKI and investigated the function of WNT10A fibroblasts.

**Methods:** Expressions of WNT10A were confirmed by immunohistochemical staining in kidney biopsy tissue from 25 male AKI patients (age, >60 years) who were received biopsy to diagnose cause of AKI in the past 6 years. In *vivo*, we used COS1(kidney fibroblasts of African green monkey) transfection of WNT10A plasmid (COS1-W10). The COS1-W10 was injected cell survival ability and proliferation against oxidative stress and high glucose stress.

**Results:** 10 Patients with WNT10A expression had a significantly lower estimated glomerular filtration rate than 15 WNT10A-negative patients (15.2 ± 8.5 vs 46.5 ± 36.9 mL/min per 1.73m², p = 0.015). COS1-W10 exhibited cell survival ability and proliferation against oxidative stress induced hydrogen oxide (p < 0.05), and the COS1-vector reduced the proliferation rate in high-glucose medium (11mM and 22mM) compared with low-glucose medium (5.5mM). However, COS1-W10 maintained proliferation ability in high-glucose medium (p < 0.05).

**Conclusions:** WNT10A expression protects fibroblasts from oxidative stress and high glucose stress. Taken together, expression of WNT10A protein in kidney fibroblasts in AKI might lead to CKD. Therefore, inhibition of WNT10A protein can improve kidney function in AKI patients and prevent progression to kidney dysfunction.

**TH-PO572**

**Hyaluronan Exacerbates Renal Fibrosis in NZB/W Mice through Increased Monocyte Chemotactic Protein-1 and Transforming Growth Factor-β Secretion by Mesangial Cells**

Susan Yang, Wan Wai Tse, Mel Chau, Daniel Tak Mao Chan. Dept of Medicine, The Univ of Hong Kong, Hong Kong.

**Background:** Lupus nephritis is characterized by the production of anti-dsDNA antibodies and immune-mediated renal injury leading to glomerular and tubulointerstitial fibrosis. We have previously demonstrated that circulating hyaluronan (HA) level and glomerular HA expression are increased in patients and lupus-prone mice with active lupus nephritis, and are associated with increased glomerular matrix protein accumulation. This study investigates the role of HA on disease manifestations and renal fibrogenesis in a murine model of lupus nephritis.

**Methods:** Pre-disease female NZB/W mice were randomized to receive sterile PBS or high molecular weight HA by tail-vein injection (1mg/ml, 200μl) once weekly for periods up to 24 weeks, after which the mice were sacrificed, blood and urine collected, and kidneys harvested to assess renal histology and expression of fibrosis mediators. Mesangial cells were isolated from the renal cortex of NZB/W mice to investigate the mechanisms that mediate increased HA synthesis.

**Results:** Treatment of mice with HA had no effect on survival, proteinuria or anti-dsDNA antibody level compared to control mice, but was associated with increased glomerular IgG and C3 deposition, significantly increased glomerular and tubulointerstitial expression of HA receptor CD44, MCP-1, TGF-β1, fibronectin and collagen type I from 18 to 24 weeks. Exogenous HA for 24h had no effect on mesangial cell proliferation, but significantly increased CD44, HA synthase III, fibronectin, laminin and collagen synthesis, in part through the induction of MCP-1 and TGF-β1 secretion (P<0.01 for both). Stimulation of mesangial cells with exogenous MCP-1 and TGF-β1 significantly increased cell associated and secreted HA levels respectively (P<0.05 for both).

**Conclusions:** These results suggest that HA plays a significant role in renal fibrosis of lupus nephritis by inducing MCP-1 and TGF-β1 secretion, which in turn increase HA synthesis resulting in a positive feedback loop that amplifies the fibrotic process.

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

**TH-PO573**

**Periostin Staining as Novel Biomarker in Progressive Glomerular Injury**

Bancha Satirapoj, 1 Wiwat Charungkiattikul, 1 Peepattra Wantanasiri, 2 Prajee Ruangkanchanasert, 1 Naowanan Nata, 1 Ouppatham Supasandy, 1 Panbabpa Chovochivan, 1 "Div of Nephrology, Dept of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand; 2 Dept of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Bangkok, Thailand.

**Background:** Periostin (an embryonic fibronectin, FN) is a common known component of the extracellular matrix which facilitate fibrotic activation and collagen deposition. The alternative splicing away from EDA inclusion could provide a therapy to treat human chronic kidney disease.

**Methods:** In a pilot study 20 ASO targeting overlapping sequence within both exon-intron junctions were assessed for their ability to inhibit EDA+ protein and mRNA in primary tubule epithelial cells. Selected ASOs were administered pre and post TGFβ1.

**Conclusions:** Periostin staining was predominantly located in the injured regions and the sites of fibrosis including periglomerular and tubulointerstitial areas. Periostin staining had significantly increased patients with LN (14.97±8.41, p=0.02) and IgAN (18.50±9.69, p=0.01) when compared to MCD patients (5.80±4.76). Periostin staining correlated positively with renal activity index in GN patients. It also correlated positively with renal chronicity index in GN and LN patients. Multivariate analysis, renal perirostin was inversely related to GFR. After a median follow-up of 34 weeks, a trend for declining of GFR was found in patients with higher periostin scores (-0.19 [Q2.1 to 0.46] vs -0.05 [Q2.54 to 0.46] 3m/mn/1.73 m²/mun, p=0.239), and higher periostin scores were not predictor of end stage renal disease.

**Conclusions:** Periostin is markedly induced in glomerular disease and the levels correlated positively with the severity of renal lesions. Periostin staining may serve as a marker of progressive glomerular injury.

**TH-PO574**

**Antisense Oligonucleotides Targeting Kirsten Ras Reduce Interstitial Fibrosis and Protect Kidney Function in the Chronic Folic Acid Nephropathy Model**

Lucy Jade Newbury, 1 Gene Hung, 2 Bruce M. Hendry, 1 Claire C. Sharpe. 1 Dept of Renal Sciences, Kings College London, London, United Kingdom; 2 Isis Pharmaceuticals, Carlsbad, CA.

**Background:** Previously we have demonstrated the importance of Kirsten Ras (Kras) in the pathogenesis of renal fibrosis secondary to ureteric obstruction. In this study we have characterised a novel mouse model of chronic folic acid nephropathy (CFAN) and have used antisense oligonucleotides (ASO) to silence Kras expression within this model. Here we report the effects of these ASOs on interstitial fibrosis and renal function.

**Methods:** CFAN model: Male CD1 mice were given Folic acid (FA) 125mg/kg iv in NaHCO3, on day 0 (d0) and d21. Shams received NaHCO3, CFAN and Shams were sacrificed at d35, d56 and d85 for model characterisation. Therapeutic study: CFAN groups received saline (vehicle) or ASO (20mg/kg) SC 3X per week from d35 reducing to 2X per week from d49 and were sacrificed at d85.

**Results:** CFAN model: Induction of fibrosis was seen at d56 and d85 with a 3.4 fold mean increase in collagen staining and a 2 fold increase in collagen mRNA by ASO injection. At d85 CFAN and Shams were sacrificed and collagen and fibronectin were stained. Therapeutic study: ASO groups received saline (vehicle) or ASO (20mg/kg) SC 3X per week from d35 reducing to 2X per week from d49 and were sacrificed at d85.

**Conclusions:** CFAN model: Induction of fibrosis was seen at d56 and d85 with a 3.4 fold mean increase in collagen staining and a 2 fold increase in collagen mRNA by ASO injection. At d85 CFAN and Shams were sacrificed and collagen and fibronectin were stained. Therapeutic study: ASO groups received saline (vehicle) or ASO (20mg/kg) SC 3X per week from d35 reducing to 2X per week from d49 and were sacrificed at d85.

**Conclusions:** We report the effects of these ASOs on interstitial fibrosis and renal function.

**TH-PO575**

**Modulating Alternative Splicing of Fibronectin with Antisense Oligonucleotides**

Felicia Heidebrecht, 1 Vaishnavi Gnanananthan, 1 Benjaman To, 1 Frank Rigo, 1 Susan M. Freier, 2 Mark Edward Dockrell. 1 SWT Institute for Renal Research, London, United Kingdom; 2 Isis Pharmaceuticals, Carlsbad, CA.

**Background:** The EDА+ splice variant of Fibronectin(Fn) is an important component of fribroic extracellular matrix facilitating fibroblast activation and collagen deposition. Directing the alternative splicing away from EDА inclusion could provide a therapy to limit fibrosis. The aim of this study was to test the possibility of modulating the TGFβ1-induced Fn splicing using RNase-H independent antisense oligonucleotides (ASO).

**Methods:** In a pilot study 20 ASOs targeting overlapping sequence within both exon-intron junctions were assessed for their ability to inhibit EDА+ protein and mRNA in primary tubule epithelial cells. Selected ASOs were administered pre and post TGFβ1.
TH-PO576
Gremlin1 Displays Differential Affinities for Bone Morphogenetic Proteins – Implications for Diabetic Nephropathy
Derek P. Brazil, Rachel Church, Arjun Krishnakumar, Stefan Geschwindner, Barbo Basta, Maria Stromstedt, Finian Martin.
1Centre for Vision and Vascular Science, Queen’s Univ, Belfast, United Kingdom; 2Dept of Pathology, University of Newcastle upon Tyne, Newcastle, Tyne, 3AstraZeneca, Gothenburg, Sweden.

Background: Grem1 is a secreted glycoprotein that limits the action of bone morphogenetic proteins (BMP) in multiple cell types in the body. Grem1 dimers bind directly to BMP dimers preventing binding to their membrane receptors. Our group has shown that levels of Grem1 increase in the kidneys of patients with DN, and correlate well with decreased renal function. We also demonstrated that mice lacking one copy of the grem1 gene are partially protected from early DN-like changes.

Methods: Therefore, the aim of this project was to determine the relative affinities of Grem1 for various pro- and anti-fibrotic BMPs in vitro and in vivo.

Results: Surface plasmon resonance (Biacore) kinetic and affinity analysis allowed us to rank order of affinity for Grem1 to be determined with BMP-2 > 27 > 4 > 6 > 7. In HK-2 cells, the addition of 25ng/ml rhGrem1 caused complete inhibition of pSmad1/5/8 phosphorylation, whereas cells treated with rhBMP-4 required 200ng/ml rhGrem1 for maximal inhibition. Consistently, higher concentrations of Grem1 were required to inhibit BMP4-mediated gene expression in HK2 cells compared to BMP2, with little or no inhibition of BMP7 responses seen. Overexpression of Grem1 inhibited BMP2 and 4, but not BMP7-mediated Smad1/5/8 phosphorylation. Analysis of grem1 +/- mice on a mixed genetic background showed that these mice survive post-natally, are smaller, and develop only one kidney that is larger than wild-type controls and display tubular damage.

Conclusions: Our data suggest that in the extracellular milieu of the diabetic kidney, secreted Grem1 is more likely to bind BMP2 than BMP4. In addition, grem1 +/- mice are viable and will be further analysed to determine which BMPs are involved during the critical stages of BMP-driven kidney development. These mice will also be useful tools to determine if the absence of Grem1 in the kidney can protect against DN, further validating current efforts to target Grem1 protein in human kidney disease.

TH-PO577
Automated Quantitation of Interstitial Fibrosis by Sirius Red Staining/ Polarization Microscopy Is More Objective Than Masson Trichrome
Jonathan Street, Alejandro Alvarez-Prats, Taro Horino, Xuzhen Hu, Robert A. Star, Peter S.T. Yuan. NIDDK, NIH, Bethesda, MD.

Background: Histological measurement of interstitial fibrosis by Masson Trichrome staining is only semi-quantitative because of subjective scoring by an ordinal scale, which limits statistical power. Sirius Red staining enhances the birefringence of type 1 and III collagen fibrils which appear bright against a dark background with polarization contrast microscopy. This striking contrast is more amenable to automated analysis than the subtle color differences of Masson Trichrome. An automated technique to measure the fibrotic area and fibrosis index to reduce the inter- and intra-degree of errors in HK-2 cells compared to BMP2, with little or no inhibition of BMP7 responses seen. Overexpression of Grem1 inhibited BMP2 and 4, but not BMP7-mediated Smad1/5/8 phosphorylation. Analysis of grem1 +/- mice on a mixed genetic background showed that these mice survive post-natally, are smaller, and develop only one kidney that is larger than wild-type controls and display tubular damage.

Conclusions: Our data suggest that in the extracellular milieu of the diabetic kidney, secreted Grem1 is more likely to bind BMP2 than BMP4. In addition, grem1 +/- mice are viable and will be further analysed to determine which BMPs are involved during the critical stages of BMP-driven kidney development. These mice will also be useful tools to determine if the absence of Grem1 in the kidney can protect against DN, further validating current efforts to target Grem1 protein in human kidney disease.

TH-PO578
Comprehensive Analysis of Hypoxia-Regulated Gene Transcripts in Chronic Kidney Disease and Renal Cells
Nataliya Shvey, Maria Luidenmeyer, Matthias Kreutzer, Peter Wild, Christian Dahmen.
1Univ of Zurich, Zurich, Switzerland; 2Univ Hospital Zurich, Zurich, Switzerland; 3Univ of Michigan, Ann Arbor.

Background: Most chronic kidney diseases (CKD) are initiated as glomerular damage with loss of glomerular capillaries. The best morphologic indicator of disease progression and development of end-stage renal disease, however, is interstitial fibrosis accompanied by capillary rarefaction. As hypoxia has been associated with fibrosis the question arises whether renal cells indeed face hypoxia in CKD and respond with a transcriptional program which could lead to progression of renal disease.

Methods: Proximal tubular cells (HK-2 cells) and podocytes with stable hypoxia-induced transcription factors (HIF1α and/or HIF2α) suppression were generated. Gene expression profiles from cell lines and more than 160 renal biopsies from patients with different CKD stages were obtained using Affymetrix arrays.

Results: Expression of hypoxia-associated genes in genome-wide expression profiles revealed correlation of HIF-target genes with eGFR in the cortical tubulointerstitial and glomerular samples. These correlations were both positive and negative and in part compartment-specific. To study the cell-type specific response to hypoxia and the relevance of given HIFs we investigated gene expression profile of HK-2 cells and podocytes with stable HIF1α and/or HIF2α suppression under hypoxic conditions. In HK-2 cells hypoxia analysis revealed 163 (86% HIF1α and/or HIF2α dependent) significantly upregulated and 31 (81%) downregulated hypoxia target genes. In podocytes, 416 (47% HIF1α and/or HIF2α dependent) genes were significantly up- and 318 (95%) downregulated. To validate the results on protein level immunohistochemistry of HIF-target genes in human biopsies with different eGFRs was established and showed a similar pattern to correlation analysis.

Conclusions: Our gene expression studies do not indicate an over-all hypoxic milieu in acquired kidney diseases. However, the data clearly point to compartment- and cell-type-specific dysregulation of hypoxia-associated gene transcripts.

TH-PO579
Transcriptome Analysis of Human Hypertensive Chronic Kidney Disease Highlights the Role of Peroxisome Proliferator-Activated Receptor (PPAR) Pathway in Tubulointerstitial Fibrosis
Hyun Mi Kang, Peter Choi, Jinliang Tao, Sang Youb Han, Ae Seo Deck Park, Yi-An Ko, Katalin Susztak.
1Renal Electrolyte and Hypertension Div, Univ of Pennsylvania, Philadelphia; 2Dept of Medicine, Ilsan Paik Hospital, Korea.

Background: Hypertensive chronic kidney disease (H-CKD) is the second most common cause of end stage renal disease in the United States. Very little is known about the pathomechanism of H-CKD. Here we perform gene expression analysis on tubule samples obtained from control, hypertension and H-CKD patients to catalogue differentially expressed genes and pathways. The results were compared mouse models of kidney fibrosis.

Methods: Human kidney tissues (n=92) were obtained from elective nephrectomies and they were grouped based on the clinical and histological parameters. Tubular epithelial cells were isolated by manual microdissection. Affymetrix GeneChip expression arrays (U133A 2.0) were used to analyze transcript levels. We also cultured renal epithelial primary cells from control and H-CKD samples. The results were compared mouse models of non-diabetic kidney fibrosis induced by Notch overexpression or folic acid administration.

Results: We identified 1,792 differentially expressed probesets in CKD tubules, with 1372 unique gene transcripts. Among them, the probesets with the highest fold change were albumin, EGF, and uromodulin known to play a role in CKD. Pathway analysis highlighted differences in PPAR alpha and gamma signaling. Lipid oxidation, mitochondrial biogenesis and lipid synthesis pathways were also differentially expressed. We also found that these pathways are also regulated in mouse models of fibrosis induced by folic acid administration or Notch1 overexpression. PPARs seems to have a direct role in fibrosis development as cell type (mesangial, tubular) and expression variability significantly reduced the expression of fibronectin, collagen1, SMAD7 and sMMA following TGFβ1 treatment.

Conclusions: This is the first genome wide transcriptome analysis of tubular epithelial cells in human hypertensive nephropathy. These results demonstrate that PPAR pathways are regulated in the H-CKD and PPAR agonists could present a novel treatment approach in H-CKD patients.

TH-PO580
Thrombin-activated Fibroinhibin Inhibitor (TAFI) Inhibition Increases Survival and Halts the Progression of Renal Fibrosis in the Rat 5/6th Subtotal Nephrectomy Model
John M. Atkinson, Nick Pullen, Timothy Scott Johnson.
1Sheffield Kidney Institute, United Kingdom; 2Pifer PGRD.

Background: Previously we reported that application of the TAFI inhibitor UK 39082 increased plasmamin activity & reduced ECM levels Induced by high glucose treatment of NRR252 cells.

sections is more easily automated and would support high-throughput preclinical screening of anti-fibrotic therapeutics and validation of non-invasive biomarkers for interstitial fibrosis.

Funding: NIDDK Support

Funding: Private Foundation Support

Funding: Government Support - Non-U.S.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author/disclosure.
Methods: To test whether TAFI inhibition could inhibit renal fibrosis and improve renal function, we tested UK-396082 in the 5/6 subtotal nephrectomy (SNx) rats in a preventive & remission phase. Rats were fed normal diet or chow containing UK-396082 (60mg/kg/d) from day 12 post SNx (prevention, p) or 35 (remission, r). Results: Serum TAFI activity increased & plasmin activity decreased in untreated SNx animals. UK-396082 reduced TAFI activity (45%–30%, p/r) & increased plasmin activity (52%–52%, p/r). 16% of untreated SNx rats survived to d60 c.f. 80% treated from d14. 75% of SNx rats receiving UK-396082 from d35 survived to d60 c.f. 27% left untreated. Creatinine clearance increased (+35%, p/r), while serum creatinine (+35%–29%, p/r) & urea fell (-65%–32%). Tubular damage biomarkers NGAL (-31%–24%, p/r) & KIM-1 (-68%–31%, p/r) were lower in urine. Scarring was ameliorated as measured by Masson’s Trichrome staining (-77%–45%, tubules/glomeruli) due to decreases in collagen I (-60%–52%), IV (-57%–52%) and III (-55%). Collagen synthesis was also measured. In a mixed cohort of CKD patients, serum TAFI activity was 1.5x elevated c.f. normal individuals serum and TAFI activity showed a strong correlation with the extent of renal function impairment.

Conclusions: In conclusion, we demonstrate here that TAFI inhibition with UK-396082 is highly effective in the rat SNx model. Collagen reduction suggests some benefit is by protecting plasmin activation of matrix metalloproteinases as collagen are poor plasmin substrates. These data support the hypothesis that TAFI is a potential therapeutic target for CKD.

Funding: Pharmaceutical Company Support - Pfizer

TH-PO581
Biglycan Fragmentation Is Associated to Survival in Patients Undergoing Hemodialysis
Federica Genovese,1 Diana Julie Leeming,1 Morten Asser Anders Karsdal,1 Alexandra Scholz,1 Martin Tepel.1 Biomarkers and Research, Nordic Bioscience, Herlev, Denmark; 2Nephrology, Institute for Molecular Medicine, Cardiovascular and Renal Research, Odense, Denmark.

Background: Biglycan is a small leucine-rich proteoglycan which is found in the extracellular matrix (ECM) of many organs, including kidneys. It is a key regulator of lateral assembly of collagen fibers and by binding to TGF-β, biglycan is able to inhibit its activity. MMP-mediated tissue turnover has clearly been described to be associated with many connective tissue diseases. BGM is a neo-epitope of biglycan generated by matrix metalloproteinase-9 (MMP-9) degradation and has previously been associated with ECM remodelling and fibrosis. The objective of the study was to investigate the association of plasma BGM levels with survival among hemodialysis patients.

Methods: BGM was measured by means of a specific enzyme-linked immunosorbent assay (ELISA) in an observational cohort study of 371 hemodialysis patients followed-up for 5 years. Survival was analyzed in an adjusted Cox model.

Results: Hemodialysis patients with a plasma BGM concentration higher than the median of 7.87 ng/mL had increased risk of death (hazard ratio, 1.35; 95% confidence interval, 1.01 to 1.81), with a survival of 388 days compared to 744 days. Multivariable-adjusted Cox regression showed increased odds for death with higher age and higher BGM concentrations.

Conclusions: Biglycan fragmentation can lead to TGF-β release and activation, with a consequent worsening of the fibrotic process and it is highly deposited in sites affected by fibrotic tissue. It is the first report of a fibrosis biomarker in patients with chronic kidney disease whose longitudinal monitoring might be associated with the progression of renal fibrosis and mortality in kidney failure has been observed.

TH-PO582
Tamoxifen Ameliorates UUO-Induced Tubulointerstitial Fibrosis by Modulation of Renal TGF-β1/Smad Pathway in Mice
Kyung Pio Kang, Dal Kim, Aesin Lee, Yujin Jung, Sik Lee, Won Kim. Internal Medicine, Chonbuk National Univ Medical School, Jeonju, Korea.

Background: After insult to the kidney, renal fibrotic process is initiated with sustained inflammation, activation of matrix-producing fibroblast and accumulation of extracellular matrix, which is part of repair process. Tamoxifen, known as selective estrogen receptor modulator, has been used anti-estrogen for the prevention and treatment of the breast cancer and also has antifibrotic properties. Therefore, we investigated the effect of tamoxifen on unilateral ureteral obstruction (UO)-induced renal tubulointerstitial fibrosis and their mechanism.

Methods: Renal fibrosis was induced by UUO in the six-week-old C57BL/6 mice for 14 days. Tamoxifen (50 mg/kg) was treated by oral for 5 days before induction of renal fibrosis. Histologic examination and Western blot analysis for α-SMA, vimentin, fibronectin and ICAM-1 were performed. We also evaluated TGF-β1/Smad signaling pathway after ureteral obstruction.

Results: Renal tubular injury and fibrosis was increased after ureteral obstruction. The number of FSP1 (+) fibroblast and expression of α-SMA (+) myofibroblast were increased in UUO kidney. Tamoxifen treatment significantly decreased UUO-induced fibrosis by upregulation of α-SMA (+) and fibronectin (+) in the peritubular interstitium. Tamoxifen treatment significantly decreased UUO-induced ER-HR3 (+) macrophage infiltration and ICAM-1 expression. Finally, tamoxifen was effectively suppressed UUO-induced activation of TGF-β1/Smad signaling.

Conclusions: These results suggest that tamoxifen has a beneficial effect on UUO-induced tubulointerstitial fibrosis and inflammation by modulation of renal TGF-β1/Smad pathway.

Funding: Government Support - Non-U.S.

TH-PO583
Silencing of Pericyte MicroRNA-132 Reduces Renal Fibrosis and Myofibroblast Proliferation and Is Associated with Altered Sirt1 and ER-HR3 Expression
Roel Buikers,1 Jacques van der Laan,1 Rebekka T. M. Dymburg,1 Benjamin D. Humphreys,2 Anton Van Zonneveld,3 Nephrology and Endothel Research Laboratory for Experimental Vascular Medicine, LUMC, Netherlands; 2Renal Div, Dept of Medicine, Brigham and Women’s Hospital and Harvard Medical School.

Background: Lineage analysis has shown that during nephrogenesis, FoxD1-positive mesenchymal cells give rise to adult interstitial pericytes. These FoxD1-derived interstitial (FDI) cells expand and differentiate into smooth muscle actin (u-SMA)+ positive myofibroblasts during renal fibrosis, accounting for a large majority of myofibroblasts. MicroRNAs (miRNAs) involved in this differentiation could serve as a target to decrease myofibroblast formation in fibrotic kidney disease.

Methods: Fibrosis was induced in FoxD1-Cre;Z/Red mice by unilateral ureteric obstruction (UUO) and FDI cells (dsRed positive) were isolated using FACs sorting. To identify differentially expressed miRNAs we profiled these cells in UUO and healthy controls. To investigate the role of miRNA-132 in vivo in renal fibrosis we injected antagonists i.v. to silence its function. Mice were sacrificed both 5 and 10 days after surgery.

Conclusions: MiR-132-3p targets the most highly upregulated miRNAs in the FDI cells in the fibrotic kidney. In vitro we demonstrated that silencing miR-132 results in reduced myofibroblast marker u-SMA, reduced proliferation and increased levels of its established target Sirt1. In vivo silencing of miR-132 in the UUO model resulted in a 35% decrease in collagen deposition and decreased tubular apoptosis after 10 days as compared to scramble miRNA controls, while no difference was observed yet after 5 days. IHC analysis demonstrates that the number of interstitial u-SMA positive cells is similarly decreased, which is confirmed by both western blot and qRT-PCR analyses. No difference is observed in glomerular density. Surprisingly, silencing miR-132 is associated with reduced levels of Sirt1. Furthermore, we demonstrated that miR-132 silencing decreases the number of proliferating interstitial cells.

Conclusions: MiR-132 is a new microRNA that regulates pericyte and fibroblast activation during renal fibrosis.

TH-PO584
Human Anti-dsDNA Antibodies Induce Amplification Loop of Transforming Growth Factor-β1, Fibronectin and Collagen Type I in Proximal Renal Tubular Epithelial Cells
Dale Tak Mao Chan, Shirlf S.K. Ho, Claudia Ng, Kwok Fan Cheung, Susan Yong. Dept of Medicine, The Univ of Hong Kong, Hong Kong.

Background: Nephritis affects up to 60% of patients with systemic lupus erythematosus and is characterized by the production of anti-dsDNA antibodies and immune-mediated renal injury. Severity of tubulointerstitial fibrosis is a strong predictor of reduced renal survival. Fibronectin (FN) is amongst the matrix components showing early deposition during the process of tubulointerstitial fibrosis. This study investigates the mechanisms through which FN is induced in renal proximal tubular epithelial cells (PTEC) following stimulation with human anti-dsDNA antibodies, and its role in tubulointerstitial fibrosis of lupus nephritis.

Methods: Confluent growth-arrested PTEC were incubated with serum free medium (SFM), control IgG or human polyclonal anti-dsDNA antibodies (10µg/ml) for 24h in the presence or absence of G60976 or TGF-neutralizing antibody, and the synthesis of FN assessed. In separate studies, PTEC were stimulated with soluble FN to determine its effect on fibrotic processes.

Results: Control IgG had no effect on FN synthesis compared to SFM. Anti-dsDNA antibodies significantly increased cell-associated and soluble FN compared to SFM and control IgG (6.4- and 5.2-fold respectively for cell-associated FN; 1.85- and 1.62-fold respectively for soluble FN, P<0.01 for all). This was accompanied by significantly increased TGF-β1 secretion (P<0.05), and increased PCK-α (P<0.05) and PCK-β (P<0.01) but not PCK-β phosphorylation. Pre-treatment of PTEC with G60976 (20µM) and TGF-neutralizing antibody (100µg/ml) significantly suppressed anti-dsDNA antibody-induced FN (P<0.01 for both cell-associated and soluble FN). Incubation of PTEC with soluble FN significantly increased TGF-β1 secretion and collagen type I synthesis in a dose-dependent manner (P<0.05 and P<0.01 respectively for 10µg/ml soluble FN).

Conclusions: These results suggest that anti-dsDNA antibodies induce an amplification loop comprising TGF-β1, FN and collagen type I in PTEC through PCK activation.

Funding: Government Support - Non-U.S.
Th-POS58

Fibroblast-Specific Pai-1 Depletion Ameliorates Renal Interstitial Fibrosis in Mice after Unilateral Ureteral Obstruction (uuO): Lan Yao, Laura S. Peterson, Amir Khan, Haichun Yang, Agnes B. Fogo. Pathology, Microbiology, and Immunology, Vanderbilt Univ Medical Center, Nashville, TN.

Background: Plasminogen activator inhibitor-1 (Pai-1), a member of the serine protease inhibitor family, inhibits matrix breakdown and regulates cell migration and proliferation. Systemic Pai-1 knockout mice have decreased interstitial fibrosis after uuO, but whether injury is crescentic anti-GBM model. Multiplexed renal expression Pai-1 after injury. We explored impact of fibroblast-specific Pai-1 depletion on interstitial fibrosis in the uuO model.

Methods: We bred floxed Pai-1 mice with tenascin C Cre mice, in which Pai-1 in fibroblasts can be knocked down after tamoxifen administration. UUO was performed in Pai-1 flox/+Cre mice after tamoxifen treatment (Cre/lox, n=11) and control Pai-1 flox/+ (cont, n=8), and kidneys were harvested and injury assessed after 10 days.

Results: Pai-1 flox/+Cre mice showed no Pai-1 immunostaining in fibroblasts and cortex. Pai-1 mRNA was decreased 41% in Cre/lox vs. control mice. Sirius red staining, a marker of interstitial fibrosis, decreased in Cre/lox mice (0.88±10 vs. Cont 1.34±0.16, P<0.05). In parallel, collagen I mRNA was decreased in Cre/lox vs. control (0.32 vs. 1.23±0.82, P<0.05). The number of fibroblasts in obstructed kidneys, measured by FSP-1 immunostaining, was decreased in Cre/lox mice (21.33±1.7 vs. Cont 31.8±1.1 HPF, P<0.05). Less fibroblast proliferation was found in Cre/lox vs. control mice, detected by PCNA-α-SMA double staining (Cre/lox 253.4±34.3 vs. Cont 405.4±53.4 mm2, P<0.05). E-cadherin mRNA level in obstructed kidney cortex, was preserved in Cre/lox mice (Cre/lox 1.5±0.5 vs. Cont 1.99±0.5, P<0.05). Surprisingly, F4/80 positive cells were increased in Cre/lox (32.9±1.1 vs. Cont 24±1.2, HPF, P<0.05).

Conclusions: Deletion of Pai-1 in fibroblasts ameliorates interstitial fibrosis, in part by reducing fibroblast proliferation, despite increased macrophage F4/80 infiltration. Whether these cells’ phenotype is altered in paracrine fashion by fibroblast Pai-1 knockdown awaits further study.

Funding: NIDDK Support

Th-POS86

Fibrosis of Kidneys and of Other Solid Organs: Towards a Unifying Classifier across Species: Hans-Peter Marti, James C. Fuscone, Joshua C. Kweckel, Aikaterini Anastagopoulou, Andreas Scherer. Dept of Clinical Medicine, Univ of Bergen, Bergen, Norway; Div of Systems Biology, National Center for Toxicological Research, FDA, Jefferson, AR; Institute of Anatomy, Univ of Bern, Bern, Switzerland; Spheronics, Kontiolaituri, Finland.

Background: Fibrosis causes solid organ failure. We described a transcriptomic classifier consisting of metazincins and related genes (MargBs) discriminating renal allograft biopsies with/without fibrosis and extended analyses to non-transplant solid organs (ATL-9,2009; Virchows Arch,458:2011). We have also used our classifier in experimental, lithium-induced nephropathy (Nephrology,17,S2:2012). We now apply our MargBs-based algorithm to a rat model of age-induced interstitial renal fibrosis.

Methods: Untreated Fisher 344 rats (n=76) were sacrificed from 2 to 104 weeks of age. For gene expression studies we used single color (Cy3) Agilent Whole Rat Genome microarrays; males: n=4 each at 2, 5, 6, and 8; n=5 at weeks 15, 21, 78, and 104; females: n=5 at weeks 2, 5, 6, 8, 15, 21, 78 and 104. Intensity data were subjected to variance stabilization (including log2 transformation from www.Partek.com). Data were analyzed with ANOVA using gender/age as factors and with Pearson correlation.

Results: Fibrosis severity increased with age. Across age groups 60 MargBs were differentially expressed. PCA visualized segregation of age groups by gender from week 6. More MargBs were differentially expressed in older males than in older females. Expression level of MMP-7 correlated best with 6. More MargBs were differentially expressed in older males than in older females. Expression level of MMP-7 correlated best with age. For gene expression studies we used single color (Cy3) Agilent Whole Rat Genome microarrays; males: n=4 each at 2, 5, 6, and 8; n=5 at weeks 15, 21, 78, and 104; females: n=5 at weeks 2, 5, 6, 8, 15, 21, 78 and 104. Intensity data were subjected to variance stabilization (including log2 transformation from www.Partek.com). Data were analyzed with ANOVA using gender/age as factors and with Pearson correlation.

Conclusions: Our MargBs classifier represents a cross-organ and cross-species classifier of fibrosis irrespective of etiology. This finding provides evidence for a common pathway leading to fibrosis and helps to design a PCR-based clinical test.

Funding: Government Support - Non-U.S.

Th-POS87

Apelin Receptor Blockade Exaggerates Unilateral Ureteral Obstruction Induced Tubular Injury in Rats: Gurdal Birdal, Zarife Ozdemir, Nazife Ozkan, Dilek Ozbyeli, Aydin Tulunay, Sule Cetinel, Berrak Yegen, Mehmet Indir, Aysel Tufan, Dilek Ozbeyli, Aysin Tulunay, Sule Cetinel, Berrak Yegen, Mehmet.

Background: Unilateral ureteral obstruction (UUO) is a well-characterized fibrosis model that can be knocked down after tamoxifen administration. UUO was induced in Apelin (Ap), a peptide identified as the endogenous ligand of the human orphan G-protein-coupled receptor, is reported to have anti-fibrotic and anti-inflammatory actions in the cardiovascular system, while the blockade of Ap receptor was shown to be effective in reducing hepatic fibrosis and angiogenesis. However, the role of Ap in the development of UUO model has not been elucidated.

Methods: In male Wistar albino rats under ketamine anesthesia (100 mg/kg; intraperitoneally), ip UUO was performed by ligating left ureters. The rats were injected ip with either saline (n=8) or the Ap-receptor blocker Ala-Ap (75 mg/kg/day; n=8) for 7 days. On the 7th day, obstructed and non-obstructed kidneys were removed for the isolation of leukocytes by flow cytometry and for the assessment of histopathological changes.

Results: Tubular injury scores, which were calculated by grading interstitial edema, tubular dilatation, hyalinization and atrophic/necrotic tubular cells, were similar in non-obstructed and saline-treated obstructed kidneys. On the other hand, in the obstructed kidneys with Ala-Ap-treatment, injury score was significantly elevated (P<0.05), but the interstitial fibrosis score determined by Masson-trichrome staining was not increased. The percentages of CD3 T-lymphocytes and CD3+/CD8+ T-lymphocytes infiltrating obstructed kidneys were increased in the Ap-receptor-blocked and Ala-Ap-treated obstructed kidneys (P<0.001) as compared to corresponding saline-treated groups.

Conclusions: The present data demonstrate that pharmacological blockade of Ap exaggerates UUO-induced tubular injury that appears to involve the infiltration of lymphocytes. These data suggest that Ap may have a regulatory role in protecting against obstruction-induced tubular injury.

Th-POS88

Reversal of Epithelial to Mesenchymal Transition following Relief of Unilateral Ureteral Obstruction in the Rat: Nan Shen, Hong Li Lin, Wang Da Peng, Dept of Nephrology, The 1st Affiliated Hospital of Dalian Medical Univ, Dalian, Liaon Ning Province, China.

Background: Renal fibrosis begins with renal tubular epithelial mesenchymal transition (EMT); the progression thereafter depends upon a number of fibrotic factors. Unilateral ureteral obstruction (UUO) is a well-described model of EMT. We used an improved reversible unilateral ureteral obstruction (RUUO) model to investigate whether a progressive renal injury model of EMT could be reversed into the opposite direction, into mesenchymal-to-epithelial transition (MET) after relief of UUO in rats.

Methods: Rats were subjected to UUO or sham operation and the obstruction was removed five days later (or was left in place). Rats developed EMT after reversal of 2 or 4 weeks of arterial obstruction as assessed by the expressions of fibrotic factors, MET and EP factors in this post-obstructive model.

Results: We found a significant decrease in the kidney weight and renal cortical thickness in the UUO group compared with the sham groups. This rise in the RUUO group was significantly reduced. The elevated level of TGF-β1, TGF-β1 receptors and c-Fos/c-Jun and c-Fos/c-Jun complex in the UUO group was significantly reduced in the RUUO groups. The MET markers staining showed results parallel to those of TGF-β1 expression levels. In addition, RUO rats exhibited pronounced inflammatory and immature proliferative cellular responses, and ultimately fibrosis. By comparison, RUO mice had more controlled inflammation and extracellular and intrinsic responses to EMT with a return to MET within several weeks after release of ureteral obstruction.

Conclusions: Our findings provide a model that allows investigation of the fibrotic factors during reversal of EMT that contribute to the development of fibrosis. EMT of the progressive renal injury could be actively reversed into MET and renal architecture is better maintained throughout injury and recovery from injury after relief of UUO in rats.

Funding: Private Foundation Support

Th-POS89

Long-Term Amiloride Therapy Ameliorates Lithium-Induced Kidney Interstitial Fibrosis: Privyashik Kalita, Andrew Bahn, Jennifer J. Bedford, John P. Leader, Robert J. Walker. Physiology, Univ of Otago, Dunedin, New Zealand; Medicine, Univ of Otago, Dunedin, New Zealand.

Background: Long-term lithium therapy may produce chronic interstitial fibrosis. Short term amiloride attenuates lithium-induced nephriosis. However, the effect of amiloride on renal interstitial fibrosis induced by long-term lithium treatment is unknown. This study investigated the effects of long-term amiloride on lithium-induced interstitial kidney fibrosis.

Methods: Male Wistar rats were divided into control, lithium alone, and lithium + amiloride groups (N=6 each group). Lithium was provided in rat chow (60 mmol/kg food) for 6 months. Amiloride was introduced in drinking water (0.2 mmol/l) 1 month after the lithium treatment and continued for 5 months. At 6 months, rats were euthanized and kidneys were processed for histology, immunohistochchemistry and Western blotting.

Results: On rats given lithium alone, histology revealed extensive dilatations of the cortical collecting ducts and focal areas of cortical fibrosis (0.5±0.04% area) vs controls (0.1±0.003% area), p<0.001. Rats given lithium for 1 month, followed by lithium + amiloride for a further 5 months showed significantly less fibrosis (0.1%±0.01 area), p<0.01. The tubular morphology was normal. Western blotting (%) demonstrated greater expression of fibrotic markers in the rats treated with lithium alone compared with the rats given lithium + amiloride, and both groups showed greater expression than in the controls.

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

Underline represents presenting author/disclosure.
Conclusions: This study reveals that amiloride appears to limit the fibrosis induced by lithium, although the abnormal morphology remains. Decreasing intracellular lithium concentration may affect AMP regulation of key pro-fibrotic pathways. Additional studies are underway to examine these possibilities.

Funding: Government Support - Non-U.S.

TH-PO590
Therapeutic Efficacy of DNA-Demethylation Therapy Initiated during Progressive Renal Fibrosis

Background: Acute kidney injury (AKI) can lead to chronic kidney disease (CKD). Research in animal models demonstrated that a DNA-demethylating treatment, when started immediately after induction of AKI, is able to attenuate development of chronic renal fibrosis, the hallmark of CKD. In patients diagnosed with CKD, however, fibrosis often has already developed to a substantial degree. Therefore, the efficacy of such a treatment, when initiated late in the progression of fibrosis, was tested in a mouse model of ischemia/reperfusion (I/R)-induced renal fibrosis.

Methods: Male C57BL/6J mice underwent left renal I/R (30 min, 37°C) and were treated with (a pre-optimized dose of) 0.25 mg/kg/day decitabine (AdC) or 0.9% NaCl, injected s.c. for 10 days. Treatment started either at 6 (early chronic phase) or 9 weeks (late chronic phase) after I/R. Sham operated mice were included as controls. Animals were killed either 1.5 week after end of treatment or 12 weeks after I/R. Kidney fibrosis was evaluated through gene expression (PCR analysis of TGFβ1 and collagen I) and immunohistochemistry. The impact of AdC on gene expression of the various Dnmts is limited, although all Dnmts showed a (non-significant) reduction by ca. 13% Dnmt 1, 28% Dnmt 3a and 37% Dnmt 3b) decrease when treatment was started at 6 weeks post I/R.

Conclusions: In this model of rather severe AKI induced renal fibrosis, a demethylating therapy is not that effective in attenuating progression of fibrosis. Whether AdC treatment as anti-fibrotic therapy might be effective only when administered during AKI or in a milder model of kidney damage remains to be determined.

Funding: Government Support - Non-U.S.

TH-PO591
AqF026 Is a Pharmacologic Agonist of the Water Channel Aquaporin-1
Olivier Devy,1 Johann Morel,2 Andrea J. Yool.1 UZH, Zurich, Switzerland; UCL, Brussels, Belgium; Univ Adelaide, Adelaide, Australia.

Background: Aquaporin-1 (AQP1) facilitates the osmotic transport of water across the capillary endothelium, among other cell types, and thereby has a substantial role in water removal during peritoneal dialysis. At present, pharmacologic agents that enhance AQP1-mediated water transport, which would be expected to increase the efficiency of peritoneal dialysis, are not available.

Methods: In the present study, we tested the capacity of the novel agent AqF026 (Aq: aquaporin ligand; F: furosemide scaffold) to potentiate the water channel activity of AQP1 in vitro and in vivo.

Results: In the Xenopus laevis oocyte system, extracellular AqF026 potentiated the channel activity of human AQP1 by >20% but had no effect on channel activity of AQP4. In silico modelling suggested the binding of AqF026 to the intracellular loop D domain, a region involved with channel gating. Site-directed mutagenesis of intracellular residues in the human AQP1 loop D domain showed that the agonist effect of AqF026 could be reversed by mutations of Thr157 or Arg159. In a mouse model of peritoneal dialysis, AqF026 enhanced the osmotic transport of water across the peritoneal membrane but did not affect the osmotic gradient, the transport of small solutes, or the localization and expression of AQP1 on the plasma membrane. Furthermore, AqF026 did not potentiate water transport in Aqgl-null mice, suggesting that indirect mechanisms involving other channels or transporters were unlikely. Last, in a mouse gastric antrum preparation, AqF026 did not affect the Na-K-Cl cotransporter NKCC1.

Conclusions: These results are the first to define a pharmacological ligand that potentiates AQP1 water channel activity, to show that it is effective in vitro and in vivo, and to identify a candidate molecular site of action. The data are consistent with direct binding of the alyxo/furosemide compound AqF026 at a site involving the intracellular regulatory domain loop D in AQP1. AqF026 directly and specifically potentiates AQP1-mediated water transport, suggesting a potential interest for peritoneal dialysis and clinical situations associated with defective water handling.

Funding: Pharmaceutical Company Support - Baxter Extramural Grant, Private Foundation Support, Government Support - Non-U.S.

TH-PO592
Ser-261 Phosphorylation Is an Endocytotic Signal of Aquaporin-2 Trafﬁcking in LLC-PK1 Cells
Julian R. Arthur,1 Jianmin Huang,1 Dennis Brown,1 Hua Ann Jenny Lu,1,2 Center for Systems Biology, Program in Membrane Biology, Div of Nephrology, Massachusetts General Hospital, Boston, MA; 1Harvard Medical School, Boston, MA.

Background:Phosphorylation dependent apical accumulation of water channel Aquaporin-2 (AQP2) mediates water reabsorption in the principal cells of kidney collecting ducts (CD). Modulation of AQP2 trafficking (VT), contributing to water homeostasis in mammals. Using an unbiased mutational analysis of all the potential phosphorylation sites in AQP2 we investigated intracellular trafficking of pS261-AQP2 in rat kidney tissue. We then introduced phosphorylation mimics (D, aspartic acid) to each individual site in the S261-AQP2. For Western blots, membranes were incubated with Goat anti-AQP2 and HRP-conjugated anti-Goat IgG. For AQP2 mRNA expression, total RNA was isolated from cells treated with 10 μM VP, 10 μM Forskolin (FK), or 10 mM methyl β-cyclodextrin (MCBD) for 30 min. For cold block, cells were pre-treated with cycloheximide for 60 min, then incubated at 20°C for various timepoints to visualize the formation of AQP2 “perinuclear patches.” Fixed cells were visualized using the Nikon 80i.

TH-PO594
Characterization of the Putative Phosphorylation Sites of Aquaporin-2 C-Terminus and Their Role in Aquaporin-2 Trafficking in LLC-PK1 Cells
Jeffrey G. Seltzer,2 Seiji Tomita,1 Brian E. Ariceci,1 Yoko Sato,1 Lisa L. Cerny,1 Dennis Brown,1 Hua Ann Jenny Lu,1,2 Center for Systems Biology, Program in Membrane Biology, Div of Nephrology, Massachusetts General Hospital, Boston, MA; 1Harvard Medical School, Boston, MA.

Background: Aquaporin-2 (AQP2) mediates water reabsorption in the principal cells of kidney collecting ducts (CD). Modulation of AQP2 trafficking (VT), contributing to water homeostasis in mammals. Using an unbiased mutational analysis of all the potential phosphorylation sites in AQP2 C-terminus, we were able to identify the role of each potential site in regulated trafficking and constitutive recycling of AQP2.

Methods: We generated stable LLC-PK1 cell lines with point mutations of alanine (A) or glycine (G) to replace all seven potential C-terminal phosphorylation sites in AQP2. We then introduced phosphorylation mimics (D, aspartic acid) to each individual site in the S261-AQP2. For Western blots, membranes were incubated with Goat anti-AQP2 and HRP-conjugated anti-Goat IgG. For AQP2 mRNA expression, total RNA was isolated from cells treated with 10 μM VP, 10 μM Forskolin (FK), or 10 mM methyl β-cyclodextrin (MCBD) for 30 min. For cold block, cells were pre-treated with cycloheximide for 60 min, then incubated at 20°C for various timepoints to visualize the formation of AQP2 “perinuclear patches.” Fixed cells were visualized using the Nikon 80i.

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

236A
Results: S all A/G AQP2 showed no membrane accumulation in response to VP/FK, but accumulated in response to MjCJD, which disrupts endocytosis. S all A/G AQP2 with either S225D, S229D, T243D, S265S, N267D, S264D, or S269D did not exhibit membrane accumulation under basal conditions. These mutant AQP2 accumulated at the plasma membrane after MjCJD treatment and in the trans Golgi network after cold block. S all A/G AQP2-S265S showed membrane accumulation in the absence of VP/FK, and was largely resistant to cold block as previously reported. S all A/G AQP2-S265S responded to VP/FK similarly to AQP2-WT.

Conclusions: Our data suggest for the first time that constitutive recycling of AQP2 does not require any phosphorylation in its C-terminus. Phosphorylation of S256 alone is sufficient to cause membrane accumulation of AQP2.

Funding: NIDDK Support

TH-PO595
Changes in the Excretion of Urinary Exosomal AQP1 and AQP2 in Rats with PAN-Induced Nephrotic Syndrome
Ayaha Kaito, Hiroko Sonoda, Saki Takahashi, Masahiro Ikeda. Veterinary Pharmacology, Univ of Miyazaki, Miyazaki, Japan.

Background: Nephrotic syndrome exhibits abnormal handling of renal water excretion and this abnormality is thought to be associated with the level of expression of renal aquaporin water channels (AQPs). Urinary exosomes are small vesicles sequestered into urine from all renal epithelial cell types and known to contain proteins that are involved in renal secretion and reabsorption. Among these proteins, the level of urinary exosomal AQP1 or AQP2 excretion has been reported to be altered by renal insults such as renal ischemia/reperfusion and cisplatin, accompanied with the changes of their renal expression levels. However, it is unclear whether the urinary exosomal AQP1 and AQP2 excretion are affected by nephrotic syndrome.

Methods: In this study, we examined the levels of urinary exosomal AQP1 and AQP2, excretion in a well-characterized animal model viz. puromycin aminonucleoside (PAN) nephrosis. PAN (125 mg/kg) or saline was intravenously injected to rats. Urine exosomes were isolated from the urine samples by differential ultracentrifugation.

Results: Plasma creatinine concentration and urinary protein level were significantly increased 96 hr or later after the injection of PAN. Urine osmolality was higher 96 hr and lower 168 hr after the injection, in comparison with controls. Urinary exosomal AQP1 was increased 120 hr or later, whereas reduced urinary exosomal AQP2 excretion was detected even 24 hr after the injection. We then examined the abundance of AQP1 and AQP2 proteins in the renal cortex and medulla. Both proteins were not changed 48 h, but significantly decreased only in the cortex 120 h after the injection of PAN.

Conclusions: With these results, only urinary exosomal AQP2 excretion was decreased before proteinuria without being accompanied with renal protein level, whereas both urinary exosomal AQP1 and AQP2 excretion were reduced after proteinuria, associated with renal protein levels. These data suggest that urinary exosomal AQPs may be potential biomarkers for nphrotic syndrome.

TH-PO596
Kidney Stone Risk during Microgravity and Long-Term Bed Rest: Role of Hypercalciuria and Aquaporins
Grazia Tamma, Annarita Di Mise, Maria Cristina Gherardi, Maria Svelto, Giancarlo Bilancio, Massimo Cirillo, Natale Grazia Tamma, Annarita Di Mise, 1Dept Biosciences, Biotechnologies and Biopharmaceutics, Univ of Bari, Bari, Italy; 2Dept of Medicine, Univ of Salerno, Salerno, Italy; 3Dept of Medicine, Second Univ of Naples, Naples, Italy.

Background: Kidney stone formation occurs directly or indirectly, as a means of narrowing the scope of its possible actions. These phosphorylation sites in Bad, Ser-112 and Ser-155, are known to inhibit pro-apoptotic activity. Pre-incubation of cells with H989 blocked dDA VP-induced phosphorylation of protein kinase A (PKA).

Conclusions: This study provides evidence that AQP can inhibit apoptosis through the V2 receptor and downstream cAMP-mediated pathways in mammalian kidney, a process that may be relevant in the context of renal proliferative disorders such as autosomal dominant polycystic kidney disease (ADPKD).

Funding: Other NIH Support - National Heart, Lung, and Blood Institute intramural budget (Z01-HL001285)

TH-PO598
Cyclooxygenase-2 Mediates Induction of the Renal Stanniocalcin-1 Gene by Arginine Vasopressin
Graham F. Wagner, Richard L. Hebert. 1 Physiology & Pharmacology, Western Univ, London, Canada; 2Dept of Cellular and Molecular Medicine, Univ of Ottawa, Ottawa, Canada.

Background: The stanniocalcin-1 (STC-1), is expressed in most nephron segments. But the gene is differentially induced in cortical and medullary segments in response to dehydration. The cortical gene is upregulated solely by hyperosmotic, whereas that in medulla is induced by hypovolemia. In both cases gene induction is mediated by arginine vasopressin (AVP) acting via V2 receptors (V2R). V2R occupancy activates two pathways in response to dehydration; 1) antidiuresis mediated by direct V2R occupancy and 2) AVP complex formation and activation mediated indirectly via COX-2 (cyclooxygenase-2). Because the role of renal STC-1 is still unknown, we sought to establish whether V2R mediated gene upregulation occurred directly or indirectly, as a means of narrowing the scope of its possible actions.

Methods: Models of COX inhibition and COX gene deletion were employed to address the possible involvement of V2R-dependent regulation.

Results: Both general and specific inhibitors of COX-2 blocked STC-1 gene induction in response to dehydration. Gene induction in response to dehydration was also abolished in COX-2 null mice (cortex and medulla), but not in COX-1 null mice.

Conclusions: The findings clearly showed that all V2R-mediated rises in renal STC-1 gene expression are wholly dependent on functional COX-2 activity. This implies that STC-1 is not part of the antidiuretic pathway and that it likely has actions that include AVP and renal osmoregulation.

Funding: Government Support - Non-U.S.

TH-PO599
Transcriptional and Translational Heterogeneity of the SLCA2A9 Gene Encoding the GLUT9 Urate Transporter
Asim Mandal, 1 David B. Mount. 1 1Renal Div, Brigham and Women's Hospital, Boston, MA; 2Renal Div, VA Boston Healthcare System, Boston, MA.

Background: There are ~30 genes linked to serum uric acid (SUA) levels and gout, yet variation in the SLCA2A9 gene encoding the urate transporter GLUT9 remains the major single genetic determinant; however, the causative variants are unknown. Two distinct N-terminal isoforms, GLUT9a and GLUT9b, are generated by alternative 5' endsanking a novel 5' UTR exon that is ~35 kb 5' of
exon 1b. Alternative splicing that deletes coding exons 3 +/- 4 was also identified; exon 3 is a cassette exon encoding most of transmembrane domain 1 (TM1) and part of the first, glycosylated extracellular loop. Surprisingly, GTL9b constructs with deletion of exon 3 (GLUT9b-delta3) were functional, generating urate uptakes that were 10-fold higher that of water-injected control Xenopus oocytes - versus 40-fold higher in oocytes injected with full-length GLUT9b cRNA. Western blotting indicated that GLUT9b-delta3 protein is not glycosylated, likely due to altered topology of the first extracellular loop.

**Conclusions:** We have identified substantial 5’ heterogeneity of SLC2A9 transcripts, with five novel 5’ UTR exons and at least two transcriptional initiation sites. There are multiple 14-3-3 isoforms that form homo- and hetero-dimers and play proteins that have numerous roles in protein interaction, phosphorylation, and enzymatic activities.

14-3-3s are regulatory factors that are capable of modulating the activity of NFAT5 and other transcription factors. 14-3-3s can interact with transcription factors and transcriptional coactivators to modulate their activity. They are involved in a wide range of cellular processes, including cell growth, differentiation, and apoptosis. 14-3-3s are also known to modulate the nuclear localization of NFAT5, and thus control its activity. The effects of knocking down 14-3-3s on NFAT5 function were examined in this study. Both low (5 mM) and high (150 mM) intracellular NaCl concentrations were used to control the composition of both the extracellular and intracellular solutions.

**Background:** SGLT2 inhibitors are a new class of drugs that have been developed to treat diabetes. They lower glucose levels by blocking the renal Na/glucose cotransporter SGLT2, thereby decreasing the amount of glucose reabsorbed in the proximal tubule.

**Results:** Our results confirmed that SGLT2 is a potent inhibitor of NFAT5 and that the effects of SGLT2 inhibition on NFAT5 activity are dose-dependent.

**Conclusions:** We conclude that SGLT2 inhibitors only bind to SGLT2 from the extracellular side of the plasma membrane and suggest that they act on the luminal membrane and not from the blood through the tubular epithelium.

**Funding:** Pharmaceutical Company Support - Janssen Pharmaceuticals

---

**TH-PO600**

**SGLT2 Inhibitors Act from the Extracellular Surface of the Cell Membrane**

**Chiara Ghezzi, Ezdrone Gorraitza, Erika Patino, Bruce A. Hirayama, Donald D.F. Loo, Ernest M. Wright.** Physiological Dept, David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Background:** SGLT2 inhibitors are a new class of drugs that have been developed to treat diabetes. They lower glucose levels by blocking the renal Na/glucose cotransporter SGLT2, thereby decreasing the amount of glucose reabsorbed in the proximal tubule.

**Methods:** We used Luciferase reporters to measure NFAT5 transcriptional activity. We quantified the transcriptional activity of ORE-X and TAD activities, but knockdown of the other isoforms had no significant effect on the transcriptional activity of NFAT5.

**Results:** Knockdown of SGLT2 inhibitors significantly inhibited high NaCl-induced ORE-X and TAD activities, but knockdown of the other isoforms had no significant effect on the transcriptional activity of NFAT5.

**Conclusions:** W have demonstrated that SGLT2 inhibitors act from the extracellular surface of the cell membrane and not from the intracellular side.

**Funding:** NIDDK Support, Veterans Affairs Support

---

**TH-PO602**

**Mechanisms of Erythropoietin Production by Aldosterone in the Intercalated Cells**


**Background:** Erythropoietin (Epo) production occurs in the peritubular cells, which experimentally requires severe anemia and hypoxia. Other site maintaining basal Epo production is speculated. We have shown that cultured intercalated cells of the collecting ducts (CD) (IN-IC cells) produce Epo by hypoxia and aldosterone and that vasopressin V1a receptor (V1aR) is required for the effect of aldosterone. In the present study, we investigated the Epo production in basal condition and the mechanisms of aldosterone-induced erythropoiesis in intercalated cells.

**Methods:** Mice in basal condition, blood-draw induced anemia with 4-h hypoxia and hypoxia and aldosterone and that vasopressin V1a receptor (V1aR) is required for the effect of aldosterone. We knocked down 14-3-3 isoforms that form homo- and hetero-dimers and play proteins that have numerous roles in protein interaction, phosphorylation, and enzymatic activities.

**Conclusions:** IC-B is the main site of Epo production in basal conditions. Aldosterone stimulates Epo production in IC-B through the activation of HIF1a, HIF1b and the TRH-PO603

**Urine Citrate Excretion in NaDC1 Knockout Mice**

**Kathleen S. Hering-Smith, Federico Teran, Lee Hamm.** Medicine, Tulane Univ, New Orleans, LA; Research, SLVHCS, New Orleans, LA.

**Background:** Citrate is an important inhibitor of calcium stone formation. Citrate in the urine has been thought to be predominantly regulated by NaDC1 (Na-dicarboxylate cotransporter 1) in the apical membrane of the proximal tubule. However, since we have recent evidence of another citrate reabsorptive process in the proximal tubule, we reexamined citrate excretion in NaDC1 knockout mice.

**Methods:** Citrate and other Krebs cycle intermediates were measured by LC/MS in plasma and spot urine collections from wild type (WT), KO and heterozygotes (Het) and are expressed in μg/mL.

**Results:** Renal function and urine concentration were not different in the three groups of animals as indicated by plasma and urine creatinines. Excretion of succinate, fumarate, and malate was significantly higher in KO compared to WT and Het, 92 ± 29, 37 ± 17, 3 ± 2; 6: fumarate 45 ± 11, 3 ± 0.7, 3.8 ± 0.9; malate 161 ± 47, 24 ± 3, 32 ± 11, respectively in KO, Het, and WT. However, citrate excretion was not higher in KO animals compared to Het or WT: succinate 92 ± 29, 37 ± 17, 3 ± 2; 6: fumarate 45 ± 11, 3 ± 0.7, 3.8 ± 0.9; malate 161 ± 47, 24 ± 3, 32 ± 11, respectively in KO, Het, and WT. However, citrate excretion was not higher in KO compared to WT and Het, 89 ± 15, 115 ± 42, 149 ± 24. Interestingly lactate excretion in urine was significantly lower in KO compared to WT or Het, 92 ± 29, 37 ± 17, 3 ± 2.

**Conclusions:** In sum, NaDC1 KO animals exhibit increased excretion of several Krebs cycle intermediates but not increased urinary citrate. This data is consistent with transporters other than NaDC1 having a potentially important role in regulation of urinary citrate excretion and hence in prevention of calcium stone formation.

**Funding:** NIDDK Support

---

**TH-PO604**

**Effect of Direct Renin Inhibitor Aliskiren on the Urinary Concentrating Deficit in Obstructive Nephropathy**

**Weidong Wang, Renfei Luo, Yu Lin, Moshe Levi, Tianxin Yang, Chunling Li.** Institute of Hypertension and Kidney Research, Zhongshan School of Medicine, Sun Yat-sen Univ, Guangzhou, Guangdong, China; Div of Hypertension and Kidney Diseases, Univ of Colorado Denver, Aurora, CO.

**Background:** Urinary obstruction is associated with reduced renal aquaporins (AQPs) and urinary concentrating defect, in which renin-angiotensin system (RAS) may play an important role. We evaluated whether RAS blockade by injecting renin inhibitor aliskiren in mice would prevent decreased protein expression and intratubular trafficking of AQPs in bilateral ureteral obstruction (BUO) and unilateral ureteral obstruction (UO).

**Methods:** BUO was performed for 24 hours and UO was performed for 3 days and 7 days. Protein, mRNA expression and staining of aquaporins were examined by western blots, RT-PCR, and immunohistochemistry.

**Funding:** BUO was performed for 24 hours and UO was performed for 3 days and 7 days. Protein, mRNA expression and staining of aquaporins were examined by western blots, RT-PCR, and immunohistochemistry.

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

Underline represents presenting author/disclosure.
RESULTS: There were no significant changes in serum osmolality, sodium, and potassium concentrations between BUO/UOO mice and aliskiren-treated groups. During BUO, aliskiren (BUO+Ali) prevented the reduction of AQP2 protein expression (1.06±0.07 in BUO+Ali vs. 0.73±0.05 in BUO, P<0.05), but not AQP1 and AQP3. Aliskiren reversed the weak intracellular and apical staining of AQP2 in the cortical and inner medullary collecting duct (CD) principal cells during 24 hr BUO. In UOO mice, at day 3 (3U) and day 7 (7U) of obstruction, outer medullary NKA-α was unchanged with water restriction, whereas AQP2 gene expression increased 2-fold. ATP hydrolysis was determined by measuring release of Pi. NKA activity is the difference between ATP hydrolysis in the presence and absence of ouabain. Real-time PCR analysis was conducted on 1

CONCLUSIONS: RAAS blockade with renin inhibitor was associated with increased AQP2 expression in the kidney and activation of renal RAAS may play an important role in urinary concentrating defect seen in obstructive nephropathy.

Funding: Government Support - Non-U.S.

TH-PO606

Primary Cilia Modulate the Effects of TRPM3 and TRPV4 on Survival of Renal Epithelial Cells Exposed to Osmotic Stress

Bradley P. Dixon, Brian J. Siroky,1 Raven Gail Comer,1 Nancy Kleene,2 John J. Bissler.1

1 Div of Nephrology and Hypertension, Cincinnati Children’s Hospital Medical Center; Cincinnati, OH; 2 Dept of Cancer and Cell Biology, Univ of Cincinnati College of Medicine, Cincinnati, OH.

Background: Primary cilia detect osmolality, but the mechanism is unclear. Both TRPV4 and TRPM3 channel activities are inhibited by hyperosmolality. We investigated the role of primary cilia in response to acute hyperosmolal stress, and whether TRPV4 and TRPM3 mediate this response.

Methods: TRPV4 and TRPM3 expression in ciliated (176-5) and nonciliated (176-5) renal epithelial cells was determined by qPCR. Cells were challenged with 16-24 hours of osmotic stress at 400, 500, or 600mOs/mg with NaCl, or maintained under control conditions. This stress was applied either in the presence or absence of a TRPV4 agonist (GSK1016970A), or a TRPM3 agonist (pregnenolone). Cell number was measured by crystal violet DNA binding assay, and viability was determined by calcein uptake. Markers of apoptosis were measured by immunoblotting.

Results: Both ciliated and nonciliated renal epithelial cells expressed TRPV4 and TRPM3, and TRPV4 expression was several fold higher in ciliated cells. Nonciliated cells had reduced cell number and viability at and above 400mOs/mg in comparison to ciliated cells. Nonciliated cell survival following osmotic stress was not altered in the presence of a TRPV4 agonist, suggesting that TRPV4 may be critical for osmosensation in the absence of cilia. Cleavage of caspase 3 and PARP was seen in nonciliated cells treated with TRPV4 agonist under hyperosmolal and, to a lesser extent, isosmolal conditions. Cell viability was reduced in ciliated cells pretreated with TRPM3 agonist at 600mOs/mg, suggesting the importance of this channel for osmotic response in ciliated cells.

Conclusions: These findings support a role for TRPV4 and TRPM3 in osmosensation by renal epithelial cells. In ciliated cells, TRPM3 may be the predominant osmosensor, and increased expression of TRPV4 in nonciliated cells may represent a compensatory adaptation to loss of ciliary osmosensation.

Funding: NIDDK Support, Private Foundation Support

TH-PO607

Na-K-ATPase and the Urine Concentrating Mechanism in the Rodent Medulla

Thomas Pannabecker, C. Michele Nawata, Tamara M. Armstrong, Kristen K. Evans, Mohammad Shahidullah. Physiology, Univ of Arizona, Tucson, AZ.

Background: Na reabsorption by medullary thick ascending limb and collecting duct is driven by basolateral Na-K-ATPase (NKA) with apical transport via NHE3/NKCC2 or ENaC. Reabsorption rates are influenced by regulated apical transport. By comparing NKA activity and expression in water-restricted Sprague-Dawley rats and in the kangaroo rat, a desert rodent that drinks no free water, we are investigating regulatory mechanisms that
directly impact the active transport step.

Methods: Outer medullary tissue from control rats (ad libitum access to water) and water-restricted rats (water reduced to 40% of controls) was homogenized and a crude 200,000 x g supernatant was used for Western blotting with antibodies to total NKA-α and NKA-β proteins. NKA activity is the difference between ATP hydrolysis in the presence and absence of ouabain. Real-time PCR analysis was conducted on 1 μg total RNA from tissue homogenates.

Results: Urine osmolality (mOsm/kg H2O) of Sprague-Dawley rats increased from 1185 (control) to 2121 with 72 hr water restriction. Outer medullary NKA-α gene expression was unchanged with water restriction, whereas AQP2 gene expression increased 2-fold. Inner medullary NKA-α gene expression increased 2-fold. Prior studies have shown outer medullary NKA-α protein expression levels increase with restricted water intake. In the kangaroo rat (urine osmolality ~4159), outer medullary NKA-α protein expression levels are 2 to 3-fold higher than Sprague-Dawley control rats; however, NKA activity is no different.

Conclusions: Low correlation between outer medullary NKA-α gene expression and total NKA activity in Sprague-Dawley rat suggests multiple regulatory mechanisms, possibly including lower protein degradation rate. Greater expression of outer medullary NKA-α protein but with equivalent NKA activity, in a species with sharply higher concentrating capacity could be consistent with greater fractional NKA-α: expression in the plasma membrane. NIDDK DK08338, NSF IOS0950285.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO608

Missing Link between Hyponatremia and Impaired Thyroid Function

Christian Stefan Haas, Matthias J. Berndt, Birgit Harbeck, Ulrich Lindner. Dept of Medicine I, Univ of Luebeck, Luebeck, Germany.

Background: Hyponatremia (HN) is the most common electrolyte disorder in both out- and in-patients. Hypervolemic states (e.g. heart failure, liver cirrhosis), hypovolemia, and the syndrome of inappropriate ADH secretion account for most of the cases, while endocrine disorders are less frequently responsible. Despite insufficient data on a relationship between thyrotophin (TSH), free thyroxine (fT4) and serum sodium, hypothyroidism is often cited as a possible cause of HN. The study objective was to assess the association between impaired thyroid function and HN.

Methods: In a retrospective analysis, patients admitted to the emergency room (ER) or the intensive care unit (ICU) having manifest hypothyroidism (TSH>10 mU/L and fT4<2 ng/L) were identified. Serum sodium levels and distribution were determined, HN prevalence in the control group was 21% (n=259), with 87 patients (7%) having even moderate (Na<130 mEq/L) or severe HN (Na<120 mEq/L). In the hypothyroid group, HN prevalence was comparable; of note, most patients had mild HN, while moderate or severe HN was virtually not present in patients with severe hypothyroidism (TSH>50 mU/L).

Results: In summary, we showed that: (1) mean sodium in hypothyroid patients and controls is comparable; (2) HN prevalence in hypothyroidism is not higher than in control patients; and (3) there is no correlation between serum sodium and TSH levels.

These data suggest that hypothyroidism is not likely to be a cause for the development of HN and that measurement of TSH may be waived in the differential diagnosis of the electrolyte disorder.

Funding: Other U.S. Government Support

TH-PO609

Chronic Hyponatremia: A Novel Risk Factor for Bone Fractures in Chronic Kidney Disease

Sagar U. Nigwekar, Julia Beth Wenger, Ravi I. Thadhan, Ishir Bhan. Massachusetts General Hospital.

Background: Chronic hyponatremia is associated with reduced bone density and increased fracture risk in the general population. Given the high fracture risk and prevalence of chronic hyponatremia in chronic kidney disease (CKD), we evaluated whether chronic hyponatremia is associated with increased fracture risk in CKD.

Methods: Subjects for this case-control study were enrolled from the Partners Healthcare Research Patient Data Registry. CKD was defined as estimated glomerular filtration rate < 60 mL/min. Chronic hyponatremia was defined as serum sodium (Na)< 135 mEq/L at least 2 occasions (prior to fracture for cases). Cases comprised ambulatory elderly (60+) CKD patients with femoral and/or vertebral fractures diagnosed between January 2009 and December 2011. Controls were ambulatory elderly CKD patients without femoral or vertebral fractures and were matched to cases by age, gender, and race. Associations between chronic hyponatremia and fractures were evaluated in univariate and multivariable logistic regression analyses.

Results: We identified 3,027 eligible subjects (cases=937; controls=2,090). Chronic hyponatremia was more common in cases than controls (13 vs. 9%; p=0.03). Amongst the hyponatremic subjects, sNa was between 130 and 134 mEq/L in 85%. Subjects with chronic hyponatremia had higher prevalence of lung disease (30 vs. 25%, p=0.04), diuretic use (61 vs. 51%, p<0.01), and cirrhosis (4 vs. 2%, p<0.01), but similar rates of congestive heart failure, hypothyroidism, psychiatric disorders, and antidepressants use compared to those without chronic hyponatremia. Chronic hyponatremia was associated with increased odds of fracture in univariate analysis (OR 1.32, 95% CI 1.03 - 1.69). Additional significant associations with fracture included female gender, hyperparathyroidism, osteoporosis, lung disease, and absence of obesity. Adjusted for these covariates and demographic factors, chronic hyponatremia remained a significant predictor of fracture (OR 2.20, 95% CI 1.19 - 4.07).

Conclusions: Chronic hyponatremia is associated with increased fracture risk in CKD. Future studies are needed to examine whether correcting chronic hyponatremia can reduce fracture risk.

Funding: Private Foundation Support

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

Underline represents presenting author/disclosure.

239A
Sensitivity to Ang II. We hypothesized that a moderately-enriched fructose diet increases Na reabsorption in proximal tubules by enhancing their transport, but TBC1D4 may play a role for GLUT4-mediated basolateral glucose uptake in adipo- and myocytes. We recently demonstrated that TBC1D4 functions in the kidney, but its specific role in renal sodium and water transport is unknown.

**Conclusions:** These data suggest that AC3 in the CD regulates AVP-stimulated cAMP accumulation, but this effect is modest and likely elicits changes that fully compensate for its absence.

**Funding:** Veterans Affairs Support

**TH-PO610**
The Rab-GAP Protein TBC1D4 (AS160) Regulates GLUT4 but Not ENaC

**Background:** The Rab-GAP protein TBC1D4 (AS160) regulates vesicle trafficking in a variety of cell types and plays a role in regulating glucose and lipid metabolism. However, its role in renal sodium and water transport is unknown.

**Methods:** We generated CD-specific knockout (KO) of AC3 mice using the Cre/loxP system. AC3 DNA recombination in microdissected nephron segments was determined by PCR and AVP-stimulated cAMP levels were determined in primary cultures of isolated kidney collecting ducts. We also measured plasma renin concentration and urinary aldosterone excretion.

**Results:** Plasma ion concentrations, aldosterone levels, and plasma renin concentration were similar in both genotypes. No difference was observed in potassium excretion between KO and control mice.

**Conclusions:** Our results suggest that AC3 in the CD regulates AVP-stimulated cAMP accumulation, but this effect is modest and likely elicits changes that fully compensate for its absence.

**Funding:** Veterans Affairs Support

**TH-PO613**
Amiloride Inhibits uPA Activity and Plasminogen Activation in Urine from Rats with PAN-Induced Nephrotic Syndrome

**Background:** Urokinase-type plasminogen activator (uPA) is a serine protease that plays a role in renal sodium and water transport. The gamma subunit of ENaC is proteolytically activated in nephrotic syndrome. Aberrant filtration of serine protease zymogen plasminogen and conversion to active plasmin in the urine space is a likely mediator. Urokinase-type plasminogen activator (uPA) is thought to mediate activation of plasminogen to plasmin. Amiloride is an inhibitor of uPA in vitro.

**Methods:** Urine and kidney tissue uPA was determined in the PAN-treated rat model of acute nephrotic syndrome and amiloride was tested for its ability to inhibit uPA. Rats were kept in metabolic cages and the effect of treatment was compared to vehicle treated nephrotic and healthy control groups.

**Results:** Development of proteinuria in the PAN rat model of nephrosis coincided with increased urinary serine protease activity as judged by gelatin zymography. PAN rats showed significant elevated urinary uPA activity. Immureactive uPA was detectable in urine samples of control and PAN treated rats. Amiloride significantly reduced uPA activity in nephrotic rat urine; it reduced urine gelatinolytic activity and concurrently increased the ratio of plasminogen/plasmin and normalized 24 hour sodium excretion.

**Conclusions:** Urokinase-type plasminogen activator (uPA) is a target for amiloride in urine. Amiloride counteracts urinary plasminogen activation in proteinic disease in vivo. ENaC is responsible for excess renal sodium retention in nephrotic syndrome.

**Funding:** Private Foundation Support

**TH-PO615**
Incidence and Factors of Post-Adrenalectomy Hyperkalemia in Patients with Aldosterone Producing Adenoma

**Background:** Adrenalectomy is the treatment of choice for patients with aldosterone producing adenomas (APA). However, hyperkalemia is a potential complication post-adrenalectomy. The aim of this study is to analyze the incidence and risk factors for hyperkalemia after adrenalectomy in patients with APA.

**Methods:** We retrospectively analyzed the records of 55 patients who underwent adrenalectomy for APA over the past 9 years. Demographic features, biochemical and hormonal profiles, imaging, and relevant medications were reviewed. Nadir serum K+ was defined as the serum K+ level when APA was first diagnosed. Hyperkalemia was defined as serum K+ > 5.0 mmol/L and the exclusion of pseudohyperkalemia. Hyperkalemia that required dialysis during the first 3 months after adrenalectomy was defined as “transient,” those lasting more than three months requiring mineralocorticoid supplementation was defined as “persistent.”

**Results:** Sixteen of 55 APA patients (29.1%) developed hyperkalemia (mean serum K+ 5.6 ± 0.3 mmol/L) after adrenalectomy and three had persistent hyperkalemia. The most important factors for post-adrenalectomy hyperkalemia were age and BMI.

**Conclusions:** Post-adrenalectomy hyperkalemia in patients with APA is not rare and associated with impaired renal function and longer duration of hypertension. Serum K+ must be cautiously monitored in patients with long-term hypertension and kidney disease.
TH-PO614
Etiological and Therapeutic Analysis in Patients with Hypokalemic Paralysis due to Potassium Deficit
Chih-Chien Sung, Chih-Jen Cheng, Sung-Sen Yang, Shih-Hua P. Lin. Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Background: Non-hypokalemic periodic paralysis (non-HypoPP) represents a group of diseases caused by low levels of potassium (K⁺) deficit. To rapidly diagnose its underlying causes with appropriate management is still challenging.

Methods: Fifty-eight patients (43 male and 15 female) with non-HypoPP and the exclusion of HypoPP were consecutively enrolled over an eight-year period. Blood and spot urine samples were collected for electrolytes, acid-base and biochemistry measurement on admission and during therapy. Intravenous potassium chloride (KCl) at a rate of 10-20 mmol/hour was administered until muscle strength recovered.

Results: The average K⁺ concentration was 1.8 ± 0.3 mmol/L. Their electrolyte could be simplified by the urinary K⁺ excretion rate and blood acid-base status. For a low urinary K⁺ excretion, chronic alcoholism, anorexia/bulimia nervosa, and remote diuretics use were the most common causes. For a high urinary K⁺ excretion, patients were divided into two subgroups: metabolic acidosis, renal tubular acidosis and chronic tubulo-alveolar abuse were common causes. Mineralocorticoid excess state with primary aldosteronism, Gitelman’s or classic Bartter’s syndrome, and diuretics use were common causes for metabolic alkalosis with high and normal blood pressure, respectively. Muscle strength was restored at serum K⁺ concentration of 2.6 ± 0.2 mmol/L after administering approximately 245 mmol (3.8 ± 0.8 mmol/kg) KCl. Of note, non-HypoPP patients with high urinary K⁺ excretion needed a higher KCl dose than those with low K⁺ excretion (4.0 ± 0.8 vs 3.2 ± 0.5 mmol/kg, p < 0.001). KCl supplementation was higher in patients who developed a paradoxic fall in serum K⁺ concentration (1.6 ± 0.2 mmol/L) than those without (4.1 ± 0.7 vs 3.4 ± 0.7 mmol/L, p < 0.001). These patients often had typical volume depletion with higher plasma renin activity.

Conclusions: Understanding the common etiology of non-HypoPP may aid in early diagnosis. Non-HypoPP patients associated with renal K⁺ wasting or hypovolemia that tend to develop paradoxical hypokalemia require a larger dose of KCl to prevent life-threatening complications.

TH-PO615
Revisiting the Effectiveness of Sodium Polystyrene Sulfonate in Treating Hyperkalemia
Baidaa Najeeb Mohammed, 1 Farhad Mohammmed-Hasan, 1 Richard H. Sterns. 1, 2 Medicine, Rochester General Hospital, Rochester, NY; 3 Medicine (Nephrology), Univ of Rochester School of Medicine and Dentistry, Rochester, NY.

Background: Sodium polystyrene sulfonate (SPS) is a K⁺-binding resin commonly used to treat hyperkalemia. No studies in humans or animals show that SPS increases K⁺ elimination [Sterns RH, J Am Soc Nephrol. 2010;21(5):733-5]. A recent study cited a dose-response relationship as evidence that SPS is effective [Kessler C, J Hosp Med.](including dialysis); repeated doses < 6 hrs apart; hemolysis and absence of follow up labs.

Methods: Fifty-eight patients (43 male and 15 female) with non-HypoPP and the exclusion of HypoPP were consecutively enrolled over an eight-year period. Blood and spot urine samples were collected for electrolytes, acid-base and biochemistry measurement on admission and during therapy. Intravenous potassium chloride (KCl) at a rate of 10-20 mmol/hour was administered until muscle strength recovered.

Results: The average K⁺ concentration was 1.8 ± 0.3 mmol/L. Their electrolyte could be simplified by the urinary K⁺ excretion rate and blood acid-base status. For a low urinary K⁺ excretion, chronic alcoholism, anorexia/bulimia nervosa, and remote diuretics use were the most common causes. For a high urinary K⁺ excretion, patients were divided into two subgroups: metabolic acidosis, renal tubular acidosis and chronic tubulo-alveolar abuse were common causes. Mineralocorticoid excess state with primary aldosteronism, Gitelman’s or classic Bartter’s syndrome, and diuretics use were common causes for metabolic alkalosis with high and normal blood pressure, respectively. Muscle strength was restored at serum K⁺ concentration of 2.6 ± 0.2 mmol/L after administering approximately 245 mmol (3.8 ± 0.8 mmol/kg) KCl. Of note, non-HypoPP patients with high urinary K⁺ excretion needed a higher KCl dose than those with low K⁺ excretion (4.0 ± 0.8 vs 3.2 ± 0.5 mmol/kg, p < 0.001). KCl supplementation was higher in patients who developed a paradoxic fall in serum K⁺ concentration (1.6 ± 0.2 mmol/L) than those without (4.1 ± 0.7 vs 3.4 ± 0.7 mmol/L, p < 0.001). These patients often had typical volume depletion with higher plasma renin activity.

Conclusions: Understanding the common etiology of non-HypoPP may aid in early diagnosis. Non-HypoPP patients associated with renal K⁺ wasting or hypovolemia that tend to develop paradoxical hypokalemia require a larger dose of KCl to prevent life-threatening complications.

TH-PO616
Relowering Sodium after Overcorrection of Hyponatremia: Save the Brain.

Relowering Sodium after Overcorrection of Hyponatremia: Save the Brain.

TH-PO618
Tritheryth (Saline, Urea, Desmopressin = SUD) as Initial Therapeutic Regimen for Sodium Rate Control in Patients with Non-Oedematous Severe Hyponatremia
Alain Soupart,1 Guy Decaux, 2 Michel Coffernils, 1 Bruno Couturier, 1 Frédéric Vanderghynst, 1 Internal Medicine, Jolimont/ Tubize Hospital, Tubize; Internal Medicine, Erasmus Univ Hospital, Brussels.

Background: There is no consensus about optimal treatment of severe hyponatremia (HN) [Severe risks of inadvertent overcorrection and ODS exists with the usual methods of correction (normal or hyperoncotic saline ± furosidem)]. We evaluate the effect of a treatment combining normal saline with urea and DDAVP (SUD regimen) during the first 24hr as initial treatment in non-oedematous HN owing to control the rise (ASNa < 12 mEq/l/24h) in SNa (DDAVP) and to protect brain against ODS (urea).

Methods: Ten consecutive non-oedematous patients with severe HN were included in the study. Patients with severe symptoms (coma, epilepsy) were excluded. Treatment consists in: [normal saline 1 l + oral urea 30 gr + DDAVP 4 µg s.c.] every 12 hours during the first 24hr. Treatment was adapted at 12hr depending on the correction level (if ASNa ≥ 5 mEq/l, no second urea dose; ≤ 2 mEq/l, no second DDAVP dose; ≥ 10 mEq/l at any time, active treatment stopped).

Conclusions: SUD regimen is associated with a good sodium rate control and a favourable outcome in patients with non-oedematous HN of various origins.

TH-PO619
Hyponatremia Is Associated with Increased Osteoporosis and Bone Fractures in a Large Health System Population
Laura Cowen, 1 Stephen Fernandez, 2 Nawar M. Shara, 1 Julianna Barsony, 1 Joseph G. Verbalis, 1 Endocrinology, Georgetown Univ, Washington, DC; 2 Medstar Health Research Institute, Washington, DC.

Background: Four independent studies have shown increased bone fractures in patients with hyponatremia (HN). Likely major contributors include gait instability and increased falls in HN patients. Recent animal studies have also demonstrated HN-induced bone loss, and analysis of human subjects in NHANES III showed a significantly increased odds ratio for osteoporosis in HN subjects.

Methods: To assess the clinical significance of these findings, we analyzed the patient database of the MedStar Health system using the Explorys electronic health record (EHR) tool.

Results: A search of >2.8 million unique EHR records showed that 55,510 patients had osteoporosis by ICD-9 coding; of this group, 8,060 had HN by either ICD-9 coding or laboratory measurement (serum Na < 135 mmol/L) and 47,450 did not. The prevalence of osteoporosis in the HN patients was 4.6% (8,060/177,100 total HN patients), compared to 1.8% in the non-HN patients (47,450/2,623,200 total non-HN patients). Because not all bone fractures are associated with osteoporosis, we also analyzed the occurrence of fractures with hyponatremia. A larger number of patients, 112,840, had bone fractures by ICD-9 coding; of this group, 16,820 had HN and 96,020 did not. The prevalence of fractures in the HN group was 9.5% (16,820/177,100 total HN patients), compared to 3.7% in the non-HN patients (96,020/2,623,200 total non-HN patients). Demographic analysis of HN and non-HN subjects with osteoporosis and fractures indicated a larger percentage of affected men in the HN group (17.5%) versus the non-HN group (14.2%). Age group predominance

The outcome was good in all the patients and brain CT or MRI were normal.

Conclusions: SUD regimen is associated with a good sodium rate control and a favourable outcome in patients with non-oedematous HN of various origins.
was similar in both groups with the majority of affected patients aged 70-89. This analysis indicates that both osteoporosis and bone fractures are increased approximately 2.6-fold in HD patients compared with non-HN patients.

Conclusions: These results support the hypothesis that IN is a risk factor for both osteoporosis and bone fractures in patients; our results also demonstrate the power of focused analysis of the EHR to assess the clinical relevance of findings generated from translational studies.

Funding: Other NIH Support - Supported by grant ULTR00101

TH-P0620
Hypnotizatia Is a Surrogate Mark of Severity in Uremic Patients with Peritoneal Dialysis-Related Peritonitis
Min-Hau Tseng,1 Shih-Hua Li,1 Sung-Sen Yang,1 Chih-Jen Cheng,2 Div of Nephrology, Dept of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan; 2Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, Taipei, Taiwan.

Background: The association of hypotonia with clinical outcome in dialysis patients is not well studied, especially in peritoneal dialysis-related peritonitis (PDPR). The aim of this study was to evaluate the impact of hypotonia in patients with PDPR.

Methods: We retrospectively reviewed the medical records of the dialysis patients admitted with PDPR over the past eight years. Patients were divided into two groups: one with serum Na+ <130 mEq/L (group I) and the other ≥130 mEq/L (group II). The primary endpoint was mortality during hospitalization. Secondary outcomes included length of hospital stay, removal of peritoneal dialysis (PD) catheter, peritonitis occurrence, and failure of PD.

Results: Of 99 patients with PDPR, group I had 27 and group II 72 patients. Gram-negative bacilli and gram-positive cocci accounted for the majority of PDPR in Group 1 and 2, respectively. There was no significant difference in age, duration of dialysis, PD catheter removal rate and technique failure between 2 groups. Group I had a significantly higher serum CRP (p < 0.001), lower serum albumin (p < 0.01) and phosphate (p < 0.05). There was a positive correlation between serum Na+ and albumin concentration (p = 0.001) as well as serum phosphate level (p < 0.04). Length of hospital stay (p < 0.001) and hospital mortality (p < 0.001) were also significantly higher in group I than II. In a multivariable logistic regression, hypotonia on admission remained an independent predictor of hospital mortality (OR 76.89, 95% CI 3.39-1744.67, p < 0.05) and independently associated with length of hospital stay (OR 3.75, 95% CI 1.56-18.19, p < 0.05).

Conclusions: The degree of hypotonia in uremic patients with PDPR reflects the severity of peritonitis and is associated with length of hospitalization and mortality.

Funding: Clinical Revenue Support

TH-P0621
Prognostic Impact of Hypotonia Occurring at Various Time Points During Hospitalization on Long-Term Mortality in Patients with Acute Myocardial Infarction
Jeon Seok Choi,1 Ha Yeon Kim,1 Yong Un Kang, Chang Seong Kim,1 Eun Hui Bae,2 Seong Kwon Ma, Soo Wan Kim.1 Dept of Internal Medicine, Div of Nephrology, Gungwu, Korea.

Background: We investigated the incidence and prognostic impact of hypotonia occurring at various time points during hospitalization on long-term mortality in patients surviving an episode of acute myocardial infarction (AMI).

Methods: We retrospectively studied 1,863 patients diagnosed with AMI. Baseline, nadir, discharge, and average sodium levels during hospitalization were recorded and statistically analyzed. Hypotonia was defined as a sodium level <135 mEq/L.

Results: On the basis of baseline, nadir, discharge, and average sodium levels during hospitalization, hypotonia was diagnosed in 309 (16.6%), 518 (27.8%), 147 (7.9%), and 140 (7.5%) patients, respectively. In a multivariate Cox-proportional regression analysis, discharge sodium level had the strongest significant relationship to long-term mortality (hazard ratio [HR] as continuous variable = 1.07, 95% confidence interval [CI] 1.01-1.13, P = 0.014; HR as categorical variable = 1.75; 95% CI: 1.09-2.80; P = 0.021), but baseline sodium had no prognostic impact on long-term mortality after adjustment.

Conclusions: The serum sodium level and incidence of hypotonia varied at different points during hospitalization. In addition, the association between sodium level and long-term mortality differed at these various time points. The discharge sodium level appears to be the best predictor of long-term mortality in patients surviving an acute episode of AMI.

TH-P0622
The Physiological Role of Adaptor Protein 1B on the Surface Trafficking of Kidney Anion Exchanger 1
Emsal Yousuf Almamoun, Emmanuelle Cordat. Physiology, Univ of Alberta, Edmonton, Canada.

Background: Distal Renal Tubular Acidosis (dRTA) is a disease characterized by metabolic acidosis, an inability to acidify urine, the development of kidney stones and renal failure if untreated. DRTA patients may carry a mutation on the SLC4A1 gene encoding the kidney anion exchanger 1 (kAE1), a Cl-/HCO3−-exchanger basolaterally expressed in acid-secreting kidney intercalated cells. KAE1 binds to the epithelial-specific adaptor protein 1B (AP-1B) complex, which is essential to trafficking and recycling cargo proteins. The apically mis-targeted kAE1-R901X that occurs naturally, and the engineered Y904A/V907A or mutants in porcine epithelial kidney cells (LLC-PK1) that are naturally devoid of endogenous AP-1B.

Methods: To study the role of AP-1B, we stably expressed kAE1 wild-type (WT) or mutants in porcine epithelial kidney cells (LLC-PK1) that are naturally devoid of endogenous AP-1B.

Results: Cell surface biotinylation and immunoblotting showed that the expression of AP-1B significantly increased the amount of total and cell surface kAE1-WT in LLC-PK1 cells treated with cycloheximide for 8 hours, but not that of kAE1-R901X or Y904A/V907A mutants. The AP-1B independent Na+/K+-ATPase did not show such a significant difference of surface expression upon AP-1B expression, suggesting that the effect of AP-1B is specific to kAE1. We further examined the effect of AP-1B on kAE1 endocytosis and recycling to the cell surface.

Conclusions: This study highlights the importance of AP-1B for kAE1 stability at the cell surface. Loss of mutated kAE1 and AP-1B interaction may explain the pathogenicity of dRTA.

Funding: Private Foundation Support

TH-P0623
Comparison of Arterial Blood Gas versus Laboratory Electrolyte Measurements in Critically Ill Patients at Cleveland Clinic Florida
Julianne M. Parente, Rute C. Paixao, Mauro Braun, Diane T. Sanny. Nephrology, Cleveland Clinic Florida, Weston, FL.

Background: Electrolyte measurements are performed by Arterial Blood Gas (ABG) analyzers and laboratory analyzers. However, a significant time gap exists between availability of these results, with ABG giving faster results. The aim of the present study was to investigate whether ABG analyzers can provide an accurate measurement of electrolytes as compared to laboratory based analysis. ABG results may enable the critical care team to make faster clinical decisions, improve quality of care and decrease mortality rates. Data on serum potassium and chloride were obtained and compared.

Methods: We retrospectively studied 111 patients admitted to the Cleveland Clinic Florida (CCF) Intensive Care Unit (ICU) between February and June 2013. ABG electrolyte results were compared with results from that day’s laboratory results when the samples were obtained within one hour of each other. All patients with any acute or chronic condition were considered possible subjects for the study. The research protocol was approved by the Institutional Review Board.

Results: A total of 111 blood samples were analyzed. The mean patient age was 66.7 years. 64.8% of the subjects were males. 57% of the patients were admitted to the Surgical ICU and the remainder to the Medical ICU. 66.6% of the patients had an arterial line in place at the time of the sample collection. The mean sodium concentration was 140.6 mmol/L (SD 5.74) using the serum and 137.7 mmol/L (SD 5.66) (p=0.293) using the ABG analyzer. Mean potassium level was 4.1 mmol/L (SD 0.63) using the serum and 3.96 mmol/L (SD 0.63) (p=0.006) using the ABG analyzer. Mean chloride values were 102.4 mmol/L (SD 7.58) and 104.8 mmol/L (SD 7.37) (p=0.016) using the laboratory and ABG analyzers, respectively.

Conclusions: Based on the above analysis, we found no significant difference between the sodium values measured by the blood gas machine and the laboratory analyzer. However, the differences between the measured potassium and chloride were found to be significant. We therefore conclude that critical decisions can be made by trusting only the sodium levels obtained from the blood gas analysis.

TH-P0624
Analysis of Chondroitin Sulfate Proteoglycans and Reactive Astroglia In a Rat Model of Osmotic Demyelination Syndrome
Bruno Couturier,1 Fabriche Gankam,2 Alain Soupert,3 Guay Decaux.1 1Internal Medicine, Erasme Hospital Free Univ of Brussels, Brussels, Belgium; 2Nephrology, Erasme Hospital Free Univ of Brussels, Brussels, Belgium; 3Internal Medicine, Jolimont Hospital Free Univ of Brussels, Brussels, Belgium.

Background: Osmotic demyelination syndrome (ODS) results from overly rapid correction of chronic hypotonia (HypoNa) and its pathophysiology is not yet fully understood. Specifically it is not clear which factors might promote or impede remyelination and clinical recovery. Using a rat model, we studied several molecules known as markers of glial activation (nestin and vimentin) and inhibitors of axonal growth including chondroitin sulphate proteoglycans (CSPG’s) in order to determine their role in CNS regeneration after osmotic insult.

Methods: Chronic hypotonia were induced in rats by continuous infusion of ADH and corrected with hypertonic saline. At various times after the correction we used immunohistochemistry to assess expression of vimentin, nestin and several CSPG’s. Immunofluorescence was used to identify which cells expressed these molecules.

Results: We confirmed an increase in glial fibrillary acidic protein at the borders of the ODS lesions after rapid correction of chronic hypoNa. Moreover, we showed an upregulation of Nestin and vimentin in astrocytes of corrected animals from day-to-day after the correction. We also confirm the expression of three CSPG’s, CD44, neurocan and phosphacan KS in the direct vicinity of osmotic lesions following a peculiar pattern. CD44 and neurocan were distributed in the lesions penumbra whereas phosphacan KS was mainly found in the lesion core. CSPG’s deposition only appeared 72h after correction and was more prominent 6 days after correction.

Conclusions: These results suggest a specific pattern of CSPG’s and nestin/vimentin expression in brain after osmotic insult. Their role in myelin regeneration after osmotic insult remains to be determined.

Funding: Private Foundation Support
Role of Tubular Luminal H(+)/Organic Cation Antipporter, MATE, in Natriuresis as a Dopamine Transporter

Moto Kawai,1 Tsuyoshi Ban, Kazu Matsumbara, Satohiro Masuda. Clinical Pharmacology and Therapeutics, Kyoto Univ Hospital, Kyoto, Japan.

Background: The intrarenal dopaminergic system is likely responsible for regulating over 50% of net renal salt and water excretion when salt intake increases. Although dopamine synthesis is localized at proximal tubular cells, the molecular mechanism underlying dopamine secretion from the kidney remains unknown. Multidrug and toxin extrusion (MATE, SLC47A) was identified in 2005; it is expressed in high levels in the brush border membrane of proximal tubular cells mediating the efflux of organic cations such as methotrexate and cisplatin, from epithelial cells into urine. Therefore, we hypothesized that MATE mediates dopamine secretion, a cationic catecholamine, into tubule lumen and consequently regulates natriuresis.

Methods: Sodium levels in the urine and whole blood of mice were respectively measured using an ion-selective electrode (cobas6000, Roche) and an iSTAT analyzer (Abott). Urinary dopamine concentration was measured with a liquid chromatography-tandem mass spectrometry.

Results: To determine whether dopamine is a substrate of MATE, we examined [3H]dopamine uptake in HEK293 cells transiently expressing human (h) MATE1, hMATE2-K, and mouse (m) MATE1. Uptake of [3H]dopamine by cells expressing hMATE1, hMATE2-K, and mMATE1 was higher than that of vector-expressing cells. In vivo acute saline-loading experiments using infusion pump were performed to examine MATE contribution on urinary dopamine transport in mice. Urinary dopamine was detected in wild-type mice (WT), but was hardly present in MATE1-knockout mice (KO). Another experiment showed that the amount of urinary sodium excretion in WT increased to 12.3-fold than that of the control group, although the amount in MATE1-KO increased to only 1.5-fold than that of the control group. In intact mice, average whole blood sodium levels were significantly higher (mean ± SD, P > 0.003) in MATE1-KO (146.7 ± 0.58 mmol/L) than those in WT (143.7 ± 0.58 mmol/L).

Conclusions: In conclusion, our results indicated a critical role of MATE in dopamine secretion into tubular lumen, along with MATE’s regulation of sodium excretion into urine.

Funding: Government Support - Non-U.S.

Mapping of pH Sensor, GPR4, to Peritubular Capillaries

Doris P. Molina,1 Xuming Sun,1 Glen S. Mars,1 Thomas D. Dubose,2 Snezana Petrovic,1,2 Yu-Wei Fang,1 Sung-Sen Yang,1 Chih-Jen Cheng,1 Shih-Hua P. Lin,1,2 'Diabetes, Vanderbilt Univ, Nashville, TN; 2Medicine, Wake Forest School of Medicine, Winston Salem, NC.

Background: Proton secretion increases in the OMCD in response to an acid load that occurs as a product of the metabolism of protein derived from a typical Western diet to defend against metabolic acidosis. We have shown that proline-rich tyrosine kinase-2 (Pyk2), a putative pH sensor, participates in the regulation of apical ATPase-mediated proton transport in the OMCD.

Methods: In the current study we used the NH4Cl pre-pulse technique to generate an acid intracellular pH (pHi, ~6.7) in mouse-derived inner medullary (mOMCD1) cells in vitro (control pHi, ~7.4). We then analyzed rates of pHi recovery after an NH4Cl pre-pulse using spectrofluorometry of BCECF-AM-loaded cells. Pyk2 inhibition was accomplished by two approaches: using an adenovirus expressing a truncated Pyk2 construct (AdCRNK), and inhibition of p38, using the inhibitor SB203580.

Results: Analysis of protein phosphorylation using immunoblot shows that Pyk2 and MAPK p38 are rapidly phosphorylated at acid pH (3.4 and 3.8 fold increase, respectively, after 1 minute). H+-ATPase-mediated pHi recovery was significantly inhibited after an NH4Cl pre-pulse (68% by the adenovirus construct and 69% by SB203580). We assume that the unaffected pHi recovery may be attributed to unaffected H+-ATPase-mediated pHi recovery.

Conclusions: In summary, we show that Pyk2 is required for p38 phosphorylation and subsequent H+-ATPase activation in response to acid pHi in the outer medullary collecting duct. Taken together with our previous study (Am J Physiol Renal Physiol 363: F1353–F1362, 2012), these new results indicate that a decrease in pHi, two distinct MAPK pathways (p38 and ERK1/2) regulate H+-ATPase and H+,K+-ATPase activity, respectively, via the pH sensor, Pyk2.

Funding: Clinical Revenue Support

Dietary Protein Restriction Induces an Integrated Response Involving Multiple Aspects of Renal Ammonia Metabolism

Hyun-Wook Lee,1 Jesse M. Bishop,1 Mary E. Handlogten,1 Jill W. Verlander,1 I. David Weiner,1,2 Renal Div, Univ of Florida, Gainesville, FL; 1Nephrology and Hypertension Section, GVAMC, Gainesville, FL.

Background: Both low protein diets and systemic acid-base status have important effects on the progression of chronic kidney disease. Because ammonia metabolism is a major determinant of renal acid-base homeostasis, we examined the effect of dietary protein restriction on renal ammonia metabolism. Because we identified novel effects of protein restriction on expression of the ammonia transporter family member, Rhbg, we also determined the effect of collecting duct-specific Rhbg deletion (CD-Rhbg-KO) on the response to protein restriction.

Methods: C57Bl/6 mice were acclimated in metabolic cages and then randomly assigned to either low (6%) or control (20%) protein diets for two weeks. Daily 24 hr urine was collected. At the end of the study, tissue was obtained for immunoblot analysis and immunohistochemistry. CD-Rhbg-KO mice were generated using Cre-loxP techniques and were studied using an identical protocol.

Results: Low protein diet decreased urinary ammonia excretion by 85–90%. It also decreased by 40% renal cortical PEPC, did not alter either renal cortical or outer medullary red blood cell glutamine synthetase expression. Rhbg expression increased in the outer medulla, and immunohistochemistry demonstrated changes in expression were limited to intercalated cells in the outer medullary collecting duct (OMCD). However, CD-Rhbg-KO did not alter changes in urinary ammonia excretion in response to low protein diet, nor alter urine pH or low-protein induced changes in PEPC, PDG or GS in renal homogenates.

Conclusions: We conclude: (1) Low protein diet decreases renal ammonia excretion through mechanisms involving both decreased ammoniagenesis involving PEPC and increased ammonia assimilation involving glutamine synthetase; (2) low protein diet results in increased OMCD intercalated cell Rhbg expression which is not necessary for the reduced urinary ammonia excretion; and, (3) Rhbg may have previously unidentified roles in the renal response to low protein diet which are unrelated to ammonia excretion.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Affairs Support

Th-P0628

Acid-Stimulated Pyk2 Regulates H+/K+-ATPase Activity via a p38 MAPK Signaling Pathway in Outer Medullary Collecting Duct Cells

Kimberly Fisher,1,2 Thomas D. Dubose,2 ‘Medicine, Vanderbilt Univ, Nashville, TN; 2Medicine, Wake Forest School of Medicine, Winston Salem, NC.

Conclusions: Proton secretion increases in the OMCD in response to an acid load that occurs as a product of the metabolism of protein derived from a typical Western diet to defend against metabolic acidosis. We have shown that proline-rich tyrosine kinase-2 (Pyk2), a putative pH sensor, participates in the regulation of apical ATPase-mediated proton transport in the OMCD.
(6.70±0.4% vs 2.5±0.6% in WT, n=7, P<0.05) and WT mice with NH4Cl (FeNa 7.8±1.5% vs 2.7±0.4% in WT without NH4Cl, n=5, P<0.05). However, the SCC expression and activity was not increased in SPAK null mice with NH4Cl.

Conclusions: Chronic metabolic acidosis might alter SCC phosphorylation and function at least in part through SPAP-dependent signal cascade. Whether WNK1/4 kinase, the upstream stimulators of SPAK, is involved needs to be further investigation.

TH-PO630
A Mouse Model of Kidney Stone Cause by Double Deletion of Pendrin and the Na-CI Cotransporter (NCC) Sharon L. Barone, 1, 2 Jie Xu, 1, 2 Hassanne Amlal, 1, 2 Kamyaar A. Zahedi, 1, 2 Manoocher Soleimani. 2 Internal Medicine, Univ of Cincinnati, Cincinnati, OH; 2Research Services, VA Administration, Cincinnati, OH.

Background: Kidney stones are a major cause of morbidity due to associated infection and kidney failure. The Cl-HCO3’ exchanger pendrin and NCC are expressed on the apical membranes of distal nephrons and mediate salt absorption. In mice, solitary KO of NCC causes hypocaliuria whereas KO of pendrin in isolation causes mild hypercalciuria. Neither NCC- nor pendrin-KO mice have salt wasting under baseline conditions. Mice with simultaneous knockout of pendrin and NCC (dKO), on the other hand, show severe salt wasting and volume depletion.

We hypothesize that NCC deletion offsets the hypercalciuric effect of pendrin deletion in dKO mice.

Results: 24 h urine analysis showed a 3-fold increase in calcium excretion in dKO mice. The histological analysis of kidneys demonstrated multiple calcium stones in the medullary collecting ducts in dKO mice but not in pendrin or NCC single KO mice. The stones did not polarize under microscope but stained with Von Kossa stain, consistent with calcium phosphate stones. Phosphate excretion increased by 2-fold and correlated with significant reduction in NaPi2a expression in proximal tubule in dKO mice. Serum calcium was mildly reduced in dKO mice but remained normal in single KO or WT mice. Blood levels for PTH, 1,25 Vitamin D and FGF23 in dKO mice were comparable to WT or single KO mice. Urine pH in dKO mice was comparable to WT animals (~6.2) even though it was reduced in pendrin KO mice (~5.0). Salt loading for 7 days in dKO mice rectified the volume depletion, increased the urine output and dissolved the kidney stones, but did not affect the hypercalciuria or hyperphosphaturia.

Conclusions: We were wrong about our prediction of calcium excretion in dKO mice. We conclude that the combined deletions of NCC and pendrin cause profound hypercalciuria and hyperphosphaturia and result in calcium phosphate kidney stones, which were resolved by salt repletion. Whether the combination of pendrin deletion, which down regulates TRPV5, and volume depletion predispose dKO mice to kidney stones remains to be determined.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO631
Key Insights into the Regulation of Pendrin and AE1 Transporter Expression in Cortical Collecting Ducts by 3D Morphometric Analysis Jeffrey M. Parkerson, George J. Schwartz. Pediatrics, Univ of Rochester School of Medicine, Rochester, NY.

Background: Previous studies utilizing kidney sections suggested altered distribution or trafficking of pendrin or AE1 as possible mechanisms for adaptation of the cortical collecting duct (CCD) to acid/base disturbances.

Methods: To better understand regulation of anion exchanger function in intercalated cells (ICs), we examined pendrin and AE1 morphology via 3D cell reconstruction of confocal images of microdissected CCDs. The IC cell shape was measured by calculating the width:depth (W:D) ratio of AE1 staining. During acidosis, the outer edge (Normal= 1.1±0.03, Acidosis =1.6±0.09; p<0.0004). Upon recovery from acidosis, the ratio returned to near normal (1.2±0.04 vs. NL, p<0.05).

Conclusions: Pendrin traffics through early endosomes, and adaptation to acidosis occurs at least in part via reduction in recycling pendrin. The observed changes in α-cell shape and AE1 distribution likely function to increase basolateral surface area and the supply of AE1 available for anion exchange.

Funding: NIDDK Support

TH-PO632
The Thick Ascending Limb Is an Important Site of Furosemide-Induced Urinary Acidification Pauline L.A. de Brujin, 1, 2 Nina Himmerkus, 1 Markus Blech, 1 Helle A. Praetorius, 1 Jens G. Leipziger. 1 Dept of Biomedicine-Physiology, Aarhus Univ, Aarhus, Denmark; 2Institute of Physiology, Christian-Albrechts Univ, Kiel, Germany.

Background: Furosemide is a loop diuretic that inhibits NaCl reabsorption in the thick ascending limb (TAL). In addition, furosemide causes urinary acidification and eventually metabolic alkalosis. It is traditionally explained by an increased Na’ load to the distal tubule, which is suggested to facilitate H’ secretion via the apical H’-ATPase in α-intercalated cells. The direct role of TAL on the urinary acidification, however, has never been investigated.

Methods: We measured pH and pHe in single perfused mouse mTALs with BCECF-AM and BCECF acid, respectively.

Results: Interestingly, luminal furosemide (100 µM) caused a major, stable and reversible intracellular alkalization both in HEPES (0.33 ± 0.04, n=7) and CO2/HCO3’, -buffered conditions (0.14 ± 0.03, n=5). This alkalization likely indicates increased H’ excretion from the mTAL cytosol. Intriguingly, the furosemide-induced alkalization was completely blocked by 1 mM thalidomide, an agent that fully inhibits the NHE3 anion transporter. This was confirmed with the NHE3 specific blocker #4167, which also was capable of fully inhibiting the alkalization by furosemide. Blocking of the basolateral NHEs did not have any effect on the furosemide-induced alkalization. Thus, furosemide likely acts upstream of NHE3 and blocks a secretory pathway.

Conclusions: We show that furosemide causes an intracellular alkalization in the mTAL that is mediated through activation of apical NHE3. This alkalization is mirrored by an acidification of the tubular fluid, suggesting that furosemide-induced urinary acidification already takes place in the TAL. These results revise the mechanistic understanding of furosemide-induced urinary acidification.

TH-PO633
Acid-Induced Off-Response of PKD2L1 Channel in Xenopus Oocytes and Roles of Ca Shaimaa Hussein, Chris Dyte, Wang Zheng, Jungwoo Yang, Xing-Zhen Chen. Membrane Protein Disease Research Group, Dept of Physiology, Univ of Alberta, Edmonton, Canada.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is due to mutations in PKD1 or PKD2. PKD2L1 is a homologue of PKD2 but does not seem to be implicated in sensing extracellular pH in the tongue as well as in the nervous system. Nevertheless, PKD2L1 is activated by Ca and acid. Ca-induced activation was demonstrated when PKD2L1 alone was expressed in Xenopus oocytes while acid-induced activation was shown when PKD1L3, a homologue of PKD1, was co-expressed. Acid induces an off-response, ie; channel is not activated until the extracellular acid is removed. The mechanisms of, and relationship between, Ca- and acid-induced activations remain unclear.

Methods: Here, we showed by the two-microelectrode voltage clamp technique that PKD2L1 over-expressed alone in Xenopus oocytes exhibits acid-induced off-response current that was augmented with decreasing the extracellular pH than pH 4.5, in a dose-dependent manner.

Results: Neither acid application time nor extracellular trace amounts of Ca is essential for the off-response. Interestingly, addition of Ca to extracellular solution at pH 7.5 resulted in an off-response current, with a Ki value ~150 µM, a phenomenon that we called ‘Ca reset’. In addition, pre-injection of Ca chelator, EGTA, to PKD2L1-expressing oocytes abolished Ca-induced activation as reported but did not block the off-response. Further, EGTA pre-injection abolished the ‘Ca reset’, ie; extracellular Ca no longer blocked the channel in current, suggesting that the off-response is inhibited by intracellular Ca. Finally, we showed that PKD2L1 mutation D523N abolished Ca-induced activation and substantially reduced the off-response.

Conclusions: Taken together, our study showed that Ca- and acid-induced activations have distinct mechanisms and that Ca plays an important role in the off-response. PKD2L1 expressed alone in oocytes exhibits acid-induced off-response current that have similar characteristics as those previously reported for the PKD2L1/PKD1L3 channel complex. Supported by CIHR, AHF (to XZC) and ATP (to SH).

Funding: Government Support - Non-U.S.

TH-PO634
The Role of Sevelamer Carbonate in Increasing Serum Bicarbonate in Hyperphosphatemic CKD Patients with Metabolic Acidosis Sarah Bezaaoucha, 1 Vincent Picchette, 1 Jean-Philippe Lafraence, 1 Robert Zoel Bell, 1 Louis-Philippe Laurin, 2 Michel Vallee. 1 Nephrology, Hopital Maisonneuve-Rosemont, Montreal, Canada; 2UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.

Background: Chronic metabolic acidosis and hyperphosphatemia are prevalent complications in patients with advanced chronic kidney disease. Sevelamer-HCL, a phosphate binder for which the hydrochloride acid is loaded in exchange for phosphate in the intestinal tract, has been previously shown to worsen metabolic acidosis in CKD-patients. However, the use of sevelamer carbonate, a buffered form of sevelamer-HCL in

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

244A
which chloride is replaced by bicarbonate, is expected to increase serum bicarbonate and has been proposed as an alternative strategy for the treatment of CKD patients.

To further study the role of increased serum bicarbonate, we retrospectively studied the effects of sevelamer carbonate on serum bicarbonate level in 56 acidotic CKD patients not yet receiving maintenance dialysis and for whom sevelamer carbonate was started in order to control their hyperphosphatemia. Serum phosphorus and serum bicarbonate concentrations were assessed before and at monthly intervals (up to 4 months) after receiving sevelamer carbonate.

Results: Bicarbonate mean levels were compared using paired Student’s-t-tests and mixed-effects linear regression models. The mean bicarbonate level increased from 19.1 ± 5.5 mmol/L before sevelamer carbonate to 21.9 ± 2.9 (p<0.008), 22.2 ± 2.2 (p<0.001), and 22.9 ± 2.5 mmol/L (p<0.001) after the 2nd, 3rd and 4th months of sevelamer carbonate treatment, respectively. In the use, the sevelamer carbonate was associated with a statistically significant decrease in the mean serum phosphorus levels: from 1.62 ± 0.22 mmol/L to 1.38 ± 0.26 (p=0.006) and 1.42 ± 0.23 mmol/L (p<0.005) at the 3rd and 4th months, respectively.

Conclusions: Our study clearly shows that sevelamer carbonate is actually not only effective as a phosphate binder but also at increasing serum bicarbonate levels to normal values. This could be advantageous for patients who do not receive alkali benefits from dialysis and for whom sodium bicarbonate supplementation is problematic.

Funding: Government Support - Non-U.S.

TH-PO635

Regulation of the Vacular H+-ATPase by 14-3-3 Proteins

Mohammad M. Al-Bataineh,1 Fan Gong,1 Hui Li,2 Vivek Bhalla,2 Kenneth R. Hallows,1 Nuria M. Pastor-Soler.1 1 Medicine, U. of Pittsburgh, Pittsburgh, PA; 2 Medicine, Stanford U., Stanford, CA.

Background: The vacuolar H+-ATPase (V-ATPase) mediates ATP-driven transport of H+ across membranes against a gradient. The V-ATPase is expressed at the apical membrane of kidney cells, including the intercalated cells. We used Clone C cells of intercalated cell origin, Clone C cells, and determined that the A subunit is phosphorylated directly by AMPK. In addition, AMPK activators induce an apical chloride transport that is enhanced in Clone C cells treated with the AMPK activator AICAR as compared with untreated cells. Moreover, additional preliminary results show that the phosphorylation-deficient Ser-to-Ala A-subunit mutant has decreased binding to 14-3-3 proteins. Moreover, AMPK activation inhibits V-ATPase activity and expression at the apical membrane of ICs, with an effect that was prevented in expression of this Ser-to-Ala mutant.

Conclusions: 14-3-3 proteins may directly bind the V-ATPase A subunit at the AMPK phosphorylation site and perform co-immunoprecipitation and immunoblot studies. Extracellular pH measurements, immunofluorescence labeling and confocal microscopy were also performed on polarized Clone C cells to examine V-ATPase activity and subcellular localization.

Funding: NIDDK Support, Pharmaceutical Company Support - Sanofi Fellowship

TH-PO636

Changes in Intercalated Cell Subtypes in Response to Chronic Furosemide Administration

Su-Youn Lee,1 Ji-Eun Kim,2 Jin Seo Lee,1 David Weiner,2,3 Ki-Hwan Han.1 1 Dept of Anatomy, Ehwa Womans Univ, Seoul, Korea; 2Div of Nephrology, Hypertension, and Transplantation, Univ of Florida, Gainesville, FL; 3 Nephrology and Hypertension Section, North Florida/South Georgia Veterans Health System, Gainesville, FL.

Background: Renal intercalated cells play a critical role in acid-base homeostasis and also contribute to the regulation of intravascular volume via CI transport. The diuretic furosemide causes intravascular volume depletion and stimulates proton secretion. The purpose of this study was to examine the effect of chronic furosemide administration on intercalated cell subtypes in the rat kidney.

Methods: Male Sprague-Dawley rats received furosemide (12 mg/kg/day) via an osmotic minipump for 7 days; control rats received vehicle.

Results: We detected increased co-immunoprecipitation of 14-3-3 proteins to wild-type A subunit in Clone C cells treated with the AMPK activator AICAR as compared with untreated cells. Moreover, additional preliminary results show that the phosphorylation-deficient Ser-to-Ala A-subunit mutant has decreased binding to 14-3-3 proteins. Moreover, AMPK activation inhibits V-ATPase activity and expression at the apical membrane of ICs, an effect that was prevented in expression of this Ser-to-Ala mutant.

Conclusions: 14-3-3 proteins may directly bind the V-ATPase A subunit at the AMPK phosphorylation site and perform co-immunoprecipitation and immunoblot studies. Extracellular pH measurements, immunofluorescence labeling and confocal microscopy were also performed on polarized Clone C cells to examine V-ATPase activity and subcellular localization.

Funding: NIDDK Support, Pharmaceutical Company Support - Sanofi Fellowship
Association of Serum Bicarbonate with Incident Chronic Kidney Disease in Community Living Elders: The Health ABC Study

Background: In populations with prevalent chronic kidney disease (CKD), lower serum bicarbonate (HCO₃⁻) is associated with more rapid CKD progression, independent of baseline eGFR. Metabolic acidosis may also be a risk factor for development of CKD but that has not been studied in addition. High bicarbonate may mark lung disease and smoking and may be associated with CKD.

Methods: We evaluated 1,076 well-functioning community-living elders who had HCO₃⁻ measured at baseline, creatinine and cystatin C at baseline and 7 years later, and diuretic use at follow-up. We adjusted the associations for baseline risk factors: diabetes, hypertension, smoking, race, sex, and age. HCO₃⁻ was centered on the mean at each visit to adjust for secular changes in the reference population.

Results: At baseline, the mean age was 75±3 years, eGFR was 86±13 mL/min/1.73m², and HCO₃⁻ was 25.2±1.9 mmol/L. Factors associated with lower HCO₃⁻ included male gender, white race, and smoking. In models adjusted for baseline eGFR, demographics, and CKD risk factors, individuals with HCO₃⁻<23mmol/L had a nearly 2-fold odds of incident CKD (Table). Higher levels were not associated with incident CKD.

Conclusions: Metabolic acidosis is a novel risk factor for development of incident CKD in community-living elders. If confirmed, HCO₃⁻ may give insights into kidney tubule health even among persons without CKD by standard clinical definitions.

Table. Association of HCO₃⁻ with Incident CKD in Community-Living Elders

<table>
<thead>
<tr>
<th>HCO₃⁻ group (mmol/L)</th>
<th>Incidence (n=48)</th>
<th>Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21.9</td>
<td>21 (0.72)</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>21.9-23.7</td>
<td>18 (0.63)</td>
<td>1.33 (0.73, 2.40)</td>
<td>0.85</td>
</tr>
<tr>
<td>&lt;21.9</td>
<td>5 (0.18)</td>
<td>0.20 (0.05, 0.82)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Funding: Other NIH Support - Ruth L. Kirschstein National Research Service Award

TH-PO640

Lack of Interaction between APOL1 Variants and Hypertension Treatment: The African American Study of Hypertension and Kidney Disease (AASK) Study

Background: APOL1 is a strong risk factor for CKD progression in African Americans. However, the interaction between APOL1 and blood pressure control is unknown.

Methods: The AASK trial was a multicenter, randomized trial of African American men ages 30-75 years, with stage 1 hypertension and eGFR between 60 and 90 mL/min/1.73m². The trial compared an intensive antihypertensive regimen with a standard regimen. A total of 3359 participants was randomized to the intensive or standard treatment group. APOL1 variants were assessed in a subsample of 2956 participants.

Results: The interaction between APOL1 and blood pressure treatment was not significant (p=0.85). The association between APOL1 and CKD progression was stronger in the standard treatment group than in the intensive treatment group. The effect of APOL1 on CKD progression was stronger in participants with lower baseline eGFR.

Conclusions: The lack of interaction between APOL1 and blood pressure treatment suggests that APOL1 is a useful genetic marker for CKD progression in African Americans, regardless of blood pressure control.
progression among African Americans with hypertension-attributed nephropathy by APOL1 risk allele status.

Methods: We performed a retrospective cohort study including 693 African American Study of Kidney Disease and Hypertension (AASK) participants. Using multivariable Cox models, we determined the hazard ratio for CKD progression (defined as development of ESRD or doubling of serum creatinine during follow up) associated with each putative risk factor stratified by APOL1 status (those with 2 copies of the high-risk variant vs. all others).

Results: Participant mean age was 54 years and 160 (23%) had APOL1 high-risk allele status. A total of 288 (41.6%) participants experienced CKD progression during a mean follow up of 7.8 years. Our base model adjusted for age, gender, % European ancestry, baseline GFR and randomized blood pressure and drug groups. We computed the hazard ratio (HR) comparing high vs. low risk allele status was 1.87 (95% CI 1.45-2.41). When additional variables were added to the base model, none appeared to modify the association between APOL1 high-risk allele status and CKD progression.

Conclusions: Among individuals with high-risk nephropathy, we found no factors modifying the risk of CKD progression associated with APOL1 genotype. Further investigation in larger studies is warranted to determine whether other environmental risk factors for progressive kidney disease exist among individuals with high-risk APOL1 alleles.

TH-PO645

APOL1 Genotype and Racial Disparity in Chronic Kidney Disease (CKD) Progression: The CRIC Study

Aashin Parmar,1 Dawei Xie,1 Chi-Yuan Hsu,2 Harold I. Feldman,3,2 John W. Kusek,5 Lawrence J. Appel,6,7 1Dept of Medicine, Univ of Maryland; 2Dept of Biostatistics and Epidemiology, Univ of Pennsylvania; 3Dept of Medicine, Univ of Pennsylvania; 4Dept of Medicine, UCSF; 5NIDDK, NIH; 6Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Univ; 7CRIC Study Group.

Background: African Americans (AAs) are at increased risk for end-stage renal disease (ESRD) compared to European Americans (EAs). APOL1 risk variants, present in AAs but nearly absent in EAs, may partially account for this disparity. We evaluated APOL1 genotype as a mediator of differences in CKD progression between AAs and EAs.

Methods: We studied 2955 participants of the Chronic Renal Insufficiency Cohort (CRIC) Study with CKD (48% AA, 46% with diabetes). We performed hierarchical multivariate analyses of CKD progression, stratified by diabetes and APOL1 genotype. Primary outcomes were slope in estimated glomerular filtration rate (eGFR) and the composite renal event of ESRD or halving of eGFR.

Results: Among participants with and without diabetes, AAs without the APOL1 risk genotype had a persistent, but attenuated elevation in the rate of renal events compared to EAs. Parallel comparisons of eGFR decline showed complete attenuation of the AA differences in the absence of APOL1 risk genotype (Table). Table. Adjusted Differences in eGFR Slope and Rate of Renal Events.

Conclusions: Among a cohort of African Americans with hypertension-attributed nephropathy, we found no factors modifying the risk of CKD progression associated with APOL1 high-risk allele status. Further investigation in larger studies is warranted to determine whether other environmental risk factors for progressive kidney disease exist among individuals with high-risk APOL1 alleles.

TH-PO646

p.E66Q Variant of α-Galactosidase A Does Not Affect the Progression of Chronic Kidney Disease

Hirofumi Watanabe,1 Shin Goto,1 Hiroki Maruyama,2 1Dept Medicine, Niigata University Graduate School of Medicine; 2Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background: The p.E66Q variant in the α-galactosidase A (GLA) is frequently found in the screening of Fabry disease in chronic dialysis patients in Japan. However, recent studies have suggested that pathologically and biochemically, p.E66Q of GLA is not a disease-causing mutation but a functional polymorphism. To evaluate the role of p.E66Q in progression of renal diseases, we performed a genetic association study in patients with chronic kidney disease.

Methods: We extracted genomic DNA from the blood of 2691 patients who attended medical institutions in Niigata Prefecture, Japan and agreed to genome analysis. These patients included 1705 chronic hemodialysis patients and 986 non-dialysis patients. The p.E66Q was detected using TaqMan SNP genotyping assay. We compared the allele frequency of p.E66Q in chronic hemodialysis patients with that of non-dialysis patients and Japanese general population (Eur J Neurol 2013). Furthermore, in non-dialysis patients, we compared eGFR in the presence or absence of p.E66Q variant.

Results: Among 2401 alleles in the chronic hemodialysis patients, 21 alleles were homozygotes from 1009 males, 14 were heterozygotes from 696 females, and one was homozygote from one female. The allele frequency in the chronic hemodialysis patients was 0.87%. Among 1505 alleles in non-dialysis patients, 8 were found to harbor p.E66Q variant, and allele frequency was 0.53%. There was no significant difference in the p.E66Q frequency of chronic hemodialysis patients compared with non-dialysis patients (P = 0.22) and with Japanese general population (0.64%, P = 0.25). The eGFR of non-dialysis patients harboring p.E66Q was not significantly different compared with that of patients with wild-type allele (6.3 ± 11.4 vs. 6.2 ± 7.0 ml/min/1.73 m², P = 0.701).

Conclusions: The present genetic association study indicated that the p.E66Q variant of GLA does not affect the progression to end stage renal disease.

TH-PO647

Discovery of Novel Candidate Genetic Markers Associated with Pediatric CKD Progression in the PediGFR Study

Jayanta Gupta,1 Peter A. Kanetsky,1 Nandita Mitra,1 Elke Wuehl,1 Anna Kottgen,1 Matthias Wuttke,2 Susan L. Furth,4 Bradley A. Warady,1 Franz S. Schafer,2 Craig S. Wong,6 1Dept Biostat/Epi, U Penn, Philadelphia, PA; 2Ped Neph Div, U Heidelberg, Heidelberg, Germany; 3Renal Div, Frieberg, Frieberg, Germany; 4Div Neph, Children’s Mercy Hosp., Kansas City, MO; 5Div Neph, U New Mexico Children’s Hosp., Albuquerque, NM.

Background: Traditional risk factors for chronic kidney disease (CKD) only partially explain the varying rate of GFR decline in children with CKD. The PediGFR study is determining the genetic contribution linked to CKD progression via meta-analysis of the most promising SNP markers observed in the genome-wide scans from the pediatric CKD cohort studies:CKiD, ESCAPE, and 4C.

Methods: Each prospective study collected genetic samples and longitudinal data on GFR (measured or estimated). We genotyped DNA using the Illumina® Omni 2.5 BeadChip. For each study, we used linear regression models to determine associations between SNP markers and GFR slope adjusting for age, sex and population stratification. The 100 most significant markers from each of five subgroup populations [CEU ancestry in CKiD (267), 4C (599) and ESCAPE (286); and Turkish ancestry in 4C (331) and ESCAPE (66)] were selected for meta-analysis. Using METAL, subgroup-specific effect estimates were combined by the inverse variance method.

Results: Analyses are currently ongoing. To date, 11 markers surpassed a threshold of P < 1×10-5 in combined results from at least 3 subgroup populations, although we noted heterogeneity of effect (P = 0.05 for Cochran’s Q; P > 50%) at two of these markers. Of the remaining 9 markers, 8 localized to the same genomic region at 2q22.3, and one to 15q21.1.

Conclusions: The PediGFR will continue analyses to include association testing of SNP markers with ESRD outcomes and within subgroups defined by glomerular and non-glomerular disease. We will assess the putative biological importance of these markers using publicly available databases such as ENCODE. We will replicate these identified SNP markers in the adult Chronic Renal Insufficiency Cohort study.

Funding: NIDDK Support

TH-PO648

Genetic Markers Associated with Erythrocyte Traits in the Chronic Renal Insufficiency Cohort (CRIC) Study

Hirofumi Watanabe,1 Shin Goto,1 Hiroki Maruyama,2 1Dept Medicine, Niigata University Graduate School of Medicine; 2Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background: Anemia is a prevalent comorbidity in CKD. However, across patients with CKD there is variability in the severity of anemia, likely due in part to genetic determinants of erythrocyte traits. Previous genome-wide association studies (GWAS) in healthy subjects have identified genetic variants associated with a variety of erythrocyte traits, but the associations in CKD patients has not been well studied.

Methods: In 1,450 African American (AA) and 1,560 European American (EA) subjects with CKD in the Chronic Renal Insufficiency Cohort Study (CRIC), we assessed...
the association of baseline measures of 6 erythrocyte traits (Hgb, Hct, MCV, MCHC, MCH, and RBC) with previously identified single-nucleotide polymorphisms (SNPs). Linear regression models were adjusted for age, sex, baseline eGFR use of angiotensin converting enzyme inhibitors, erythropoietin stimulating agents, and population stratification (by principal components). We used Bonferroni correction to account for multiple comparisons.

Results: Among AA subjects a significant association between multiple SNPs on the 16p11.2 locus and Hgb, Hct, MCV, MCHC, and MCH was found, consistent with previous analyses. A SNP within MPP1 was associated with higher MCH (p=0.0001), higher MCV (p=0.0001), and higher RBC (p=0.003). None of the markers examined were associated with Hgb or Hct in this group. In EA subjects, a SNP within SLCL743 was associated with higher MCH (p=0.0160), higher MHC (p=0.0004), and higher MCV. A SNP within the HBSIL/MYB was associated with lower Hct (p=0.001). SNPs at SLCL743, HBSIL/MYB, and GCDDH were positively associated with MCH, and a SNP at the TMPRSS6 locus was negatively associated with MCH. Further adjustment for use of iron supplementation did not alter the significance of these findings.

Conclusions: We have confirmed the association of selected genetic variants with erythrocyte traits in a CKD cohort, including racial differences in specific loci. Further study will allow us to determine if specific SNPs are longitudinally associated with incident anemia.

Funding: NIDDK Support

TH-P0651

Next Generation Sequencing Identifies Novel Genomic Variants as Candidates for African-American Familial FSGS

Siddharth A. Shah,1 James Lyons-Weiler,2 Abhay N. Vats.3 1Nephrology, Children’s Hospital of Pittsburgh, Pittsburgh, PA; 2Genomics and Proteomics Core Laboratories, Univ of Pittsburgh, Pittsburgh, PA

Background: In the past decade, various genes have been identified for FSGS. Previously, we described a four generation African American family with phenotype of hypertension and FSGS with a new linkage to 9q31-32 region. We performed whole exome sequencing (WES) to identify the candidate gene.

Methods: We identified new affected and non affected members of this family and the collected DNA was used for WES. Individual and pooled samples were used for this approach. Barcodes and final sequencing adapters were applied to each sample prior to pooling for emulsion PCR and sequencing. WES was performed using SOLID platform with 30X coverage. The quality control, ambiguity mapping, and mapping was performed using various algorithms, databases and software tools including Lifescope V 2.5, Bamstats, Fast QC, Bacsilon, C-scoring and DbsNP.

Results: There were 101 members in the family with 37 affecteds. Unpooled analyses utilized DNA from 2 affected individuals while pooled samples utilized 13 affecteds in pool 1 and 10 non-affecteds in pool 2. DNA capture targeted human exons plus UTR totaling 71 Mb. Bamstats and Fast QC analysis revealed good quality data. The analyses of target 9q31-32 region (between bases 9108672867-114233187) identified 7648 variants in unpooled samples of which 632 were heterozygous (W-score:1.9-2). Further comparison analyses narrowed the focus to several interesting variants including rs14861534, rs11529973 and rs138519256 in AK2AP, PTPN3 and LITHD4 genes respectively.

Conclusions: We were able to generate high quality data from exome sequencing performed on archived, individual as well as pooled samples. Several novel variants were identified as candidates for autosomal dominant FSGS in a large family belonging to the high risk African-American ethnicity. 2 of the variants (rs14861534 and rs11529973) are particularly interesting as they are highly expressed in kidneys and have very low allele frequency in target population. Further functional and population genetic studies will identify the role of identified variants in FSGS pathogenesis.
Discovery, Fine Mapping and Replication of Differential Methylation Associated with MicroRNAs and Chronic Kidney Disease

Background: DNA methylation and miRNAs are associated with complex disease and are altered in uremic patients. This study investigated association between DNA methylation and chronic kidney disease (CKD) using a relatively large-scale, case-control approach. Methods: The Illumina Methylation450K Beadchip array (Illumina, Inc., USA) was used to analyse DNA methylation across the methylome in 255 CKD cases and 152 unaffected controls (MMDR ECFR:60:60:1:1:1). Following stringent quality control, methylation levels were analysed and results adjusted for multiple testing using the Benjamini-Hochberg procedure. Quantitative methylation values were obtained at single CpG level for 2,249 sites associated with miRNA genes across the genome.

Results: Six miRNA genes on autosomes were selected for fine mapping and replication based on P<10−5 in the discovery mixture; MIR530-2, MIR940, MIR34A, MIR429, MIR132-3p, and MIR132-2. Association analysis identified five significant CpG sites in interest (OR=4.4, 95% CI 1.7–11.1). Nonfunction of the ECT2 gene may cause renal tubulointerstitial injury leading to focal segmental glomerulosclerosis. Akane Izu, Keisuke Sugimoto, Tomoki Miyazawa, Hitomi Nishi, Mitsuru Okada, Tsukasa Takemura, Pediatrics, Kinki Univ School of Medicine, Osaka, Japan.

Background: Secondary focal segmental glomerulosclerosis (FSGS) follows congenital or acquired tubulointerstitial alterations as in Den’s disease, Lowe syndrome, and reflux nephropathy. Failure of adequate regeneration after tubulointerstitial injury, or abnormal tubulogenesis, can disturb intrarenal blood circulation, causing excessive glomerular filtration. The epithelial cell-transforming sequence 2 gene (ECT2) contributes to tight junction function in epithelial cells.

Methods: Gene expression was screened by the comparative genomic hybridization (CGH) in 15 FSGS patients under treatment at our department. In one patient, a-actinin 4, located on chromosome 19q13, was deleted. In another, a deletion-associated E2F3 gene aberration was found. Downregulation of ECT2, located at 3q26.1 to q26.2, was observed in both patients. To confirm ECT2 deletions, PCR for ECT2 and immunohistochemical staining for ECT2 protein in renal tissues was carried out.

Results: We encountered two patients with a nonfunctioning ECT2 genotype who later developed acquired tubulointerstitial alterations as in Den’s disease. Lowe syndrome, and reflux nephropathy. Failure of adequate regeneration after tubulointerstitial injury, or abnormal tubulogenesis, can disturb intrarenal blood circulation, causing excessive glomerular filtration. The epithelial cell-transforming sequence 2 gene (ECT2) contributes to tight junction function in epithelial cells.

Conclusions: ECT2 is important for tight junction function and maintenance of cell polarity. Nonfunction of this gene may cause renal tubulointerstitial injury, progressing to glomerular sclerosis.

Nonfunction of the ECT2 Gene May Cause Renal Tubulointerstitial Injury Leading to Focal Segmental Glomerulosclerosis


TH-PO656

TH-PO655

Nonfunction of the ECT2 Gene May Cause Renal Tubulointerstitial Injury Leading to Focal Segmental Glomerulosclerosis

Research: We performed a whole-genome screening of CNVs in familial IgAN patients, their healthy relatives and healthy subjects (HS). A total of 217 individuals consisting of 51 familial IgAN patients and 166 healthy relatives were included in the study. We used a statistical approach (MSA) that allowed us to identify aberrations that were concordant across multiple samples and that allowed to use relatively little sample-size, simultaneously increasing the power of the analysis and the resolution.

Results: 178 IGAN-specific aberrations were identified, specifically 114 loss and 64 gain. Several CNVs overlapped with regions evidenced by our previous genome-wide resequencing studies (AJHG, 2006). Moreover, we found that patients without our characterized by a deteriorated renal function carried low copy numbers of a CNV in chromosome 3p21.1. This CNV contains the TLR9 gene whose expression significantly correlated with the

Genome-Wide Scan of Copy Number Variations (CNVs) Identifies a Variable Region at 3p21.1 Regulating the TLR9 Expression in Familial IgA Nephropathy Patients

TH-PO657
loss aberration in patients with progressive renal damage. Data were validated by RT-PCR. Conversely, IgAN patients with normal renal function did not have this aberration and the TLR4 mRNA was expressed at the same level as HS.

Conclusions: We performed the first genome-wide CNV study in familial IgAN. We identified some structural variants specific to IgAN patients and provided a collection of new candidate genes and loci that could help to dissect the complex genomic pattern of the disease.

TH-PO658

Elevated Klotho Promoter Methylation Is Associated with Deterioration of Renal Function in IgA Nephropathy Patients

Xiaoxu Zhang, Jing Chen, Han Zhang, Yi Fang, Xiaoqiang Ding. Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China.

Background: Recent studies prove Klotho (Kl) functions as a renoprotective factor and methylation of Kl promoter correlates with gene hypermethylation, which suggests epigenetic modification of Kl genes may be an important pathological mechanism of renal fibrosis. Our previous study demonstrates peripheral blood mononuclear cells (PBMC) level of Kl promoter methylation is positively correlated with intra-renal level of Kl promoter methylation and has high sensitivity and specificity at predicting intra-renal Kl promoter hypermethylation in chronic kidney disease patients. The aim of this study is to analyze the relationship of PBMC Kl promoter methylation level with eGFR in IgA nephropathy.

Methods: 70 Patients admitted to Shanghai Zhongshan hospital between 2012 April and 2013 April for renal biopsy and diagnosed as primary IgA nephropathy were included in the study. All patients provided informed consent. PBMC Kl methylation level was examined by pyrosequencing.

Conclusions: PBMC Klotho promoter methylation level was an independent risk factor of deterioration of renal function in IgA nephropathy.

TH-PO660

Is There an Epigenetic Predisposition to New Onset Diabetes after Transplantation?

Jennifer A. McCaughan,1,2 A.J. McKnight,1 Alexander P. Maxwell,1,2 ‘Nephrology Research Group, Queen’s Univ, Belfast, United Kingdom; 2Regional Nephrology Unit, Belfast City Hospital, Belfast, United Kingdom.

Background: New onset diabetes after transplantation (NODAT) is an increasingly common complication of renal transplantation. Recent evidence suggests that pancreatic beta cell toxicity, as a result of hyperglycemia in the peri-transplant period, may play a key role in NODAT pathogenesis. We recently demonstrated that single nucleotide polymorphisms in genes crucial to beta cell function predispose to NODAT in a White population. This study investigates the association between DNA methylation profiles prior to transplantation and the development of NODAT.

Methods: NODAT was defined as diabetes developing after transplantation and requiring pharmacotherapy. Epigenome wide methylation analysis was performed at 485,577 CpG sites using the Illumina HumanMethylation 450 BeadChip (Illumina) on blood-derived DNA from 348 renal transplant recipients from Northern Ireland. Quality control measures, including correction for dye bias, sample normalisation and evaluation of probe performance, were undertaken. Beta values were calculated and compared between NODAT cases and controls using ANOVA. Adjustment for multiple testing was performed.

Results: There were 46 (13%) cases of NODAT in the study cohort. All individuals were White. Following quality control analysis, methylation at 14 CpG sites was associated with NODAT with a p value < 10^-4. After adjustment for multiple testing, these associations did not persist.

Conclusions: There is clinical evidence that a hyperglycemic insult within the peri-transplant period may contribute to the development of NODAT. Variation in genes influencing pancreatic beta cell function may also predispose renal transplant recipients to NODAT. This study did not provide evidence that DNA methylation profiles prior to transplantation are associated with NODAT. However, it is plausible that hyperglycemia alters DNA methylation in key genes following transplantation and may contribute to NODAT pathogenesis in this manner.

TH-PO661

SNP Associated with the Coefficient of Variation in 24-h Urinary Calcium Excretion Linked to Parathyroid Hormone and WD Repeat Domain 33

Guy M.L. Perry,1 Martin R. Pollak,2 Hakan R. Toka,2 David B. Mount,2 Gary C. Curhan,2 Steven J. Scheiman.1 SUNY Upstate Medical University, Syracuse, NY; 1Harvard Medical School, Boston, MA; 2Brigham and Women’s Hospital, Boston, MA; 1The Commonwealth College, Scranton, PA.

Background: Residual variance (RV) is heritable in some systems. Our epidemiological and model work on this phenomenon suggests that residual variance in urinary calcium excretion is heritable in humans, and might have effects on conventional genetic analysis.

Methods: We performed a genome-wide association study on the coefficient of variation for paired measurements of 24-h urinary calcium (CVCa) in 1251 individuals with a history of confirmed stone disease and randomly-sampled unaffected (368 males, 342 females total).

Results: No single nucleotide polymorphism (SNP) was associated with CVCa in the complete sample, or in males. A T/C polymorphism at rs463056 (Chr 11, 13.5 MB) was significantly associated with CVCa in females (P = 6 x 10^-4). This region is syntenic with a chromosomal region (Chr 1, 170-227 MB) in rats carrying a quantitative trait locus for CVCa. Fourteen SNP in 7 WD repeat domain 33 (WDRR33; Chr 2, 128.2-128.3 MB) were also associated with CVCa in females (P = 4 x 10^-4).

Conclusions: These results and our previous work indicate sex-limited genes affecting residual variance in urinary calcium. The nearest gene to rs463056 is parathyroid hormone (PTh, 34 kB downstream); notably, a syntenic genomic region carrying PTh is also associated with CVCa in rats. PTh has functions in acetylation, serum calcium regulation and bone mineralization, and WD repeat proteins with signal transduction, mRNA processing and methylation, which suggests mixed generalist/specialist genetic control

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
of this phenomenon. These SNP were not associated with mean urinary calcium; residual variance genes might dynamically control urinary solute excretion without detectable classical genetic effects.

**Funding:** NIDDK Support

**TH-PO662**

**Exon-Skipping in Gitelman’s Syndrome Families**

Yeishi Takeuchi,1 Hisato Shima,1 Ekan Mishima,2 Yasutoshi Akiyama,1 Chiho Suzuki,1 Takehiro Suzuki,1 Tomohiro Nakayama,2 Sadayoshi Ito,1 Takaaki Abe.1

1 Div of Nephrology, Endocrinology and Vascular Medicine, Tohoku Univ Graduate School of Medicine; 2Nihon Univ School of Medicine.

**Background:** More than 160 point mutations in SLC12A3 gene causing Gitelman’s syndrome have been reported and missense mutations have been examined generally by single amino acid substitution.

**Methods:** We identified three exonic mutations (A356V, S402F and M672I) as the best candidates of exon-skipping.

**Results:** We isolated three exonic mutations (A356V, S402F and M672I) as the best candidates of exon-skipping.

**Conclusions:** We found exonic mutations caused exon-skipping in SLC12A3. We need to examine not only single amino acids substitution by genomic mutations but also RNA transcripts and resultant loss-of-function.

**TH-PO663**

**Do Single Nucleotide Polymorphisms Contribute to Urine pH Variation?**

A Genetic Association Study

Benjamin Canales,1 Jennifer Smith,2 Wei Zhao,2 Gary C. Curhan,1 J. David Weiner,3 John C. Lieske.4

1Urology, Univ of Florida, Gainesville, FL; 2Epidemiology, Univ of Michigan, Ann Arbor, MI; 3Medicine, Renal Div, Brigham and Women’s Hospital, Boston, MA; 4Medicine, Renal Div, Univ of Florida, Malcom Randall VAMC, Gainesville, FL; 5Medicine, Renal Div, Mayo Clinic, Rochester, MN.

**Background:** Although a number of gene mutations have been implicated in rare urinary acid-base disorders, little is known regarding genetic control of urine pH in the general population.

**Methods:** 15 genes involved in renal acid-base homeostasis were identified. A genetic association study was performed in 2493 individuals of European descent across 4 cohorts (n=811, Minnesota cohort of the Genetic Epidemiology Network of Arteriothpy (GENOA); n=553, Health Professionals Follow-Up Study (HPS); n=494, Nurses’ Health Study (NHS) I; n=635, NHS II). Single nucleotide polymorphism (SNP) dosages from 1000 Genomes imputed data were modeled for association with 24 hr urine pH using linear regression after adjustment for age, sex and body mass index. SNPs with minor allele frequency >0.01 were studied between 5 kb from a targeted gene start or endpoint. A fixed-effects meta-analysis was used with inverse variance weighting by standard error of the beta coefficient.

**Results:** 2096 SNPs met inclusion criteria. 17 SNPs across 5 genes (ATP6V0A4, SLC9A3, RHCG, GLUD1, and OGDH) had a meta-analysis p-value <0.01 in the joint analysis, plus a consistent direction of effect and at least marginal significance (p<0.1) in both GENOA and the combined sample of HPFS/NHS NHII and NHIII. The lowest meta-analysis p-value was observed for rs6555765 in the ATP6V0A4 gene (p=0.0009). Maximal beta-

coefficients for identified SNPs were 0.20 for GLUD1, 0.06 for RHCG, 0.06 for SLC9A3, 0.08 for ATP6V0A4 and 0.20 for OGDH. Two blocks of SNPs on genes ATP6V0A4 (n=9) and SLC9A3 (n=4) were in strong linkage disequilibrium (r2=0.8).

**Conclusions:** Common genetic variants of several genes involved in renal acid-base homeostasis correlate with basal urine pH. This study suggests that genetic variation in these genes could influence urine pH in the general population.

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

**TH-PO664**

**Whether Digenic Inheritance of NPHS1 “And” TRPC6 Polymorphisms Predisposes to Progression of Steroid-Resistant Nephrotic Syndrome in Children?**

Laria Prikhodina,1 Pediatric Nephrology, Reasearch Institute of Pediatrics & Childern Surgery, Moscow, Russian Federation.

**Background:** Mutations in NPHS1 and TRPC6 genes cause steroid-resistant nephritic syndrome (SRNS) in children and adults. The role of digenic inheritance of TRPC6 and NPHS1 single nucleotide polymorphisms (SNPs) in progression of SRNS in children is unknown.

**Methods:** We aim to investigate whether digenic inheritance of NPHS1/TRPC6 SNPs predispose to progression of idiopathic pediatric SRNS to chronic renal failure (CRF). We excluded children (20F/8M) with primary non-familial SRNS, originating from Russia, were enrolled. Histological findings were FSGS in 60.7%, MPGN in 17.9%, mesangial proliferative GN in 10.7%, MN in 7.1%, MCD in 3.6% patients. The median age at onset of SRNS was 9.0 (IQR: 4.3; 10.9) years. The disease duration was 63.0 (38.4; 88.5) months. CRF defined as declining of eGFR <60 mL/min/1.73m2. NPHS1 and TRPC6 mutation analysis was performed by Sanger sequencing of all 29 and 13 exons, respectively. Patients with congenital, infantile and secondary SRNS and with identified mutations in NPHS1 or TRPC6 were excluded from the study.

**Results:** Digenic inheritance of NPHS1/TRPC6 SNPs was identified in 8/28 (28.6%) children with SRNS, including two homo/-heterozygous NPHS1 SNPs: 7.349G-A (rs3814995), c.1223G>A (rs33950747) and three heterozygous TRPC6 SNPs: c.45T-C (rs2114290), c.211T>C (rs7291350), c.163G>A (rs7291648). Children with digenic inheritance of NPHS1/TRPC6 SNPs in comparison without SNPs had no significant differences in frequency of FSGS: 87.5% vs. 100% (p=1.0), medium eGFR at the last follow up: 77.4 (52.0; 143.0) vs. 80.5 (37.1; 120.3) mL/min/1.73m2 (p=0.39), frequency of CRF: 50% vs. 83.3% (p=0.72), annual decline of eGFR (p=0.87), frequency of FSGS: 87.5% vs. 100% (p=1.0), medium eGFR at the last follow up: 77.4 (52.0; 143.0) vs. 80.5 (37.1; 120.3) mL/min/1.73m2 (p=0.46). The 5-year renal survival in patients with digenic inheritance of NPHS1/TRPC6 SNPs in comparison without SNPs had no significant differences: 72.9% vs. 66.7%, 10-year renal survival - 43.8% vs. 66.7%, respectively (p=0.88).

**Conclusions:** Our data indicate that digenic inheritance of TRPC6 and NPHS1 SNPs does not predispose to progression of idiopathic SRNS to CRF in children.

**TH-PO665**

**Molecular Effects of Three Mutations Identified in Complement Component C3 in Japanese Patients with Atypical Hemolytic Uremic Syndrome**

Akira Ashida,1 Daisuke Yamamoto,2 Yoko Yoshida,3 Fan Xinping,1 Masanori Matsumoto,1 Toshiyuki Miya,1 Motoshi Hattori,2 Yoshihiro Fujimura,1 Hiroshi Tamai.1

1Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan; 2Biomedical Computation Center, Osaka Medical College, Takatsuki, Osaka, Japan; 3Blood Transfusion Medicine, Nara Medical Univ, Kashihara, Nara, Japan; 4Genetic Epidemiology and Other Genetic Studies of Common Kidney Diseases

**Background:** Atypical hemolytic uremic syndrome (aHUS) has been associated with dysregulation of the alternative complement pathway. Mutations in complement factor H (CFH), factor I, factor B (CFB), thrombomodulin, C3, and MCP predispose to progression of idiopathic pediatric SRNS to chronic renal failure (CRF). We analyzed the molecular effects of these C3 gene mutations on the alternative pathway of complement activation.

**Methods:** We examined three missense mutations in the C3 gene identified in 10 Japanese patients with aHUS. Each three-dimensional coordinate set was listed in the RCSB Protein Data Bank as 2107 (C3b), 2Wl2 (C3-CFH), 2XwB (C3-CFB-D), 2CF (C3-CR1G) and 3SN (C3-SC1n).

**Results:** We carried out the structural analysis of the R425, S562 and N1157 residues for the molecular structures of C3b and each of its complexes with CFH, CFB, CR1g and SC1n (staphylococcal complement inhibitor). At the three mutational points, N1157 in the thioester-containing domain (TED) of C3b was located at the interface with CFH. CFH (SUH-3) with C3b lay between R425 and S562, and mutations of these residues were considered to possibly reduce the interaction between C3b and CFH. All of these mutation points were located at positions where they would have no direct effect on the interface of CFB and SC1n with C3b. From these findings, we postulate that the novel mutations R425 and S562 might cancel the inhibitory trigger of the C3b system by disturbing the interaction with CFH.

**Conclusions:** We conclude that these mutations of C3 gene including mutations R425 and S562 are causative.
Total Kidney Volume in Healthy Aging Adults

Carlos Kornhauser

Background: Total kidney volume (TKV) and its relationship with pro-inflammatory factors such as TGF-β, VEGF and aldosterone has been poorly studied in aging. We evaluated the TKV by ultrasonography, and its relationship with eGFR, microalbuminuria, TGF-β, VEGF and aldosterone in healthy aging adults.

Methods: Renal ultrasonography was performed in 30 women <75 and 30 >75 years, 20 men <75 and 20 >75 years. eGFR was estimated according to the MDRD formula. Microalbuminuria, serum TGF-β, VEGF, and aldosterone levels were assessed in all subjects.

Results: TKV was significantly higher (p=0.0000) in the two groups of men, as compared to the two groups of women. TKV was significantly higher (p<0.0001) in women <75 y as compared to women >75 y. No difference was found in the TKV between men <75 y as compared to men >75 y. A negative correlation between TKV and age in men (r= -0.28, p=0.02) and in women (r= -0.38, p=0.01) was found. TKV and TGF-β (r= -0.47, p=0.0001) showed a negative correlation only in men. The TKV and microalbuminuria showed a positive correlation only in men (r= -0.28, p=0.02). The eGFR did not show correlations with any of the variables. VEGF and aldosterone did not correlate with TKV.

Conclusions: Men have bigger total kidney volumes than women at any age. The TKV in men does not significantly change with age. In women TKV gets significantly smaller with age. Microalbuminuria correlates positively with TKV in men, but not TGF-β. The TKV and microalbuminuria showed a positive correlation only in men. In men, the smaller the TKV, the higher the TGF-β levels.

Renal Function in Healthy Aging Adults. Age and Gender Differences

Carlos Kornhauser

Background: Renal function is poorly studied in healthy aging adults. Role of TGF-β, VEGF and aldosterone in the aging process and its relationship with eGFR, and microalbuminuria needs to be more clearly established.

Methods: Two hundred normotensive subjects (100 women and 100 men) were included. Fifty women and fifty men <75 years, and 50 women and 50 men >75 years old. Serum glucose, uric acid, lipid profile, eGFR (MDRD), TKV, TGF-β and aldosterone, and microalbuminuria were assessed.

Results: eGFR was significantly higher in men (85.3 ml/min/1.73m²) as compared to women (66.5 ml/min/1.73m²) at any age (p <0.0001). eGFR values were similar in both age groups of women, as well as in both age groups of men. Aldosterone was significantly higher in men >75 y as compared to women >75 y (p<0.0000), but higher in women >75 y as compared to men >75 y (p<0.0000). Uric acid (p<0.01) and TGF-β (p<0.0000) were significantly different between each group of age. eGFR and microalbuminuria had a negative association (R= -0.41 p=0.03) in men <75 y. Aldosterone did not show associations.

Conclusions: eGFR decreases in men and women with aging, but values were never under 60 ml/min/1.73m². Microalbuminuria absence define subjects as healthy. Uric acid, aldosterone, VEGF and TGF-β levels need to be clarified in these subjects without kidney disease.

Pattern of Biopsy-Proven Renal Diseases in Geriatric Patients from a Single Center in Taiwan

Cheng-Hsu Chen,1,2,3 Ya-Wen Chuang.1

Background: The global increase in life expectancy has translated to more elderly patients affected from renal diseases. The role of renal biopsy (RB) in this subset of patients has never been explored; moreover the histological patterns of renal disease in elderly have rarely been described.

Methods: This is a retrospective study of all consecutive elderly patients (age ≥ 70 years) biopsied at S.Orsola-Malpighi Hospital of Bologna between 1st January 2000 and 31 December 2012. Data are extracted from renal biopsies database.

Results: No RB has been performed until 2005. 106 (M59, F47) elderly patients have been biopsied in the remnant study period (figure 1). The mean age was 78±4 years without difference between sexes. In 810 (7.4%) RB was not adequate. Primary glomerulonephritis were seen in 39/100 patients and secondary glomerulonephritis in 25/100. Membranous glomerulonephritis (MGN) was the most common (21/100) and was significantly more common in the elderly.

Conclusions: Renal biopsy in elderly patients is a valuable diagnostic tool that should be offered the potential to modify treatment with maximal potential benefit. Age should not be considered as a contraindication to renal biopsy.

Renal biopsy in elderly Italian: A Single-Center Experience over 12 Years

Fausta Catapano, Lucia B. De Sanctis, Antonino Santoro.

Background: The geriatric population is growing fast as a major cause of chronic kidney disease (CKD) burden in Taiwan, however, the distribution of kidney diseases in elderly patients is not well known. The aim of this study was to compare the pattern of renal disease in elderly and control patients who underwent native renal biopsy.

Methods: Among 3622 renal biopsies, excluded 588 graft biopsies and 322 inadequate criteria biopsies, we did a single-center, retrospective study (1992-2008) of the biopsy-proven renal diseases between geriatric patients (age ≥65y/o; n=327) and control (18< age<65; n=2385).

Results: The geriatric group with mean age was 71.8±4.5 (65.1-87.3 yrs), male gender (74%), age>70y (n=200, 61%), the control group was 39.7±17.6 (18-64.9yrs), male gender (41%). Membranous nephropathy (MN) was the most frequent diagnosis (35.8%), followed by minimal change disease/focal segmental glomerulosclerosis (MCD/FGS) (13.1%), diabetic nephropathy (6.4%), hypertensive nephrosclerosis (5.8%), and IgA nephropathy (4.6%).

Comparison with the control grouped showed MN to be more frequent (P<0.01), and lupus nephritis (P<0.001) and IgAN (P<0.001) less frequent in the elderly. However, ANCA-positive nephritis, and myeloma nephropathy and amyloid nephropathy were also more common in the elderly.

Conclusions: Renal biopsy in elderly patients is a valuable diagnostic tool that should be offered the potential to modify treatment with maximal potential benefit. Age should not be considered as a contraindication to renal biopsy.
Cognitive Impairment in Advanced Chronic Kidney Disease

Simon Richard Walker, Ranveer Singh Brar, Brett M. Hiebert, Frederick Eng, Paul Komenda, Claudio Rigatto, Manish M. Sood, Clara Bohm, Leroy J. Storsley, Raksh C. Arora, Navdeep Tangri. Medicine, Seven Oaks General Hospital, University of Manitoba, Winnipeg, Canada.

Background: Chronic Kidney Disease (CKD) disproportionately affects the elderly and is associated with frailty and impaired quality of life. Patients with CKD suffer from multiple comorbid conditions putting them at risk of developing cognitive impairment. The purpose of this study was to describe the prevalence of cognitive impairment in patients with advanced CKD (eGFR < 30 ml/min).

Methods: We approached all patients with advanced CKD who attended an interprofessional non-dialysis CKD clinic at a tertiary care center for enrollment in our study. We excluded patients who did not speak English or were unable to provide informed consent. We collected demographic variables, physical examination measurements, laboratory values, and performed an assessment of cognitive function using the Montreal Cognitive Assessment (MoCA).

Results: We studied 86 patients. Their mean age was 67.2 years (Standard Deviation [SD] +/- 12.8), and 34 patients were female (39.5%). The mean eGFR was 20.5 mL/min/1.73m2 (SD +/- 8.1). Sixty seven patients (77.0%) scored < 26 on the MoCA and were thus defined as cognitively impaired. In particular, the recall, visual/executive and language domains were impaired in > 60% of the participants. In contrast, naming and orientation were relatively well preserved (> 70% achieving perfect score).

Conclusions: Patients with advanced CKD have a high burden of cognitive impairment. Further studies on the pathophysiology of cognitive decline and its impact on patient decision making and outcomes are needed.

Marked Increased Risk of Prediabetes in Elderly ESRD Patients

Mark E. Williams,1 Neal Mittman,2 Lin Ma,3 Julia I. Brennan,4 Curtis D. Johnson,3 Chiu M. Jani,4 Franklin W. Maddux,1 Eduardo K. Lacson,1 Jonas Diabetes Center, Boston, MA; 2Long Island College Hospital, Brooklyn, NY; 3Fresenius Medical Care, North America, Waltham, MA; 4Spectra Laboratories, Rockleigh, NJ.

Background: Prediabetes has become a major public health problem. Diagnosing prediabetes identifies individuals at high risk for diabetes and its complications. Increased age is known to be a significant risk factor for prediabetes in the general population. Because ESRD is also associated with impairments in glucose regulation, we sought to determine the association of aging with prediabetes in a cohort of nondiabetic dialysis patients, using ADA cutoffs of hemoglobin A1c at 5.7–6.4%.

Methods: OF544 dialysis patients from 26 facilities with laboratory values obtained the first quarter of 2013, 1454 (with mean age 56.6 years; 78% on hemodialysis) were without known diabetes and had HgbA1c values. Age was categorized into decades (from <45 years to >75 years) and the HgbA1c distribution was determined for each.

Results: 2% for those over age 65 years were found to be in the diabetic range (HgbA1c > 6.5%). The per cent of patients with prediabetes by age category, using the lowest category as reference and analyzed by chi square, is shown:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N/Col Pct</th>
<th>HgbA1c &gt;5.6</th>
<th>HgbA1c &gt;5.8 &lt;6.5</th>
<th>HgbA1c &gt;6.8</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>320</td>
<td>250</td>
<td>280</td>
<td>178</td>
<td>371</td>
</tr>
<tr>
<td>%</td>
<td>87.67</td>
<td>81.97</td>
<td>82.6</td>
<td>77.99</td>
<td>79.5</td>
</tr>
<tr>
<td>&gt;75</td>
<td>44</td>
<td>45</td>
<td>51</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>%</td>
<td>12.35</td>
<td>18.03</td>
<td>17.4</td>
<td>22.01</td>
<td>20.5</td>
</tr>
</tbody>
</table>

The prevalence of prediabetes increased dramatically over age 65 years in the nondiabetic ESRD population (both p < 0.05).

Conclusions: Studies defining the natural history of prediabetes and the benefit of screening the ESRD elderly for preventive intervention are needed. Furthermore, as the population ages, the need for more studies focusing on patients with geriatric chronic kidney disease becomes increasingly apparent.

Impact of Body Mass Index on Outcomes after Acute Kidney Injury in Geriatric Patients

Chia-Ter Chao, Hung-Bin Tsai. Dept of Traumatology, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Acute kidney injury (AKI) frequently occurs in critically ill patients and impairs both short-term and long-term outcomes. However, studies on outcome-modifying factors in geriatric patients with AKI are few, and the influence of body mass has not been determined previously.

Methods: We performed a multicenter prospective observational study and enrolled elderly patients (> 65 years) that developed AKI after major surgery in the intensive care units. We analyzed in-hospital mortality within each body mass index (BMI) category utilizing Cox proportional hazard regression analysis and generalized additive modeling (GAM).

Results: A total of 2015 postoperative elderly patients (age 75.2 ± 6.4, men 57.8%) were studied. The survivors were significantly younger than the nonsurvivors (p < 0.001) and had higher BMIs (23.2 ± 3.9 kg/m² vs. 22.4 ± 4.2 kg/m²; p < 0.001). GAM modeling showed that elderly AKI patients with a BMI between 21 and 31 (normal weight) had a lower mortality risk than those with a BMI ≥ 21 (underweight) or ≥ 31 (obese). Both underweight and overweight individuals had a greater risk of hospital mortality compared with patients with normal BMI (underweight vs. normal, hazard ratio [HR] 1.60, 95% confidence interval [CI] 1.05–2.61; p = 0.038; obese vs. normal, HR 1.22, 95% CI 1.01–1.49; p = 0.042).

Association between Body Composition and Frailty among Prevalent Hemodialysis Patients: A USRDS Special Study

Kristen L. Johansen,1 Lorien S. Daly,2 Cynthia Delgado,1 George A. Kaysen,1 John Kornak,1 Barbara A. Grimes,1 Glenn M. Chertow.2 1Univ of California San Francisco; 2UC Davis; 3Stanford Univ School of Medicine.

Background: Most studies of frailty among patients on hemodialysis have relied on definitions that substitute self-reported functioning for measures of physical performance and omit weight loss or substitute alternate criteria. Associations between body composition and frailty have not been carefully examined.

Methods: We examined the association between body composition and a definition of frailty that includes physical performance and weight loss in ACTIVE/ADIPOSE a cohort study of the USRDS Special Studies Centers. We included 638 patients receiving hemodialysis in a cross-sectional analysis. Frailty was defined as three of: weight loss, weakness, exhaustion, low physical activity, and slow gait speed. We performed logistic regression with body mass index (BMI) and estimates of intracellular water (ICW), fat mass, and extracellular water (ECW) by bioelectrical impedance spectroscopy (BHS) as the main predictors and age, sex, race, and comorbidity included as covariates. BMI and BHS data were then added to these covariates in separate models, and the areas under the ROC curves or (c-statistics) of the two resulting models were compared.

Results: Thirty percent of participants were frail. Older age (1.31 per 10 years, 95% CI 1.14–1.50) and diabetes (OR 1.65, 95% CI 1.13–2.40) were associated with higher odds of frailty. BMI was not associated with frailty (OR 1.02, 95% CI 0.99–1.05). Higher ICW was associated with lower odds of frailty (OR 0.80 per kg, 95% CI 0.73–0.87), and higher fat mass (OR 1.18, 95% CI 1.02–1.37) and ECW (OR 1.33, 95% CI 1.20–1.47) were associated with higher odds of frailty. Addition of BMI did not change the c-statistic (0.66 without BMI vs. 0.66 with BMI, p = 0.91), but addition of BHS data did (0.72, p = 0.0004).

Conclusions: Our data demonstrate the high prevalence of frailty in the hemodialysis population, and in particular, the poor performance of BMI as an indicator of frailty among patients on hemodialysis. We highlight the associations among variations in body composition and the odds of frailty.

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

Underline represents presenting author/disclosure.

253A
TH-PO674

Evaluation of Nutrition in Elderly Patients with Renal Failure Rumeyva Kazancioglu,1 Banu Buyukaydin,2 Ahmet Turan Isik.2 Nephrology, Bezmialem Vakif Univ, Turkey; ‘Geriatrics, Dokuz Eylul Univ.

Background: Both malnutrition and chronic kidney diseases are clinical pathologies that increase morbidity and mortality incidence in elderly. We evaluated nutritional state and comorbidities in this group of patients.

Methods: 65 years and over 54 hospitalized patients were included in the study. The glomerular filtration rate (GFR) was calculated by using Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formulas. All of the patients’ calculated GFR was below 60 ml/min/1.73m². Nutritional status was evaluated with Mini Nutritional Assessment Short-Form (MNA-SF) and Geriatric Nutritional Risk Index (GNRI). Patients’ waist circumference, hip circumference, waist:hip ratio and body mass indices (BMI) were measured and biochemical analysis was performed.

Results: Means of patients GNRI score was 79.91±13.0 (R = 66-128), and MNA-SF score was 7.9±2.9 (R = 1-14). In older patients mean MNA-SF was lower (R = 0.269, p<0.049). Between lower GNRI and higher creatinine level, there was detected significant correlation (R = 0.340, p<0.012). In long-term hospitalized patients, GNRI and MNA-SF scores were lower (R = 0.455, p<0.001), (R = 0.356, p<0.008). Low GNRI correlated with low waist circumference, low hip circumference and low BMI, respectively (R = 0.436, p<0.001), (R = 0.554, p<0.000), (R = 0.744, p<0.000). And low MNA-SF correlated with low levels of same parameters also (R = 0.377, p<0.005), (R = 0.327, p<0.017), (R = 0.440, p<0.001).

Conclusions: In elderly patients with chronic kidney disease, GNRI is a reliable nutritional test. Also waist circumference, hip circumference and BMI are usable measures for nutritional evaluation in this group of patients.

TH-PO675

Elderly Renal Replacement Therapy (RRT) Population and an Emerging Problem: One Center Experience Haris Tantillo, Alessandra Brendolan, Monica Zacchini, Federico Nalesso, Claudio Ronco. Nephrology and IRRIT, San Bartolo Hospital, Italy.

Background: The proportion of elderly people is rising throughout the world. Very elderly chronic kidney disease (CKD) patients (pts) are a growing group diagnosed and their morbidity and outcomes have important implications for future Health policies. The aim of this study was to analyze the outcomes of incident RRT pts aged 75 years (yrs) or more between January 2008 and March 2013.

Methods: We analyzed retrospectively 97 pts (68% M, age mean 80.78±3.5 yrs), 57 hemodialysis and 40 peritoneal dialysis(PD), at least 2 months (mths) of RRT. The causes of CKD were hypertension (48.5%), glomerulopathy (13.4%), diabetes (DM) (10.3%), unknown (13.4%). In 20.6% of cases, the pts were on PD. Mean time of RRT was 17.04±12.04 mths. We defined 3 classes of age: 1) 51 pts (75-79 yrs); 2) 33 (80-84 yrs); 3) 13 ≥85 yrs. The patients were stratified into 3 groups: a) 34.7±12.8 years, b) 70-74.9 yrs c) 75-79.9 yrs contributed to 34.9% each, 18.6% were aged 80-84 yrs and finally 11.6% at ≥85 yrs. Outcomes were identified from electronic case notes and follow-up is from date of initiating dialysis to death or 30 April 2013. The data was then analyzed via SPSS programme.

Results: Among patients aged 70 years and above were started on long-term dialysis. There were 62.8% females and 37.2% males. Ethnicity was divided to Chinese, Malay, Indian and Others with a distribution of 79.4%, 14%, 2.3% and 4.7% respectively. Patients aged 70-74.9 years and 75-79.9 years contributed to 34.9% each, 18.6% were aged 80-84 yrs and finally 11.6% at ≥85 yrs.

The predominant cause of end stage kidney disease (ESKD) was diabetic nephropathy (62.8%). Initiation of dialysis in the elderly involved temporary vascular catheter in 41.9% and 30.2% of patients required continuous renal replacement therapy (CRRT). None of our patients had a functioning dialysis access during their initiation of dialysis. 29% of our patients were established on PD, and 79.1% hemodialysis. Median time to arteriovenous fistula or graft (AVF/AVG) creation was 81 days and to Tenckhoff insertion was 23 days.

There were only 3 deaths at 90 days (11%) from a total of 27 patients who had follow-ups of at least one year. Death rates were not calculated as the small number of patients may skew the results.

Conclusions: Diabetes remains a predominant aetiology of ESKD in elderly population with a large proportion requiring temporary vascular access and CRRT. Mean time to dialysis access creation was shorter with Tenckhoff catheter than AVF/AVG creation. Number of deaths appeared to be low but may not be accurate. We hope to improve the access to dialysis treatment, timely initiation, and care in our elderly population with the above findings.

TH-PO676

Unplanned Dialysis Start Despite a Follow-Up by a Nephrologist in Elderly Patients Reaching End Stage Renal Disease. The PSPA Cohort Study Olivier Moranne,1,2 Cecile M. Vigneau,1,2 Cécile Couchoud,1,3 Nephrology, CHU, Nice, France; ‘Nephrology, CHU Rennes, France; ‘For PSPA Investigators, France; ‘French Registry REIN, La Plaine St Denis, France.

Background: Elderly (i.e > 75 yrs) represent about 40% of incident dialysis patients in the French REIN Registry. These patients have an higher risk of unplanned starting dialysis (30%) which is documented as a strong prognostic factor [REIN 2011]. Unplanned starting dialysis in elderly patients despite a follow-up by a nephrologist needs to be better understood. The objective of this study is to identify predialysis patient characteristics and therapeutic project associated with unplanned starting dialysis. The starting dialysis from the French prospective multicenter cohort PSPA study [Moranne et al, J Gerontol A Biol Sci Med 2012].

Methods: From the 581 elderly patients followed by nephrologist included in the PSPA study (mean MDRD at initiation 14±4ml/min/1.73m²), 253 (43%) started dialysis during 3 years-follow-up. Patient’s clinical characteristics, way of life, share therapeutic project about the option for dialysis at inclusion in the cohort and medical reasons to start dialysis between groups starting unplanned vs planned dialysis were analysed.

Results: Median age was 82 [79-85] yrs with 64% men and 57% (232) started dialysis in an unplanned manner for (life-threatening risk). Those patients were significantly older, had more often active cancer, lower functional mobility, lived more often in institution. They had more often a “non dialysis option” as therapeutic project, because of patient’s request or stable GFR consideration according to nephrologist. Nondialysis option at nephrologist’s request was not associated with unplanned dialysis. The starting dialysis reason for those patients were significantly more often anemia and hyperkalemia.

Conclusions: These results show that elderly reaching ESRF followed by nephrologists start unplanned dialysis in 23% of cases. Unplanned dialysis start was associated with frailty and institutionalized patients and if therapeutic project about the option for dialysis was postponed by patient or according to stable GFR by nephrologist. The results should alert nephrologist about the necessity of share therapeutic project and better enhanced the organization of initiation of dialysis.

Funding: Government Support - Non-U.S.
Efficacy of Intradialytic Rehabilitation in Renal Anemia among Elderly Patients

Suzette Thompson, 1 Penny Faith Sheppard, 1 Len A. Usuyvat, 2 Mary T. Sullivan, 1 Peter Kotanko, 1 Paul M. Zabetakis, 1 Nathan W. Levin. 1

Background: Increasing numbers of elderly patients (Pts) with end-stage renal disease are starting dialysis. Previous reports have shown that the initiation of dialysis is associated with a substantial and sustained decline in functional status among them. The impact of a lower functional status may be reduced by offering rehabilitation to dialysis Pts. Correction of anemia and physical activity are effective for at least moderate improvements in physical function although these studies have been conducted primarily in younger Pts. The effect of exercise on renal anemia in elderly Pts is unclear. Therefore, we examined the efficacy of intradialytic rehabilitation (IDR) to prevent functional decline and renal anemia in elderly Pts.

Methods: We evaluated 16 hemodialysis outpatients over 65 yr of age who participated in our IDR program since September 1, 2009 to February 28, 2013. All Pts underwent our program during each dialysis session for at least 12 weeks. Pts who were initiated hemodialysis within 3 months were excluded. We prescribed the stretch of the lower limbs and progressive resistance exercise using an elastic band and the gizzard. We assessed following parameters at the start and following 3 months of our program: physical tests (e.g. muscular strength, 10-meter walking test), anthropometrics, nutritional status, erythropoiesis stimulating agents (ESA) dose and hemoglobin (Hb), and data known as risk factors for ESA hyporesponsiveness.

Results: Pts were mean age 74.7 ± 6.0 years, 78.5% male, 18% diabetic; dialysis vintage was 125.4 ± 120.3 months. 3 Pts withdrew because of offering decline from the program, and of admission due to fall and severe hypotension. In more than half of Pts, physical strength was maintained after our program. Weekly ESA dose significantly declined from 6923IU to 5423IU (p = 0.021), while mean Hb concentrations increased from 10.8g/dl to 11.4g/dl at the start and 3 months, respectively.

Conclusions: IDR for elderly Pts has a potential not only to prevent their functional decline, but also to improve renal anemia.

Relationship of Non-Compliance and Outcomes Stratified by Age Groups in Dialysis Population

Suzette Thompson, 1 Penny Faith Sheppard, 1 Len A. Usuyvat, 2 Mary T. Sullivan, 1 Peter Kotanko, 1 Paul M. Zabetakis, 1 Nathan W. Levin. 1

Background: Non-compliance is a significant issue in US hemodialysis (HD) patient population. We aim to understand whether non-compliance rates are different in different age groups as well as whether age affects relative risk of death in different groups of non-compliance.

Methods: All RRI in-center HD patients with ≥100 treatments and treated for ≥365 days between Jan 1, 2010 and Feb 28, 2013 were selected. Patients were stratified based on age (<40, 40-60, 60-80, >80) at start of the study period. For each patient, we computed % of treatments with unexcused no shows as well as % of treatments with early terminations (defined as terminated ≥15 minutes prior to their prescribed treatment time) during entire study period. Patients were divided into tertiles of no show and early termination rates. To determine if hazard risks of death are different at different levels of non-compliance, we constructed Cox proportional hazards models in each tertile of no shows and early terminations separately.

Results: We studied 7029 patients. Non-compliance was inversely related to age (not shown) as previously shown (Vega, EDTA 2011). In each tertile of no shows and early terminations, older patients had poorer survival. Compared to patients >80 years, patients <40 years had similar although increasing hazard ratios in no show tertiles 1, 2, and 3 (0.11, 0.10, 0.17) for no shows respectively and for early termination tertiles 1, 2, and 3 (0.08, 0.09, 0.17). As expected, hazard rates of death were higher in age group 40 to 60 and 60 to 80 but the effect of age diminished slightly in tertiles of early terminations.

Conclusions: Older patients appear to have better treatment compliance than younger patients. Relative impact of age on survival appears similar across tertiles of no shows but diminishes in tertiles of early terminations.

Safety and Feasibility of Structured Exercise Training in Older Deconditioned Adults with CKD

Stephen L. Seliger, 1,2 Jamie Giffuni, 1,3 Leslie I. Katz, 1,3 Andrew M. Well, 1 Christopher W. Washington, 1 Kieran Reid, 1 Daniel E. Weiner. 1

Background: CKD is associated with lower physical performance, especially in older adults. The feasibility and safety of structured aerobic and resistance exercise training in this patient group is unclear.

Methods: The AWARD study is an ongoing randomized trial among community-dwelling sedentary adults aged ≥60 years with stage 3b-4 CKD, comparing the effects of 12 months exercise training vs. health education (control). Thrice weekly in-center treadmill aerobic exercise sessions prescribed, with intensity and duration titrated over the first 8 weeks to goal of 40 minutes/session at 70-80% of the heart rate reserve. Additional resistance training is performed twice weekly. Aerobic capacity (VO2peak) is measured with graded treadmill testing, and submaximal gait with the 6-minute walk test. 28 patients have been enrolled to date. Mean age and BMI were 68.8 years and 30.3 kg/m2, mean eGFR 37 cc/min/1.73m2, and 64% had diabetes. VO2peak was 18.8±5.7 ml/kg/min (32% lower than predicted for healthy older adults), and distance walked in 6 minutes was 1330±334 feet (24% lower than predicted). 15 participants were randomized to exercise, with 803 individual exercise sessions prescribed to date. Of these, 76% were attended, with median individual adherence 87%. Target heart rate was achieved or surpassed in 55% of individual sessions. A total of 5 non-serious adverse events (AE) occurred that were potentially related to exercise (minor muscle injuries and post-exercise hypoglycemia). No serious AEs related to exercise occurred.

Conclusions: Thrice weekly training with aerobic and resistance training is feasible and safe for sedentary older adults with non-dialysis CKD. Adherence rates are excellent/high when compared with previous long-term exercise trials in frail older adults. Final results of this trial will determine whether such training is effective at improving cardiopulmonary fitness and/or lower extremity function, parameters which are markedly impaired in these patients. Funding: NIDDK Support.

Association of Chronic Kidney Disease with Falls in Nursing Home Residents

Rasheeda Howard, 1,2 Ann M. O’Hare, 1,2 Ruth A. Anderson, 1 Cathleen Colom-Emeric, 1,2 Duke Univ; 3Durham VA; 4VA Puget Sound; 5Univ of Washington.

Background: Chronic kidney disease (CKD) has been independently associated with falls in community dwelling older adults, but it is not known if this is also the case for nursing home (NH) residents. CKD may be associated with falls in NH residents because it comes with known fall risk factors (i.e., anemia, Vitamin D deficiency). To better understand fall risk in the growing population of NH residents with CKD, this study examines the association of estimated glomerular filtration rate (eGFR) with fall rate.

Methods: Secondary analyses of NH resident data obtained in a multicenter randomized controlled trial of NH staff-based fall prevention strategies (2009-2012). In each participating NH, residents with at least 1 fall during either of 2 6-month periods underwent chart abstraction for fall risk factors, serum creatinine, and subsequent fall events. We defined low eGFR using the Modification of Diet in Renal Disease equation, and CKD was defined by an eGFR less than 60ml/min/1.73m2. To test for independent association of eGFR with falls, our multivariable regression covariates included demographics, fall risk factors, resident’s time at risk, and admission rate.

Results: A total of 510 residents with falls were identified from 9 unique NHs. The mean (± SD) resident age was 77.2±11.5, 27% were female, and 63% resided in Veterans Affairs NHs. Overall median eGFR was 72 ml/min (IQR=50-95) while 35% of residents had CKD. Residents with CKD were older (79±11 vs. 76±11) and more likely to be female (34 vs. 23%). Mean fall rate was 5.6 falls per 100 patient days and did not differ by CKD status (p =0.40). In unadjusted analyses, lower eGFR was not associated with an increase in falls (p=0.58). In adjusted analyses, this relationship was unchanged.

Conclusions: In this study of NH residents who fall, one-third had low eGFR, but eGFR was not associated with the risk of recurrent falls. The absence of association suggests that CKD does not further increase falls risk in this high risk population. Given the increasing prevalence of CKD in NHs, this evidence suggests that current NH fall prevention strategies do not need to be altered for those with CKD.

Funding: Other NIH Support - NIA, NINR.
the benefits. This study aims to describe patients’ and caregivers’ perspectives on palliative care in chronic kidney disease (CKD).

Methods: We conducted a comprehensive literature search in Medline, Embase, PsycINFO, CINAHL and reference lists to May 2013. Thematic synthesis was used to analyze the findings.

Results: Twenty-four studies involving over 440 patients and 161 caregivers were included. We identified five themes: relief from suffering (bodily deterioration, loss of freedom and independence, pervasive fatigue and pain, resignation, treatment burden and harm); personal vulnerability (imminence of death, fear of misunderstanding and judgement, maintaining autonomy and dignity, medical abandonment, valuing safety and trust); relational responsibility (being a burden, demonstrating loyalty, protecting others from grief); negotiating existential tensions (accepting natural course of life, disrupted aging, worthlessness, living on borrowed time, respecting sanctity of life, life satisfaction, preserving self-identity); and preparedness (decisional clarity, information support, spirituality and hope).

Conclusions: Patients with CKD can experience physical and psychosocial frailty, and feel ambivalent about prolonging life. Caregivers believe in providing relief from suffering but are uncertain about making decisions regarding palliative care. CKD management should encourage palliative care strategies that promote emotional resilience, sense of well-being, and self-value. Also, respectful and attentive communication is needed so patients are empowered to convey their values and preferences in treatment decision making.

TH-P0684
Understanding Patterns of Place of Death in Patients with CKD 4-5
Fliss E. Murtagh,1 Natasha B. Lovell,1 Chris Jones,2 Baynes Ingrid Dawn,2 Sarah J. Dinning,2 Catherine Susanna Vinen.2 1Dept of Palliative Care, Policy and Rehabilitation, Kings College London, London, United Kingdom; 2Kings Renal Unit, Kings College Hospital, London, United Kingdom.

Background: Meeting preference regarding place of death is an important marker of quality of care; systematic review shows 42% end stage kidney disease patients prefer hospital death. These patients have high mortality, yet little research has been done to study place of death. The aim of this study was to understand patterns of place of death in patients with Chronic Kidney Disease (CKD) 4-5 known to a UK renal team.

Methods: A retrospective cohort study of CKD patients stage 4-5 known to a UK renal team, who died over 4 years (2009-2012). Demographic and clinical variables were collected, including management pathway and living circumstances. Multi-variable regression analysis was undertaken to determine relationship with place of death.

Results: 721 patients were included (mean age 73.9, SD 13.65). 59.6% male. 70.2% died in hospital (95% CI 68.3%-71.8%); 21.9% died in their usual residence (95% CI 19.0%-25.0%), and 7.9% died in an inpatient palliative care unit (95% CI 6.1%-10.1%).

1) Management pathway and 2) Residential setting were most strongly associated with place of death. 1) Patients on the conservative (non-dialytic) pathway had 4.6 times the odds of dying out of hospital (OR 4.6, 95% CI 2.8-7.3, P<0.01). 2) Patients living alone were less likely to die out of hospital (OR 0.6, 95% CI 0.4-1.0, P<0.05). 3) Patients where living status was not documented were less likely to die out of hospital (OR 0.5, 95% CI 0.3-0.8, P<0.01). Patients living in a care home had 9 times the odds of dying out of hospital (OR 9.3, 95% CI 1.4-28.7, P<0.01).

Conclusions: Hospital death predominated all groups, but place of death varied by management pathway, consistent with national data. Out-of-hospital deaths were higher in the conservative group. This may represent impact of palliative care service development for these conservatively managed patients in this unit. This work highlights importance of considering management pathway and living circumstances, so we meet preference for place of death in other management pathway groups, including patients on haemodialysis.

TH-P0685
Symptom Scores in End-Stage Kidney Disease: Can They Help U.S. with Timing of Anticipatory Care Planning?
Fliss E. Murtagh,1 Natasha B. Lovell,1 Katherine Bristowe,1 Kate A. Shepherd,2 Heather Jane Brown,1 Beverley Matthews,1 Donal O'Donoghue,1 Catherine Susanna Vinen.1 1Kings Renal Unit, King's College London, Cicely Saunders Institute, London, United Kingdom; 2Kings College Hospital, London, United Kingdom.

Background: Patients with end stage kidney disease report high fatigue (weighted median 86% [IQR 71%] and up to 58% experience depression (Murtagh AJKD 2007). Good symptom management and being prepared are patient priorities but professionals find timing of discussions challenging. We aimed to identify if routine symptom assessment had potential to inform timing.

Methods: Mixed-methods study, including experience survey, and symptom assessment (validated renal Palliative Care Outcome Scale). 3 questions concerned anticipatory care planning (ACP): Q1)Have you thought about where you would like to be cared for if you were not able to get better? Q2)Have you thought about who you would like to be involved in decisions about your medical care? Q3)When you raise these concerns do you feel they are taken seriously?

Results: 91 dialysis patients, 64.4% male, 30% aged 75 and above. 49.5% white. Fatigue and depression showed significant differences in question response: Q1 responses: 19.1% (95% CI 11.5-29.3) ’yes’, 15.7% (95% CI 7.7-30.0) ’to some extent’, 58.4% (95% CI 47.5-68.8) ’no’, and 6.7% (95% CI 2.5-14.1) ’don’t know’. Patients with high depression scores more often considered future care options (p=0.0065; OR=3.87; CI 2.2-6.3) ’yes’, 21.1% (95% CI 13.2-31.0) ’to some extent’, 20.0% (95% CI 12.3-30.0) ’no’, and 3.3% (95% CI 1.0-9.4) ’don’t know’. Patients with high fatigue more often considered who they wanted involved in decisions (p<0.001; OR=6.2; CI 3.3-11.4) ’yes’, 32.6% (95% CI 22.8-43.5) ’to some extent’, 8.1% (95% CI 3.3-16.1) ’no’, and 5.8% (95% CI 1.9-13.0) ’not applicable’. Patients with high fatigue felt less sure concerns were taken seriously (p=0.003; n=81).

Conclusions: These results highlight need to consider self-efficacy and on timing ACP discussion. Routine regular symptom assessment may help inform readiness of patients, particularly if reporting fatigue/ depression. This work is a key component in a project led by NHS Kidney Care.

Funding: Government Support - Non-U.S.

TH-P0686
Depression, Social Support, Self-Efficacy, and Fluid Adherence in Older Adults on Hemodialysis
Tiffany R. Washington, Social Work, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: Controlled fluid intake is an important aspect of kidney disease self-management, yet depression, the most common psychiatric issue affecting older end-stage renal disease (ESRD) patients, negatively impacts fluid adherence. Factors that mitigate depression’s deleterious effects are underidentified, and if identified, can aid in the design and development of psychosocial interventions to reduce its negative impact and improve fluid adherence. This paper examines four logistic regression models to determine mediating factors between depression and fluid adherence.

Methods: A total of 107 ESRD patients from four hemodialysis facilities in the southeast aged 50 and older were interviewed about their kidney disease self-management behaviors. Four logistic regression models were analyzed: 1) the primary independent variable (depression); 2) the primary independent variable (depression) with a secondary independent variable (social support); 3) the primary independent variable (depression) with a secondary independent variable (self-efficacy); and 4) the primary independent variable (depression) with a secondary independent variable (social support) and a secondary independent variable (self-efficacy).

Results: Age was associated with an increase in fluid adherence (adjusted odds ratio [AOR] = 1.08, 95% confidence interval [CI] = 1.02-1.14), and depression was associated with a decrease in fluid adherence (AOR = 0.82, 95% CI = 0.67-0.99). When self-efficacy was entered into the model, the association between depression and fluid adherence disappeared. Race comparisons showed that depression was negatively associated with fluid adherence (r = 0.26, p = 0.05), and self-efficacy and age were positively associated with fluid adherence among black participants (r = 0.24, p = 0.05 and r = 0.32, p < 0.01, respectively).

Conclusions: The findings from this study suggest that self-efficacy and age are important factors in fluid adherence, and self-efficacy can potentially mediate the negative effects of depression in older ESRD patients. Advanced statistical methods and longitudinal studies are required to determine the indirect effect of depression to fluid adherence mediated by self-efficacy.

Funding: Private Foundation Support

TH-P0687
Short Sleep Duration and Albuminuria in Advanced Chronic Kidney Disease
Andrew M. Well,1 Jamie Giffin,2 Stephen L. Seliger3 Roger A. Fielding,4 Lesli I. Katzeln,5 Daniel E. Weiner,1 1Tufts Univ, Boston, MA; 2Univ of Maryland, Baltimore, MD.

Background: Short sleep duration (SSD) is a predictor of cardiovascular disease and mortality, and, in one study of younger individuals with normal eGFR, self-reported SSD was associated with dipstick proteinuria. The association between sleep duration and albuminuria has not been evaluated in older individuals with advanced CKD.

Methods: AWARD is a randomized controlled trial evaluating the effects of exercise vs. health education in individuals 60 years and older with an eGFR of 15 to 45 ml/min/1.73m². Participants’ total sleep time (TST) at baseline was quantified by actigraphy worn for 5 consecutive nights and by self report using the Pittsburgh Sleep Quality Index. Urine albumin creatinine ratio (ACR) was assessed at baseline and at 6 months.

Results: Of 28 participants who have completed baseline testing by May 15, 2013, 27 have complete sleep data and were included. Mean age was 69 ± 7 years, 15% are women, 67% diabetic and 56% on ACEi or ARB therapy; mean eGFR is 37 ± 11 ml/min/1.73m² and median [interquartile range] ACR is 49 [17–878] mg/g. Mean actigraphy TST was 6.6 ± 1.6 hours with 41% sleeping <6 hours. Participants with TST <6 hours on actigraphy had a median ACR of 1152 [66–2580] mg/g while those with a TST ≥6 hours had a median ACR of 31 [9–63] mg/g (p=0.02).

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

256A
TH-PO688

Chronic Pain in Hemodialysis Patients
Sharmeela Saha, Robin E. Olivo, Robin L. Hensley, Julia Lewis.
Nephrology, Vanderbilt Univ Medical Center;
Nashville, TN.

Background: We conducted a retrospective analysis of narcotic prescription practices in our outpatient hemodialysis (HD) units. The purpose was to examine management of chronic pain and to develop strategies to improve patient safety.

Methods: We studied HD outpatients in 2 units from January 1, 2012 until January 1, 2013. We collected information regarding patient demographics, narcotic prescriptions and prescribers, and documentation of analgesic indication by examining the Tennessee Monitoring Database and Vanderbilt medical records.

Results: 52 of 191 (27%) HD patients were supplied with narcotics for at least a continuous 90 day period. Almost 40% of patients in the 40-49 and 50-59 age groups were treated for chronic pain. There was no predominance by gender but 32% of African Americans and 19% of Caucasians received chronic narcotics. Pain medications were most common among patients on HD for over 5 years. Arthritis and diabetic neuropathy were the most prevalent comorbidities. Hydrocodone with acetaminophen was the most commonly prescribed medication. The most frequently recorded indication was peripheral neuropathy; however, 52% (27/52) of patients had no documented indication. 90% of patients on chronic pain meds did not have a narcotics contract. 21% of patients had their narcotic prescriptions and prescribers, and documentation of analgesic indication by examining the Tennessee Monitoring Database and Vanderbilt medical records.

Conclusions: Among older adults with CKD Stage 3b-4, objectively measured sleep duration is associated with higher ACR. The elevated ACR in SSD may suggest increased inflammation or vascular risk factor burden due to SSD.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO689

Renal Function Decline in Community-Dwelling Older Adults
1Medicine, Univ of Michigan, Ann Arbor, MI; 2Biostatistics, Univ of Michigan, Ann Arbor, MI; 3Neurology, Albert Einstein College of Medicine, Bronx, NY.

Background: Decreased kidney function is associated with increased morbidity and mortality in older adults. The rate of renal function decline varies, but risk factors for accelerated decline are not well-defined in older adults. Therefore, we examined rate of renal function decline and associated clinical factors in community dwelling older adults enrolled in Einstein Aging Study (EAS), a community-based longitudinal study of aging.

Methods: We identified 250 subjects (>68 years of age), who were followed up to 7 years since 2005 and had at least three serum creatinine measurements separated by at least 11 months. We calculated creatinine-based eGFR by different formulas (CG, MDRD, CKD-EPI, and Berlin initiative study 1 (BIS1)). Rates of eGFR decline were determined by mixed effect modeling. Multivariable linear or logistic regression was used to identify factors associated with mixed effect eGFR decline rate.

Results: The mean age of the study subjects was 79 years (60% are female). Mean baseline eGFR was 55 to 74 ml/min/1.73 m² based on different formulas. The mean mixed effect eGFR annual percent change was between -3.0% to 1.3%. Cross-sectional analysis revealed that higher homocysteine was significantly associated with lower baseline eGFR (P=0.0001). Longitudinal analysis showed that in linear regression, baseline eGFR was the only factor associated with eGFR annual percent change (β=0.01-0.04, P=0.0001). In logistic regression, subjects with lower baseline eGFR were more likely to have progressive eGFR decline (OR=16.40, P<0.001 for CG, MDRD and BIS1; no significance was detected using CKD-EPI formula).

Conclusions: The average annual renal function decline in this older adult cohort is 1 to 3% per year. Baseline eGFR is an independent risk factor for faster eGFR decline. However, the risk levels are associated with cross-sectional eGFR, but not with eGFR decline. Nevertheless, additional markers are needed to identify subjects with similar eGFR at risk for future loss of renal function, in particular with CKD stage III.

Funding: NIDDK Support

TH-PO690

Assessment of Renal Function in Elderly with Chronic Kidney Disease Using CKD-EPI and MDRD Equations
Eleni Chelioti, Dimitrios Athanassopoulo, Evangelia Gkalitsiou, Evdokia Efthimiou, Maria Sotiraki, Alexia Papalexandrou, Maria Tsilivigou.
1Dept of Nephrology, General Hospital of Piraeus, Athens, Greece; 2Health Centre of Dimitsana, General Hospital of Tripoli, Tripoli, Greece.

Background: Kidney function loss in the elderly results from physiologic aging of the kidney and lifelong pathologic insults. To estimate glomerular filtration rate (eGFR), MDRD and CKD-EPI formula are the most frequently used.

Aim: The study was to assess the renal function in elderly with chronic kidney disease using the MDRD and CKD-EPI equations.

Methods: A cross sectional study was carried out. The study included elderly patients that attended the outpatient nephrology clinic within one year. The patients divided in 2 groups: eGFR<60 and eGFR>60ml/min/1.73m². Estimated GFR was calculated using MDRD and CKD-EPI formula on time 0 and 12months.

Results: 224 patients were studied (52%men, 42% diabetics, 83% hypertensive, mean age70±13years-old, mean SAP 133±61mmHg, mean DAP 73±12mmHg, mean serum creatinine 1.8±0.7mg/dl). There are not statistically differences between mean CKD-EPI and MDRD GFR on time 0 (43±30 and 42±22 respectively) and 12 months (43±20 and 43±19 respectively) in patients with eGFR<60ml/min/1.73m². Not statistically differences found between mean CKD-EPI and MDRD on time 0 (30±18 and 31±17 respectively) and 12 months (32±18 and 32±18 respectively)in patients with eGFR<60ml/min/1.73m². However, we found that there is a statistically significant correlation between eGFR>60 or eGFR<60 and sex (p=0.001) in both time 0 and 12. Also, the correlation between reduced eGFR and hypertension was statistically significant (p=0.01) in both groups and independent by the using of MDRD or CKD-EPI equations.

Conclusions: Our results suggest that at ages>70 years there is not difference between the equations for the assessment of renal function.

TH-PO691

Prevalence of Stage 3-5 Chronic Kidney Disease and Anaemia in Elderly and Very Elderly
Eleni Chelioti, Dimitrios Athanassopoulo, Evdokia Efthimiou, Maria Sotiraki, Maria Tsilivigou.
1Dept of Nephrology, General Hospital of Piraeus, Athens, Greece; 2Health Centre of Dimitsana, General Hospital of Tripoli, Tripoli, Greece.

Background: Chronic kidney disease (CKD) is a growing problem due to our aging population, many of who have increased comorbidities.Cross-sectional studies in the general population demonstrate that CKD is seen in up to 15,3% including 39% of those over the age of 65 years.

Aim: The study was to examine the prevalence of stage 3-5 CKD in elderly and very elderly at an outpatient nephrology clinic and its association with anemia.

Methods: The cohort was defined as all patients that attended the outpatient nephrology clinic within the 2012. The patients divided in 3 age groups (AG)E-GFR<65AG1-GFR=65-75AG2 and AG3=80 years old.Estimated glomerular filtration rate (eGFR) was calculated using MDRD and CKD-EPI formulae.

Results: A total of 231 patients were studied (52%men, mean age76±6years,mean eGFR 31±8ml/min/1.73m², meanHb 11,98±1,7g/dl).According to the 3 age groups the percentage of patients was:50%AG1,27%AG2 and 23%AG3. There are not statistically difference between mean CKD-EPI and MDRD GFR. The percentage of stage 3,4 and 5 CKD, was higher at AG1, AG3 and AG1 respectively.

Conclusions: The percentage of all patients who had Hb=11,5g/dl or<10g/dl was 41,3% and 10,3% respectively. Correlation between decline of eGFR and Hb was statistically significant (p<0.0001) in all age groups and not statistically significant with the age(p=0.7).
Conclusions: Our results suggest that the prevalence of stage 3 CKD is higher in the elderly but the prevalence of CKD stage 4 is highest in very elderly and lower in stage 5. Also the anemia in the elderly and very elderly seems to be in association with the decline of GFR and not with the aging.

TH-PO692

Hospitalized Elderly with Acute Kidney Injury: Are There Greater Risk of Death and Progressive Chronic Kidney Disease

Jia Liang Kwek, Hui Zhuang Tan, Cynthia Cwiwe Lim, Manish Kaushik. Dept of Renal Medicine, Singapore General Hospital, Singapore, Singapore.

Background: To determine the patient and renal outcomes in elderly patients with AKI as defined by Acute Kidney Injury Network (AKIN) criteria.

Methods: A single-center retrospective cohort study on elderly ≥ 65 years old admitted during first week of January 2011. Demographic data, co-morbidities and laboratory findings were retrieved from the electronic medical records. Patients with <2 serum creatinine values were excluded. AKI was present if serum creatinine increased ≥ 26.4 μmol/L within a 48h during hospitalization. The primary outcome was kidney function measured by MDRD estimated glomerular filtration rate (eGFR) at latest visit. The secondary outcomes were in-hospital mortality and incident end-stage renal disease (ESRD) requiring dialysis. Patients were followed up until 31 December 2012.

Results: Of 709 elderly admitted, 324 (median age 77, male 48.6%, diabetes mellitus 46%, hypertension 78.7%, ischemic heart disease 38.3%) were studied. Baseline serum creatinine was available in 264 patients (81.5%). Median baseline GFR was 71.3 ml/min/1.73m² (range 2.7-228.7) and median eGFR on admission was 58.6 ml/min/1.73m² (range 1.5-292.6). 46 patients (14.6%) had AKI at median 2 days (range 1-33) during hospitalization: 3 patients (0.9%) required dialysis. Comparing AKI group (n=46) with non-AKI group (n=278), the only significant risk factor for AKI found in this study was hypotension (34.8% vs 13.7%, p<0.001). Median follow-up period was 14.5 months (range 0-24). 52.2% of AKI group had eGFR < 30 ml/min/1.73m², compared to 20.5% of non-AKI group (p<0.001). Significantly, 34.8% of AKI group had decreased GFR from baseline by ≥ 50%, as compared to 11.9% of non-AKI group (p<0.001). In-hospital mortality was increased for AKI group (21.7% vs 3.6%, p<0.001). Significant risk factor for AKI found in this study was hypotension (34.8% vs 13.7%, p<0.001). However, there was no difference in incident ESRD requiring dialysis (4.3% vs 1.1%, p=0.149).

Conclusions: This study confirmed that even mild AKI is associated with significant risk of deterioration in renal function and death. Future interventional study can target preventive measures and timely treatment of hospitalization AKI to lower the risk of adverse outcomes.

TH-PO693

Triamterene-Hydrochlorothiazide Is Associated with Chronic Kidney Disease in Hypertensive Elderly Patients


Background: Triamterene-HCTZ (TR-HCTZ) is a commonly prescribed antihypertensive medication combination. TR can cause abnormal urinary sediment, which results in partial improvement in renal function, even when ACE/ARB and HCTZ were resumed. TR should be avoided in elderly patients to reduce the risk of chronic kidney disease. Its cessation represents a formal contraindication.

Methods: A single-center retrospective cohort study on elderly ≥ 65 years (range 2.3-20) • NSAIDs > 2 times weekly; 1 patient with unavailable data.

Results: 42 patients had no alternative CKD diagnoses identified except for TR-HCTZ exposure, at drug cessation, and at 1-3 and 6-12 month follow up; age, BMI, gender, and race; hypertension (HTN). Data was collected for: serum creatinine (CR) prior to TR-HCTZ exposure, at tertiary center in St. Paul, MN from Jan 1995 to June 2010. All received TR-HCTZ for aortic stenosis, and acute renal failure but has not been implicated in causing chronic renal failure. TR-HCTZ dosage and duration; patient reported NSAID use; UA and urinary microalbumin; eGFR at 1-3 months post TR-HCTZ 43.2 (12.3) 40.8 (12.6) 43.4 (13.5) 40.5 (11.4) vs. non-AKI group (p<0.001). In-hospital mortality was increased for AKI group (21.7% vs 3.6%, p<0.001). However, there was no difference in incident ESRD requiring dialysis (4.3% vs 1.1%, p=0.149).

Conclusions: This study confirmed that even mild AKI is associated with significant risk of deterioration in renal function and death. Future interventional study can target preventive measures and timely treatment of hospitalization AKI to lower the risk of adverse outcomes.

TH-PO694

Use of Beers Criteria Medications and Opioids among Very Elderly Hemodialysis Patients

Eric D. Weinhandl, Wendy L. St. Peter, Anne M. Murray. "USRDS Coordinating Center, MMRF, Minneapolis, MN; "Univ of Minnesota, Minneapolis, MN.

Background: The very elderly constitute the most rapidly growing segment of dialysis patients in the United States and cognitive impairment (CI) is highly prevalent among them. Beers Criteria (BC) include several medication classes that are recommended to be avoided in older adults with CI. Opioids are commonly prescribed to dialysis patients and may further worsen cognitive function. We used Medicare Part D data to assess use of both potentially inappropriate medications in CI and opioids in very elderly hemodialysis patients in 2011.

Methods: Included patients carried Medicare coverage during all of 2010; initiated dialysis no later than September 30, 2010; received hemodialysis from October 1 to December 31, 2010; were age ≥ 80 years on January 1, 2011; and carried Part D coverage from January 1, 2011, to the earliest of death or December 31, 2011. We categorized patients as unsubsidized (UN); subsidized and not institutionalized (SUB); or subsidized and institutionalized (SUB+IN).

Results: We identified 8,459 UN; 7,196 SUB; and 3,052 SUB+IN patients. Regarding BC, 44.7% of patients used ≥1 medication that is recommended to be avoided in older adults with CI, including agents with anticholinergic effects (27.8%), H2-receptor antagonists (12.1%), zolpidem (11.1%), and antipsychotics (7.0%). Factors associated with use of ≥1 BC medication were age ≥ 80 vs. 80-84 years (adjusted odds ratio, 0.75), white vs. black race (1.33), female vs. male sex (1.33), diagnosed dementia (1.28), SUB vs. UN status (1.54), and SUB+IN vs. SUB status (1.48). Regarding opioids, 31.0% of all patients used ≥1 medication; estimates of opioid use in patients with and without diagnosed dementia were 50.9% and 51.1%, respectively. Opioid use was associated with diagnosed dementia (0.88), SUB vs. UN status (1.27), and SUB+IN vs. SUB status (1.30).

Conclusions: Use of potentially inappropriate medications in cognitive impairment was common among very elderly hemodialysis patients and almost 50% more likely among patients with diagnosed dementia. Use of opioids was also common. Studies are needed to determine whether these medications are prescribed appropriately.

Funding: NIDDK Support

TH-PO695

Non Steroidal Anti-Inflammatory Drugs and Kidney Function in the Elderly

Antonio Dourou,1 Natalie Ebert,2 Olga Jakob,3 Reinhold Kreutz,4 Elke Schaefert.1 1Clinical Pharmacology, Charite, Berlin, Germany; 2Nephrology, Charite, Berlin, Germany; 3Clinical Epidemiology, Charite, Berlin, Germany.

Background: There are several limitations regarding the use of non steroidal anti-inflammatory drugs (NSAIDs) in the elderly among which impaired kidney function (KF) represents an important clinical problem. The present study investigates the relationship between intake of NSAIDs and KF in people ≥ 70 years.

Methods: Individuals included in this analysis were participants of the Berlin Initiative Study (BIS). BIS is a population-based cohort study initiated in 2009 in Berlin, Germany, in order to evaluate KF in individuals ≥ 70 years. Medication was assessed through personal interviews and coded using the Anatomical Therapeutic Chemical Classification System. For estimation of glomerular filtration rate (eGFR) we used the CKD-EPI equation.

Results: From overall 2070 individuals 440 subjects (21%) received NSAIDs, either regularly or on demand. Mean age of the NSAIDs population was 79.3±6.4 years (females 62%). Figure 1 illustrates the frequency of use for the two most commonly taken NSAIDs, and the portion of patients > 75 years receiving these agents.

Conclusions: As acute or chronic pain conditions are frequent in advanced age, use of NSAIDs in the elderly is a common topic of debate. Our data show that about 20% of this population take NSAIDs. Most of these patients were > 75 years, despite the recent classification of nearly all NSAIDs as potentially inappropriate medication for this age group by the American Geriatric Society. Presence of severe renal damage did not seem to affect the prescription behavior of physicians regarding NSAIDs, although this represents a formal contraindication.

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

Underline represents presenting author/disclosure.

258A
TH-PO696  
Antiviral Dose and Hospitalization with Urgent Computed Tomography Scan and Mortality in Older Patients with and without Chronic Kidney Disease – A Population-Based Study  
Ngan Lam,1,2 Jamie L. Fleet,1 Eric McArthur,1,3 Stephanie Dixon,1,3 Amit X. Garg,1,3  
1Nephrology, Western Univ, London, Canada; 2Epidemiology and Biostatistics, Western Univ, London, Canada; 3Institute for Clinical Evaluative Sciences, Toronto, Canada.

Background: Higher versus lower doses of antiviral drugs used to treat herpes zoster infection may lead to more adverse events in older adults, particularly those with chronic kidney disease (CKD) where drug elimination is reduced.

Methods: We conducted a matched retrospective population-based cohort study of older adults (mean 77 years) in Ontario, Canada who were initiated on a higher (n = 23,256) versus lower (n = 3,876) dose of one of three study oral antivirals (acyclovir, valacyclovir, or famciclovir) for the treatment of herpes zoster infection. Patients were enrolled between 2002 and 2011. The primary outcome was 30-day hospitalization with evidence of an urgent head computed tomography (CT) scan (a proposed proxy for acute delirium). The secondary outcome was 30-day all-cause mortality. We stratified our results based on the presence or absence of CKD.

Results: A higher dose of antiviral drug was not associated with a higher risk of hospitalization with CT head scan (247 [1.06%] events with higher dose versus 43 [1.11%] events with lower dose, relative risk 0.96, 95% confidence interval 0.69 to 1.33, p-value 0.79). There was also no significant difference in mortality between the two dose groups. Results were consistent in all subgroups, including those with and without CKD (p-value for interaction 0.25).

Conclusions: In this study, a higher vs. lower dose of antiviral drug for the treatment of herpes zoster infection was not associated with a higher risk of hospitalization with CT head scan or mortality in older patients with and without CKD.

TH-PO697  
Serum Anion Gap Is Predictive of Mortality in an Elderly Population  
Shin-Young Ahn, Seon Baek, Jiwon Ryus, Ho Jun Chin, Ki Young Na, Dong Wan Chac, Sejoong Kim.  
Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam-si, Gyeonggi-do, Republic of Korea.

Background: An elevated serum anion gap is known to be associated with hypertension, low cardiorespiratory fitness, and decreased renal function. We evaluated whether serum AG might be predictive of elderly mortality in a community-based cohort in Korea.

Methods: We analyzed the available data from 862 elderly people in the Korean Longitudinal Study of Health and Aging. In the baseline study of the KLoSHA, the participants were required to visit Seoul National University Bundang Hospital on two occasions for comprehensive interviews and laboratory tests.

Results: Over a 5-year observational period, 151,862 (17.5%) participants died, and a high albumin-adjusted anion gap (SAAG) was associated with an increased risk of all-cause mortality in unadjusted analyses (hazard ratio [HR], 1.96; 95% confidence interval [CI], 1.41 - 2.71) and fully adjusted analyses (HR, 1.77; 95% CI, 1.24 - 2.52), compared with a low SAAG group. In particular, the participants with high SAAG had higher cardiovascular and infection-related mortality rates than those with low SAAG (HR, 2.11; 95% CI, 1.06 - 4.19, and HR, 9.69; 95% CI, 1.12 - 83.43, respectively).

Conclusions: High SAAG may be an independent predictor of mortality and can affect cardiovascular- and infection-related mortality in the elderly Korean population.

Funding: Government Support - Non-U.S.

TH-PO698  
Polypharmacy Is a Risk Factor for Acute Renal Failure in the Elderly Population  
Ozaman Z. Sahin, Fatih Sumer,2 Testime Ayaz,2 Kadir Ilbk1,2,3  
1Nephrology, Recep Tayyip Erdogan Univ Faculty of Medicine, Turkey; 2Internal Medicine, Recep Tayyip Erdogan Univ Faculty of Medicine, Turkey.

Background: Because of the rapid growth in elderly population, polypharmacy has become a serious public health issue worldwide. Particularly, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are increasingly used in the elderly for heart failure and hypertension. Acute renal failure (ARF) is one negative consequence of polypharmacy. We therefore aimed to assess the impact of polypharmacy, especially usage of ACE inhibitors and/or ARBs on the development of ARF in elderly population.

Methods: 42 consecutive patients who were older than 65 years and admitted to our emergency unit or Nephrology outpatient clinic between January 2010 and June 2012 for ARF included in this study. Polypharmacy was defined as more than 5 prescriptions per day. All the patients were using an ACE inhibitor or ARB for at least 3 months. We recorded all the other medications especially diuretics and nonsteroidal anti-inflammatories (NSAIDs). We especially noted the change in medication for 10 days prior to admission. ARF was defined as a sudden increase in serum creatinine from normal to more than 2 mg/dl or an increase 50% above the baseline within 3 months.

Results: The study population consisted of 44 patients, aged 65-86 years (mean: 74.27 ± 6.60) and 44.5% of them were male. 61.4% of them had hypertension, 22.7% had diabetes, 11.4% had congestive heart failure and 22.7% had chronic renal failure. 83.3% of the patients were receiving ACE-I or ARB and 52.4% of them were using NSAIDs. Mean number of prescriptions per day was 6.1. Basal urea and creatinine levels of the patients were 4.71±2.67 mg/dl and 49.2±57.76 mg/dl respectively. Potassium levels were 2.6±0.9 mEq/L in 22.5% of the patients. ACE-I or ARB and NSAIDs were stopped. 15.9 % the patients were undergone on hemodialysis. 40.9 patients had recovered and serum creatinine level came back to normal.

Conclusions: We observed an association between the polypharmacy, usage of ACEI or ARBs and the occurrence of ARF in elderly population.

TH-PO699  
Initiatives by the Geriatric Nephrology Advisory Group (GNAG) of the American Society of Nephrology (ASN)  
Markus Bitzer,1 Mark E. Williams,2  
1Internal Medicine, Univ of Michigan, Ann Arbor, MI; 2Joslin Diabetes Center, Harvard Medical School, Boston, MA.

Background: There is growing interest in the care of older adults with kidney disease among Nephrologists and the increasing use of dialysis and kidney transplantation in older adults has attracted the attention of geriatrics and palliative care.

Methods: We describe resources and initiatives of the ASN, Geriatric Nephrology Advisory Group (GNAG) to improve care for older adults with CKD.

Results: To improve the quality of dialysis rounds of geriatric patients GNAG, in partnership with the Association of Specialty Professors (ASP) and under the direction of Mark Williams, created a video series that discusses critical aspects of care for elderly patients, including patient assessment, dialysis care, recognition of physical and mental decline, quality of life issues, and sharing decision-making information, which is freely available at www.asnrounds.org and has already over 5,000 views. To enhance education of Nephrology fellows in Geriatric Nephrology, GNAG developed and updates an on-line Geriatric Nephrology curriculum with teaching tools in the diagnosis and management of various geriatric entities (with ASP support). For an in-depth discussion of specific aspects of Geriatric Nephrology, the GNAG with support of the ASN Post-Graduate Education Community has organized the Dimitrios G. Oropoules Memorial Program in Geriatric Nephrology, a two-day course on Geriatric Nephrology included in the annual meeting of the ASN since 2008. The 2013 course is entitled “Patient-Centered Care for Older Adults with Kidney Disease”. To provide guidance in the care of older adults with kidney disease and promote the scientific collaborations to advance research in Geriatric Nephrology GNAG established the Dimitrios G. Oropoules Visiting Professor Program, which supports visits from experts in Geriatric Nephrology to Nephrology fellowship training programs, with ASP support. A Career Development Grant in Geriatric Nephrology is supported by the ASN Foundation for Kidney Research.

Conclusions: The GNAG has implemented a variety of initiatives by which health care providers can improve care of older adults with kidney disease.

Funding: NIDDK Support

TH-PO700  
Elevated Prorenin Induces Dose-Dependent Podocyte Injury in cyp1a1-Prorenin Transgenic Rats  
Chunyan Gu, Alfred K. Cheung, Yuifeng Huang.  
Div of Nephrology & Hypertension, Dept of Internal Medicine, Univ of Utah School of Medicine, Salt Lake City, UT.

Background: Plasma prorenin levels are commonly elevated in diabetic patients and appear to predict the development of albuminuria and progression of DN. Albuminuria is often the result of podocyte injury. However, the potential pathogenic role of prorenin in podocyte injury is unclear. In this study, we examined the associations of plasma prorenin levels in transgenic animals in which prorenin is produced in the liver with damages to podocytes.

Methods: Cyp1a1 prorenin transgenic rats at 12 wks of age were fed with normal diet containing incremental amounts of indole-3-carbinol (IC3) at 0.05% (n=6), 0.15% (n=6) or 0.3% (n=4) respectively. Wild-type rats with normal diet (n=6) served as healthy controls. We characterized the transgenic inducibility of IC3 by feeding 1.5 cpm of transgenic rats with IC3 at 0.05%-0.3% for 4 wks. We measured plasma prorenin levels in the transgenic by 7-, 18-, and 24-fold respectively. However, plasma renin levels are not increased. The induction of prorenin expression by IC3 resulted in a dose-dependent decrease in expression of nephrin and podocin, and WT-1-positive podocytes in the kidney as determined by immunofluorescent staining, associated with segmental podocyte foot process effacement and podocyte body hypertrophy assessed by transmission electron microscopy. These data strongly suggest that prorenin induces podocyte injury. There were also significant increases in the mean arterial pressure and urine albumin/creatinine ratio in the prorenin transgenic rats treated with IC3, although the dose-dependency of these phenomena was less apparent.

Conclusions: These findings suggest a novel link between elevated plasma prorenin levels and structural changes in diabetic kidney. Of note, treatment of transgenic rats with either amlodipine (10mg/kg/d by gavage/or equals) (200mg/L in drinking water) for 6wks prevented the development of hypertension and albuminuria, but did not prevent, the development of podocyte injury and albuminuria. Our findings further indicate that hypertension in this model is Ang II-dependent. However, the prorenin-induced podocyte injury is only partially dependent on hypertension and Ang II, suggesting additional Ang II-independent effects.

Funding: NIDDK Support, Other NIH Support - NKF of Utah & Idaho

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Critical Role of Proximal Promoter Elements and Their Interacting Factors in the Transcription of Angiotensin II Binding and Inhibitory Protein in Renal Tubule Cells

Kouichi Tamura, Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan.

Background: The Angiotensin II (Ang II) type 1 receptor (AT1R)-associated protein (ATRAP/Agtrap) promotes constitutive internalization of the AT1R so as to specifically inhibit the pathological activation of its downstream signaling but yet preserve the baseline physiological signaling activity of the AT1R. Thus, tissue-specific regulation of ATRAP gene expression is relevant to the pathophysiology of cardiovascular and renal disease. However, the regulatory mechanism of ATRAP gene expression has not been fully elucidated yet.

Methods: In the present study, we examined whether the proximal promoter of the mouse ATRAP gene, which contains the X-box, E-box and GC-box consensus motifs, is able to elicit substantial transcription of the ATRAP gene. We focused our analysis on a functional role of the E-box and characterization of its putative binding transcription factors in vivo and in vitro. We also examined a possible role of the E-box of the human ATRAP promoter in the transcriptional regulation.

Results: We showed that the E-box-US1/Usf2 binding regulates ATRAP gene expression, because: (1) mutation of the E-box so as to prevent Usf1/Usf2 binding reduces ATRAP promoter activity; (2) knockdown of Usf1 or Usf2 affects both endogenous ATRAP mRNA and ATRAP protein expression and (3) the decrease in ATRAP mRNA expression in the afflicted kidney by unilateral ureteral obstruction (UUO) is accompanied by changes in Usf1 and Usf2 mRNA. Furthermore, the results of siRNA transfection in mouse distal convoluted tubule cells and those of UUO in the afflicted mouse kidney suggest that Usf1 decreases but Usf2 increases the ATRAP gene expression by binding to the E-box. The results also showed a functional E-box-USf1/USf2 interaction in the human ATRAP promoter.

Conclusions: Collectively, these results demonstrated that an interplay between E-box and Usf1/Usf2 is important for ATRAP gene regulation. A strategy of modulating the E-box-USf1/USf2 interaction may have novel therapeutic potential.

Funding: Government Support - Non-US

TH-PO702

T Type Ca-Channel Blocker Exerts Anti-Albuminuric Effect through Amelioration of eNOS Uncoupling in Hypertensive Kidney Disease Model

Seiji Itano, Kengo Kidokoro, Minoru Satoh, Tamaki Sasaki, Naoki Kashihara, Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.

Background: Tetrahydropirbuterine (BH4), an essential cofactor for endothelial Nitric oxide (NO) synthase (eNOS), is easily oxidized by oxidative stress. In such condition, eNOS generates superoxide rather than NO (eNOS-uncoupling), thus further aggravates oxidative stress. Certain class of calcium channel blocker (CCB) has shown to improve endothelial dysfunction by 'recoupling' eNOS. We investigated the molecular mechanisms underlying recoupling of eNOS and reno-protective effects by two different classes of CCBs, Bendipin(TL type) and Amlodipin(L type).

Methods: We used 6 week-old male Dahl salt sensitive (Dahl) rats and treated them with either Bendipin (BN,3mg/kg/day) or Amlodipin (AM,3mg/mg/day) for 4 weeks. Urinary albumin excretion, glomerular BH4 level, expression of GTP cyclohydrolase I (GTPCH I), a rate-limiting enzyme of BH4 synthesis, were evaluated in the kidney tissues.

Results: Bendipin and Amlodipin significantly decreased glomerular albumin excretion and BH4 level in the kidney tissues of Dahl rat. Furthermore, glomerular BH4 level and GTPCH I expression were decreased in the kidney tissues of Dahl rat. Exacerbated ROS production and diminished bioavailable NO were observed with elevation of blood pressure, increased UAE were observed in Dahl group. Western analysis revealed eNOS uncoupling in Dahl group. In the present study, we examined whether the proximal promoter of the mouse ATRAP gene, which contains the X-box, E-box and GC-box consensus motifs, is able to elicit substantial transcription of the ATRAP gene. We focused our analysis on a functional role of the E-box and characterization of its putative binding transcription factors in vivo and in vitro. We also examined a possible role of the E-box of the human ATRAP promoter in the transcriptional regulation.

Conclusions: Collectively, these results demonstrated that an interplay between E-box and Usf1/Usf2 is important for ATRAP gene regulation. A strategy of modulating the E-box-USf1/USf2 interaction may have novel therapeutic potential.

Funding: Government Support - Non-US

TH-PO704

Renal Dopamine-Induced Diuresis and Natriuresis Is Mediated by CYP Epoxygenase 2C44

Xin Zhang, Zi-Lun Li, John A. Crane, Stephen C. Textor, Medicine, Vanderbilt Univ School of Medicine, Nashville, TN.

Background: We have recently demonstrated that intrarenal dopamine plays an important role in preventing the development of systemic hypertension. Similarly, renal cytochrome P450 (CYP)-epoxygenase-derived arachidonic acid metabolites, epoxyeicosatrienoic acids (EETs) are also anti-hypertensive. The current studies investigated potential interactions between renal dopamine and epoxygenase systems.

Methods: COMT-/- mice with increased intrarenal dopamine levels and pTAADC/-/- with renal dopamine deficiency were treated with low-salt diet or high-salt diet for 2 weeks. Wild type or Cyp2c44/-/- mice were treated with gludopa, which selectively increased renal dopamine in COMT-/- mice.

Results: In low-salt treated mice, renal EET levels correlated with renal dopamine levels, being highest in COMT-/- mice and lowest in pTAADC/-/- mice. In high-salt treated mice, total EET and individual EET levels in both kidney and urine were also highest in COMT-/- mice and lowest in pTAADC/-/- mice. Selective increases in renal dopamine in response to gludopa administration led to marked increases in both total and individual EET levels in the kidney without any changes in blood levels. qPCR and Western analysis indicated that gludopa increased renal Cyp2c44 mRNA and protein levels. Dopamine also increased Cyp2c44 mRNA levels dramatically in cultured mouse proximal epithelial cells. Gludopa induced marked increases in urine volume (ml/16-h; control: 0.95 ± 0.11; gludopa: 3.77 ± 0.23, P < 0.001, n = 4) and urinary sodium excretion (μM/16-h; control: 99.65 ± 9.93; gludopa: 302.08 ± 23.43, P < 0.001, n = 4) in wild type mice. In contrast, gludopa did not induce significant increase in urine volume (ml/16-h: control: 0.67 ± 0.11; gludopa: 0.90 ± 0.30, P > 0.05, n = 4) or urinary sodium excretion (μM/16-h: control: 116.04 ± 7.83; gludopa: 157.71 ± 21.72, P > 0.05, n = 4) in Cyp2c44/-/- mice.

Conclusions: Val-salt and TT similarly decreased blood pressure, but did not alter renal function. RAS induced LV hypertrophy (LVI), accompanied by increased markers of myocardial autophagy and mitophagy. Val alleviated LVI, lowered myocardial autophagy, normalized mitophagy, and increased mitochondrial biogenesis. In contrast, TT did not improve LVI, or affected the cellular and mitochondrial viabilities.

Funding: NIDDK Support, Other NIH Support - HL083307 and HL71731

TH-PO707

Valsartan Improves Myocardial Cellular Viability in Renovascular Hypertension

Ming-Zhi Zhang, Bing Yu, Yinjia Wang, Kimberly Fisher, Jorge H. Capdevila, Raymond C. Harris, Medicine, Vanderbilt Univ School of Medicine, Nashville, TN.

Background: The Angiotensin II receptor blocker Valsartan (VAL) lowers blood pressure and is cardioprotective, although the exact mechanisms underlying renoprotective effects of VAL are not fully elucidated yet. Autophagy and mitophagy are two redundant cellular self-digestion (autophagy) and mitochondrial digestion (mitophagy) develop in the myocardium in response to renovascular hypertension. We tested the hypothesis that VAL would alleviate autophagy and improve left ventricular (LV) myocardial cellular viability in swine RAS.

Methods: Domestic pigs were randomized to control, unilateral renal, and RAS treated with VAL (320 mg/day; RAS+Valsartan) or conventional triple therapy (Reserpine+hydralazine-+hydrochlorothiazide, RAS+TT) for 4 wks post 6-wks of RAS (n=7 each). Kidney and left ventricular (LV) myocardial cellular viability in swine RAS.

Results: VAL and TT similarly decreased blood pressure, but did not alter renal function. RAS induced LV hypertrophy (LVI), accompanied by increased markers of myocardial autophagy and mitophagy. Val alleviated LVI, lowered myocardial autophagy, normalized mitophagy, and increased mitochondrial biogenesis. In contrast, TT did not improve LVI, or affected the cellular and mitochondrial viabilities.

Conclusions: Val-salt and TT similarly decreased blood pressure, but did not alter renal function. RAS induced LV hypertrophy (LVI), accompanied by increased markers of myocardial autophagy and mitophagy. Val alleviated LVI, lowered myocardial autophagy, normalized mitophagy, and increased mitochondrial biogenesis. In contrast, TT did not improve LVI, or affected the cellular and mitochondrial viabilities.
Conclusions: These studies demonstrate that renal EET levels are maintained by intrarenal dopamine, and Cyp2c44-expressed EETs play an important role in intrarenal dopamine-induced natriuresis and diuresis.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO705

Sorting Nexin 1 Knockout Mice Manifest with Hypertension and Impaired Natriuretic Response

Van Anthony M. Villar, Laurenzo D. Asico, Jun B. Feranil, Ines Armando, John Edward Jones, Pedro A. Jose. Univ of Maryland, School of Medicine, Baltimore, MD.

Background: Dopamine is important for the regulation of blood pressure (BP), sodium balance, and renal function by engendering natriuresis via the inhibition of tubule NaCl reabsorption. The dopamine D₁ receptor (D₁R) interacts with sorting nexin 1 (SNX1), a protein involved in agonist-activated receptor trafficking.

Methods: We evaluated the effect of a congenital absence of SNX1 on the regulation of BP and sodium excretion in mice through an array of in vitro (confocal microscopy, RNAi, biochemical assays) and in vivo approaches.

Results: SNX1 deletion in human renal proximal tubule cells impaired receptor trafficking and D₁R-mediated Ga activation, cAMP response, and sodium transport, indicating that SNX1 loss results in impaired D₁R function. To evaluate the in vivo correlates of these in vitro observations, we used an innovative approach to acutely silence the renal Snx1 via subcapsular infusion of Snx1-specific siRNA in mice, which resulted in 50% knockdown of expression. Renal depletion of Snx1 in salt-sensitive C57BL/6J and salt-resistant BALB/c mice resulted in high BP (ASBP and 15 and 23 mm Hg, and ΔDBP of 15 and 23 mm Hg from baseline, respectively; P<0.05, n=3–4/group), conceivably due to perturbed D₁R function; D₁R−/− mice also develop hypertension. Moreover, salt-loaded Snx1-depleted BALB/c mice failed to excrete sodium (ΔUNaV of -13.8±13.4% and +40.5±24.1% from baseline in Snx1−/− depletes vs. control BALB/c mice, respectively; P<0.05, n=3–4/group) in response to D₁R and D₁R agonist treatment. We next extended our studies to Snx1−/− mice, which have a congenital absence of Snx1. We found that adult male Snx1−/− mice, compared to wild-type littermates, are hypertensive (131±6/3/107±5/4 mm Hg vs. 105.5±6/4/82±18±9 mm Hg, P<0.05, n=3–4/group) and have impaired natriuretic response (ΔUNaV of -17.01±5.1±3.4% and +20.1±40.1% from baseline, respectively; P<0.05, n=3–4/group), similar to the phenotypes observed in acutely (Snx1)-depleted mice.

Conclusions: These data demonstrate a novel and crucial role for SNX1 in direct D₁R and indirect D₁R regulation in the pathogenesis of essential hypertension.

Funding: NIDDK Support

TH-PO706

PACAP and Stress-Mediated Regulation of Renal Plasminogen Activator Inhibitor-1 Gene Expression In Vivo

Neill A. Gingles,1 Marc A. Olivier,2 Lindsey A. Miles,2 Robert J. Parmer.1,2

1Univ of California; 2VA San Diego Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Hypothalamic-pituitary-adrenal (HPA) axis activation elicits neuroendocrine and autonomic responses and is a potent transcriptional activator. Also, plasminogen activator inhibitor-1 (PAI-1) expression increases in response to stress and to PACAP treatment in vivo. To explore potential links among SNS stress responses, the PACAP peptidergic signaling pathway, and PACAP receptor antagonist, PACAP6-38, compared to pretreatment with vehicle.

Conclusions: Renal PACAP-1 expression is substantially increased by stress and by PACAP, suggesting key links among the SNS, the PACAP peptidergic signaling pathway, and renal PACAP-1 biosynthesis, which may contribute to SNS-mediated renal injury.

Funding: Other NIH Support - NHIBI, Veterans Affairs Support

TH-PO707

Compensatory Activation of the Sympathetic Nervous System after Deletion of Angiotensin Type 1 Receptors from Vascular Smooth Muscle Cells

Matthew A. Sparks, Johannes Stiegbauer, Susan B. Gurley, Thomas M. Coffman. Div of Nephrology, Duke Univ Medical Center, Durham, NC.

Background: Vasoconstriction is a key physiological action of angiotensin II (Ang II). Presumably how AT₁ receptors (AT₁R) on VSMCs contribute to vasoconstriction in vivo has not been completely defined.

Methods: In order to define the role of direct actions of AT₁R in VSMCs, we generated mice with deletion of AT₁R from VSMCs using a flxed Agerl allele and a mouse expressing Cre only in VSMCs.

Results: We compared vascular responses to acute infusions of Ang II in mice lacking AT₁R in VSMCs (SMKOs) and controls. Surprisingly, brisk vasoconstrictor responses to Ang II were observed only in SMKOs with peak increases in MAP only modestly reduced to ∼75% of control levels (151±2 vs. 23 ±1 mm Hg; P<0.05). Robust systemic vasoconstriction to Ang II was observed whether elimination of AT₁R was carried out in utero with a constitutively expressed SM-Cre or in adult mice with a tamoxifen-inducible SM-Cre. By contrast, Ang II-dependent vasoconstriction in the renal circulation was largely abolished in SMKOs. Moreover, despite preserved systemic vascular responses to Ang II in SMKOs, baseline BPs were reduced and susceptibility to Ang II dependent hypertension was significantly attenuated. To determine if the minor AT₁R isofrom might be responsible for their residual vascular responses, we generated SMKOs on an AT₂R-null background (SMKO 1B−), the absence of AT₁R did not affect this response (SMKO 1B−: 16±2 vs. SMKO-1B−: 15±2 mm Hg; ns). As an alternative explanation, we tested for an involvement of the sympathetic nervous system (SNS) by infusing 400 μg/kg of the α-blocker phenolamine (PT) 5 min before Ang II. While PT had no effect on Ang II dependent vasoconstriction in controls (pre-PT: 23±1 vs. post-PT: 23±3 mm Hg), it almost completely abrogated vasoconstriction in SMKOs (pre-PT: 15±2 vs. post-PT: 3±1 mm Hg; P<0.005).

Conclusions: Thus, we find a significant capacity for the activation of the SNS to maintain acute Ang II dependent vasoconstriction when AT₁R signaling in VSMCs is absent. This pathway induces brisk vasoconstriction in the systemic but not the renal circulation.

Funding: Private Foundation Support

TH-PO708

Renal Denervation Deriving Cardiorenal Protection beyond Blood Pressure Control via Sympathetic Regulation of Local Renin-Angiotensin System

Masahiro Furuichi,1 Kumiko Torisu,2 Toshiaki Nakano,3 Kosuke Masutani,1 Kazuhiko Tsuura,1 Takanari Kitazono.1 1Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 2Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Recently catheter-based renal sympathetic denervation (DNx) is beginning to be applied for clinical aim. The sympathetic nervous system (SNS) and renin-angiotensin system (RAS) would be suggested as possible cardio-renal mediators. The mechanisms behind the beneficial effects of DNx for cardio-renal vicious cycle are not fully elucidated but may include disruption of local RAS in addition to the vicious cycle of SNS-RAS.

Methods: We compared vascular responses to acute infusions of Ang II in mice lacking AT₁AR in VSMCs (SMKOs) and controls. Surprisingly, brisk vasoconstrictor responses to Ang II were observed whether elimination of AT₁AR was carried out in four groups (control, L-NAME, L-NAME with bilateral DNx and L-NAME with hydralazine group). Cardiorenal injury, SNS, circulating RAS and local RAS (heart and kidney angiotensin II (II) and urine angiotensinogen (AGT)) were evaluated. We also observed rats treated with L-NAME + unilateral DNx to confirm the sympathetic and regulatory effects of bilateral DNx. Serial measurements of kidney II and urinary AGT of both kidneys were performed to examine the laterality of local RAS in the body of the same individuals.

Results: Bilateral DNx ameliorated over-activity of SNS and circulating RAS accompanied with downregulation of heart and kidney local RAS, and prevented cardio-renal injury. Cardiorenal protective effects of bilateral DNx were greater than the hydralazine treatment that blood pressure (BP) was kept to the same level. In unilateral DNx model, kidney II and urine AGT from the denervated kidneys were smaller than the innervated kidneys under the same circulating conditions and renal injury of the denervated kidneys were alleviated compared to the innervated kidneys.

Conclusions: DNx derives the beneficial BP-independent effects associated with local RAS amelioration in cardio renal syndrome.

TH-PO709

Fruuctose Stimulates Sodium/Hydrogen Exchanger 3 Activity via Protein Kinase C Activation in the Proximal Tubule

Pablo D. Cabral, Jeffrey L. Garvin. Physiology and Biophysics, Case Western Reserve Univ, Cleveland, OH.

Background: Consumption of high-fructose corn syrup as a sweetener has increased dramatically. Fructose has been implicated in the epidemic of diabetes, obesity and salt-sensitive hypertension. However, the mechanisms are poorly understood. The proximal renal nephron reabsorbs 60-70% of the fluid and Na, and most of the filtered bicarbonate via Na/H exchanger 3 (NHE3). It has been shown that protein kinase C (PKC) stimulates fluid and bicarbonate absorption in this segment. Enhanced proximal nephron transport has been implicated in several forms of hypertension. Previous fructose stimulates NHE3 activity in the proximal tubule via a PKC-dependent mechanism.
Methods: To test our hypothesis we isolated and perfused proximal tubules from Sprague Dawley rats. NHE3 activity was measured as the recovery of intracellular pH after an NH4Cl acid pulse using the pH sensitive dye BCECF. The rate of pH recovery was measured in Fluorescent Units per second (FU/sec).

Results: In the presence of a 5.5 mM glucose-containing physiological saline the basal rate of pH recovery was 3.1 ± 0.8 FU/sec. When the luminal solution was exchanged to a 0.6 mM glucose + 5 mM fructose-containing physiological saline in a second experiment, the rate of pH recovery increased to 5 ± 1 FU/sec (p=0.03, n=8). To study whether this effect was due to the addition of fructose or the subtraction of glucose to the luminal perfusate, we performed a separate set of experiments where 5 mM glucose was substituted by 5 mM fructose. In the presence of 0.6 mM glucose the basal rate of pH recovery was 3.6 ± 1.5 FU/sec. When 5 mM fructose was added the rate of pH recovery increased to 5.9 ± 2 FU/sec (p=0.02, n=5). Control experiments showed no differences between periods when 5 mM glucose was added back to the luminal perfusate. Finally, we tested the effect of the general PKC inhibitor staurosporine on the effect of fructose. In the presence of the general PKC inhibitor staurosporine 10^{-6} M Fructose did not stimulate NHE3 activity (from 6.0 ± 1.2 to 6.3 ± 1.7; n=6).

Conclusions: We conclude that acute treatment with fructose stimulates NHE3 activity in proximal tubules.

Funding: Other NIH Support - HL28982, HL70985, and HL90550, Private Foundation Support

TH-PO710

CXCR6 Plays a Critical Role in Angiotensin II-Induced Renal Injury and Fibrosis

Yunfeng Xia, Yanlin Wang. Dept of Medicine, Div of Nephrology, Baylor College of Medicine, Houston, TX.

Background: Recent studies have shown that inflammation plays a critical role in the pathogenesis and progression of hypertensive kidney disease. However, the signaling mechanisms underlying the induction of inflammation are poorly understood. In this study, we investigated the role of CXCR6 in Ang II-induced renal injury and fibrosis.

Methods: Wild-type (WT) and CXCR6-KO mice were treated with Ang II via subcutaneous osmotic minipumps at 1500 ng/kg/min for up to 4 weeks. To accelerate renal injury, all mice were subjected to unilateral nephrectomy and received 1% NaCl in drinking water.

Results: WT and CXCR6-KO mice had virtually identical blood pressure at baseline. Ang II treatment led to an increase in blood pressure that was similar between WT and CXCR6 knockout mice. CXCR6 knockout mice were protected from Ang II-induced renal dysfunction, proteinuria, and fibrosis. Deletion of CXCR6 suppressed bone marrow-derived fibroblast accumulation and myofibroblast formation in the kidneys of Ang II treated mice, which was associated with a reduction in extracellular matrix protein expression. Furthermore, deletion of CXCR6 inhibited infiltration of F4/80+ macrophages and CD3+ T cells in the kidney of Ang II treated mice with WT mice. Finally, deletion of CXCR6 reduced gene expression of proinflammatory cytokines in the kidney of Ang II treated mice.

Conclusions: Our results demonstrate that CXCR6 plays a pivotal role in the development of Ang II induced renal injury and fibrosis through regulation of macrophage and T cell infiltration and bone marrow-derived fibroblast accumulation. These findings suggest that inhibition of CXCR6 signaling could constitute a novel therapeutic target for hypertensive kidney disease.

Funding: NIDDK Support

TH-PO711

Suppression of Insulin Resistance by Renal Sympathetic Denervation in Obese Rats

Akira Nishiyama, Daisuke Nakano. Dept of Pharmacology, Kagawa Univ Medical School, Kagawa, Japan.

Background: Recent studies have shown that renal sympathetic denervation improves glucose metabolism and insulin sensitivity in patients with resistant hypertension. To elucidate its precise mechanism, studies were performed to examine the effect of renal sympathetic denervation on glucose metabolism and blood pressure in obese rats.

Methods: Uninephrectomized obese Otsuka Long Evans Tokushima Fatty (OLETF) underwent renal denervation (RDN) at 6 weeks of age (preadipose stage).

Results: At 22 weeks of age, RDN resulted in undetectable kidney tissue norepinephrine (NE) levels and decreased plasma NE levels, but did not significantly change blood pressure (measure by telemetry system) in type 2 diabetic OLETF rats. As compared to sham-operated OLETF rats, RDN OLETF rats showed lowered blood glucose and plasma insulin levels as well as decreased areas under the glucose response curves after oral glucose loading during the oral glucose tolerance test. Whole body insulin sensitivity was also assessed by the hyperinsulinemic-euglycemic clamp study at 20 weeks of age, and RDN OLETF rats showed an improved glucose infusion rate. Furthermore, RDN improved in vivo glucose uptake by adipose tissues, soleus muscle and liver. Interestingly, RDN also decreased proximal tubular SGLT2 expression and increased urinary glucose excretion rate in OLETF rats.

Conclusions: Renal sympathetic denervation at a prediabetic stage improves glucose metabolism and insulin sensitivity by suppression of glucose uptake and enhancement of urinary glucose excretion.

Funding: Government Support - N-U.S.

TH-PO712

The Transcription Factor ETS-1 Mediates Renal Injury in Salt Sensitive Hypertension

Wenguang Feng, Philip H. Chumley, Huma Fatima, Gabriel Rezonov, Ping Hua, Edgar A. Jaimes, Medicine/Nephrology; Pathology, Univ of Alabama at Birmingham; VA Medical Center.

Background: ETS-1 regulates the expression of several growth factors and cytokines and mediates pro-fibrotic effects of Angiotensin II. Herein, we tested the hypothesis that increased expression of ETS-1 in Dahl salt-sensitive (DS) rats mediates renal injury in the model of hypertension.

Methods: DS rats (n=6 per group) were fed normal salt diet (0.5%, NS) or a high salt diet (4%, HS) for 4 weeks. Four additional groups of HS rats received: ETS-1 dominant negative peptide (HS/DS, 10 mg/kg/day), a control ETS-1 mutant peptide (HS/MU, 10 mg/kg/day), the AT1 receptor blocker Candesartan (HS/ARB 10 mg/kg/day) or a combination of DN and ARB (HS/DN/ARB).

Results: HS rats had a 3 fold increase in the cortical expression of ETS-1. Treatment with DN, MU, ARB or DN/ARB resulted in non-significant reductions in BP. HS increased proteinuria, glomerular injury score (GIS), fibronectin expression (western blot), urinary TGF-β (ELISA) and macrophage (ED1) infiltration, that were improved by DN (table). ARB partially reduced proteinuria, GIS and macrophage infiltration. Treatment with DN/ARB resulted in further improvements compared to DN as OR.

Conclusions: Increased expression of ETS-1 mediates renal injury in salt sensitive hypertension.

Funding: Veterans Affairs Support

TH-PO713

Differential Regulation of Epithelial Sodium Channel (ENaC) and Sodium-Chloride Cotransporter (NCC) by Gilz

Priyanka Rashmi, Michael Ng, David Pearce. Div of Nephrology, Dept of Medicine, Univ of California, San Francisco, CA.

The renal-angiotensin-aldosterone (RAAS) system is the central regulator of Na+ reabsorption and K+ secretion primarily through the tubular effects of aldosterone. Among the several sodium transporters involved in electrolyte homeostasis, regulation by the RAAS is the Na+ cotransporter (NCC) and epithelial sodium channel (ENaC). Electrogenic Na+ reabsorption via ENaC stimulates K+ excretion, while electro-neutral reabsorption of Na+ via NCC inhibits K+ secretion by competing with ENaC for Na+. Therefore, ENaC and NCC are the primary target for aldosterone action. Recent studies have shown that another aldosterone regulated gene, glucocorticoid-induced leucine zipper protein 1 (Gilz1) acts in concert with Sgk1 to modulate ENaC cell surface expression. We now show that in contrast to its effect on ENaC, Gilz blocks Sgk1-mediated stimulation of NCC, with important consequences for Na+ and K+ handling in vivo.

In vitro evidence from our laboratory shows that another aldosterone regulated gene, glucocorticoid-induced leucine zipper protein 1 (Gilz1) acts in concert with Sgk1 to modulate ENaC cell surface expression. We now show that in contrast to its effect on ENaC, Gilz blocks Sgk1-mediated stimulation of NCC, with important consequences for Na+ and K+ handling in vivo. When placed on a low salt diet, Gilz knock out mice are able to come to sodium balance more rapidly than the wild type animals suggesting an upregulation of another sodium transporter. Surface expression of ENaC and NCC is increased in plasma membrane fractions of kidneys from Gilz knockout animals while the expression of ENaC is decreased. In cultured HEK293 cells, Sgk1 stimulates the surface expression of NCC while simultaneous co-expression of Gilz abrogates the effect of Sgk1 in a dose dependent manner. Overexpression of Gilz in mpkDCT tubular epithelial cells results in downregulation of NCC while simultaneously inducing ENaC surface expression. Furthermore, Gilz1 overexpression inhibits the interaction between NDK4 and Sgk1 allowing NDK4-mediated inhibition of NCC. Taken together, these results suggest that Gilz is a part of a “shift” mechanism, which allows the differential regulation of ENaC and NCC in order to balance Na+ reabsorption and K+ secretion.

TH-PO714

Early Hypertensive Renal Injury Is Associated with Capillary Hypertrophy, Preceding Pathological Angiogenesis and Capillary Loss

Timo Rademakers,1 Petra Hautvast,1 Marcella M. Baldewijns,1 Sylvia Heeneman,1 Floortje Steegh,1 Huma Fatima,2 Gabriel Rezonov,1 Phillip H. Chumley,3 1Medicine/Nephrology; 2Pathology, Academic Medical Center, Amsterdam, Netherlands; 3Pathology, Academic Medical Center, Amsterdam, Netherlands.

Background: Chronic hypertension predisposes for end-organ damage in e.g. the kidney. Both patients and animal models have shown peritubular capillary (PTC) loss in chronic hypertensive renal disease, yet PTC rarefaction in early disease is poorly understood. We hypothesized that in early hypertensive renal disease PTC hypertrophy precedes PTC loss, in association with a distinct angiogenic profile.

Methods: Patient study: Healthy renal tissue from patients undergoing nephrectomy (n=50; 31 hypertensive, 19 non-hypertensive) was included. Tissue was scored histologically and PTC per tubule (PTC/tub) was assessed by CD31/CD34-staining. Animal study: Patient study: Healthy renal tissue from patients undergoing nephrectomy (n=50; 31 hypertensive, 19 non-hypertensive) was included. Tissue was scored histologically and PTC per tubule (PTC/tub) was assessed by CD31/CD34-staining. Animal study:

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

Underline represents presenting author/disclosure.

262A
C57Bl/6 mice underwent one-sided nephrectomy, after which mice (n=6/group) were left untreated (control), treated with DOCA and/or angiotensin-II (ATII). Renal tissue was scored histologically. RNA for angiogenic profiling via qPCR was isolated from the cortex.

Results: Patients with early hypertension showed increased PTC/tub (1.08±0.18 vs. 0.97±0.15; p=0.04) compared to controls. DOCA-treated mice resembled these patients, showing 1.3-fold increased PTC/tub (p=0.05) and 2.2-fold increased VEGFR-2 expression (p=0.001) in comparison to controls. DOCA+ATII-treatment, resembling clinical damage, reduced PTC/tub 1.3-fold compared to DOCA-treatment (p=0.04), reduced angiopeptin (ang)-1/ang-2 ratio 5.5-fold (p=0.01), and 2-fold increased PDGFR/β(1/α)-1 ratio (p=0.02), indicative of pathological angiogenesis and capillary loss.

We showed that capillary hypertrophy occurred in human hypertensive renal disease, preceding capillary loss. Murine hypertensive renal disease revealed specific angiogenic profiles associated with capillary phenotype, pending validation in the human cohort. Further study will allow more insights into disease processes and potential targets for therapy.

Funding: Clinical Revenue Support

TH-PO717

Simvastatin Induces a Central Hypotension Effect via Ras-Mediated Signaling to Integrate Endothelial Nitric Oxide Synthase Upregulation

Wen-Yu Ho,1 Wen-Han Cheng,2 Ching-Jiunn Tseng,2 1Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung Medical Univ, Kaohsiung City, Taiwan; 2Dept of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan.

Background: Clinical studies indicate that statins have a blood pressure (BP)-lowering effect for hypertensive hypercholesterolemic patients. Statins would modulate BP through upregulation of endothelial nitric oxide synthase (eNOS) activation in the brain. However, the signaling mechanisms through which statins enhance eNOS activation remain unclear. Therefore, we examined the possible signaling pathways involved in statin-mediated BP regulation in a BP-control center of brain stem, nucleus tractus solitarii (NTS).

Methods: BP responses of simvastatin administered intracerebroventricularly in spontaneously hypertensive rats (SHRs) were measured in the presence or absence of various inhibitors, including farnesylhydroxalic acid (FTS), geryanaglytransferase inhibitor (GTT-2133), LY294002 or PD98059. Western blotting was used to confirm the activation of various signaling molecules in the NTs.

Results: Pretreatment with a Ras-specific inhibitor, FTS, significantly attenuated the depressor effect and nitric oxide (NO) production evoked by simvastatin. Additionally, immunoblotting and pharmacological studies further showed that inhibition of Ras activity by FTS significantly abolished simvastatin-induced extracellular signal-regulated kinases 1/2 (ERK1/2), ribosomal protein S6 kinase (RSK), Akt phosphorylation and decreased eNOS phosphorylation. Likewise, administration of Akt and ERK1/2 signaling inhibitors into the NTS attenuated the depressor effects evoked by simvastatin. Furthermore, the addition of simvastatin decreased Ras1 activation and the number of ROS-positive cells in the NTS.

Conclusions: These results suggest that distinct Ras and Rac1 signaling-mediated simvastatin control of central BP regulation in SHRs. Both Akt and ERK1/2-RSK signaling at least partly contribute to the eNOS activation of simvastatin.

Funding: Government Support - Non-U.S.

TH-PO718

Fidelity of Podocyte Number in Preeclampsia due to Podocyte Regeneration

Maria Elisabeth Penning,1 Kitty Bloemenkamp,2 Tom T. Van der Zon,1 Joke M. Schutte,1 Jan A. Brujin,1 Ingeborg M. Bajema,1 Hans J. Baelde.1 1Pathology, Leiden Univ Medical Center, Leiden, Netherlands; 2Obstetrics, Leiden Univ Medical Center, Leiden, Netherlands; Obstetrics, Isala Clinics, Zwolle, Netherlands.

Background: Preeclampsia (PE) is characterized by increased numbers of podocytes in the urine. This observation led to our hypothesis that there may be a decreased number of podocytes in the glomerulus in PE. Furthermore, we evaluated possible parietal epithelial cell regeneration as this could play a role in the replacement of injured and lost podocytes.

Methods: We performed a search for renal autopsy-tissues using a nationwide computerized database (PALGA) to collect a unique large cohort of women who died during pregnancy or postpartum due to PE (n=11). Three control groups were included consisting of young women who died during pregnancy without hypertension (n=25) and non-pregnant controls with (n=14) and without (n=13) chronic hypertension. WT-1 staining was used to quantify the numbers of podocytes. To evaluate cellular proliferation Ki-67 staining was performed. To investigate parietal epithelial cell migration, but to exclude CD44-positive leukocytes, a double staining with CD68 and CD45 was performed.

Conclusions: These results do not suggest that the numbers of podocytes in the preeclamptic group and the controls. However, preeclampsia was significantly (p=0.05) more often associated with intraglomerular Ki-67 positivity. Furthermore, the numbers of Ki-67 positive parietal cells were significantly (p=0.05) higher in the women with PE than in the pregnant- and hypertension controls. CD44 positive (and CD45 negative) cells were observed within the glomerular tuft.

Conclusions: This study shows for the first time that, although PE is characterized by significantly increased numbers of podocytes in urine, glomerular podocyte numbers remain stable. Significantly increased intraglomerular Ki-67 positivity and CD44 positive parietal cells suggest that regeneration of podocytes may play an important role in the maintenance of the glomerular filtration barrier during PE.

TH-PO719

Enhanced Phosphorylation of NKCC2 by SPAK/OSR1 in a Murine Model of Diet Induced Obesity

Matthew R. P. Davies,1,2 Marina Katerolos,1 Kurt Gleicher,1 Scott Andrew Fraser,1 Peter F. Munt1,2 David A. Power.1,3 1Nephrology, Austin Health, Heidelberg, Victoria, Australia; 2Institute of Breathing and Sleep, Victoria, Australia; 3Medicine, Univ of Melbourne, Victoria, Australia.

Background: Obesity promotes salt-sensitive hypertension. Tubular mechanisms of enhanced sodium reabsorption may contribute to the salt sensitivity of obesity. We previously showed that parietal hypertrophy and cell activation as this could play a role in the replacement of injured and lost podocytes.

Methods: In this study the circadian characteristics of MAP, SBP, DBP, HR, pulse pressure (PP) and locomotor activity were measured in conscious and unrestrained 12-week old SD rats and age-matched SD control rats by the radiotelemetry system. After baseline studies were obtained, the rats were provided a high salt diet (0.9%) for a 1-wk period prior to the 7 day telemetry study.

Results: 1. The ADRs presented with the reversed circadian rhythms of MAP, SBP, DBP, and PP compared with SD control rats. 2.In the ADRs, the circadian rhythm of the urine sodium excretion was disturbed, the RUNA in Dark period was significantly lower than that in the Light period of the same group (14.69±3.65 vs. 27.66±5.84 μmol/h; P=0.001) and also significantly lower than that in the Dark period of the control group (14.69±3.65 vs. 35.82±22.44 μmol/h; P=0.023). 3.In the ADRs, the FENS in Dark period was significantly lower than that in the Light period of the same group (0.15±0.06 vs. 0.29±0.06; P=0.008) and also significantly lower than that in Dark period of the control group (0.15±0.06 vs. 0.31±0.19; P<0.050). 4.Under high salt diet, SBP and MAP in ADR group was significantly lower than that in control group by 18.8mmHg and 15.2mmHg respectively in ADRs (P<0.001). In the control group, the SBP and MAP in Light period increased significantly by 8.4mmHg and 6.2mmHg respectively. In the ADRs, the SBP and MAP in Light period increased significantly by 20.1mmHg and 17.7mmHg respectively (P<0.001). In the control group, the SBP and MAP in Light period increased by 7.2mmHg and 3.0mmHg respectively, but both differences were not significant.

Conclusions: We concluded that the ADR nephropathy rats showed a striking salt sensitive blood pressure. The ADR rat was a suitable CKD animal model with disturbed circadian BP rhythm and sodium sensitivity.

Key: TH - Thursday; FR – Friday; SA – Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Results: HD mice gained weight and developed hyperinsulinemia and hyperlipidemia. Cortical expression of NKK2C2 was reduced but activating phosphorylation (T96/T101) was increased in rats. No change in expression or phosphorylation of NCC, or expression of α1-γ-EnaC was found. Surface localisation of transporters was unchanged. SPAK/OSR1 is known to phosphorylate NKK2C2 on T96/101. Phosphorylation of SPAK/OSR1 at S373/325 was increased, consistent with increased activity of the WNK/SPAK/OSR1 pathway. AMPK expression is involved in mediating obesity-related renal injury. Active AMPK (phosT172) was reduced in HD mouse cortex. SPAK/OSR1 and AMPK were found to co-immunoprecipitate with NKK2C2, indicating a possible kinase-kinase interaction. In vitro, activation of AMPK led to a reduction in S373/325-phospho SPAK/OSR1 in β1-AMPK/+/- MEF’s, with no effect in β1-AMPK/-/- MEF’s, indicating a specific AMPK-mediated effect. Low CI solution invoked a significantly greater increase in S373/325-phospho SPAK/OSR1 in β1/+/- than in β1/+ MEF’s, supporting an inhibitory role of AMPK in modulating the WNK/SPAK/OSR1 pathway.

Conclusions: NKK2C is the most important sodium co-transporter in this model of obesity-related hypertension. Enhanced phosphorylation of NKK2C occurs due to activation of SPAK/OSR1, which itself may be secondary to AMPK inhibition. These data identify NKK2C, SPAK/OSR1 and AMPK as therapeutic targets in obesity-related hypertension.

Funding: Other NIH Support - Funding from NHMER, Australia

TH-PO722

Reduced Firing Activity of Afferen Renal Innervation in the 2K1/1C

Model of Hypertension
Wolfgang Freisinger,1 Annalena Karl,2 Tilmann Ditting,2 Sonja Heinlein,2 Roland E. Schmieder,1 Karl F. Hilgers,1 Johannes Schatz,2 Jens Lutz,1 Roland Veelken,2 "Nephrology, Med. Clinic, Universitätsmedizin Mainz, Mainz, Germany; 2Nephrology and Hypertension, Med. Clinic 4, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany.

Background: Renal denervation has been shown to be effective in hypertension. Recently, we found that renal afferent neurons show a distinctive feature, exhibiting preferentially a sustained firing upon current injection due to a specific expression of TXN resistant Na-channels. So far, the firing pattern of these specific sensory neurons in hypertension is unclear. Hence we wanted to test the hypothesis that the firing pattern of renal afferent neurons is altered in the 2K1/1C model of hypertension.

Methods: Hypertension was induced by unilateral nephrectomy of the renal artery in male Sprague Dawley rats 3 weeks prior to experiments. Labelling (DiI) allowed the identification of renal afferent Dorsal root ganglion (DRG) neurons. Current clamp was used to characterize neurons as "tonic", i.e. sustained action potential (AP) firing or "phasic", i.e. <5APs. Electrophysiological parameters and AP properties were determined in neurons of hypertensive animals and compared to controls.

Results: Renal DRG neurons of hypertensive animals (n=88) showed a significant decrease in tonic firing compared to controls (44.3% [39/88] vs. 59.5% [50/84], p<0.05). Current Clamp analysis revealed no significant change in action potential shape e.g. overshoot, firing threshold in hypertensive animals. Tonic cells had a higher capacity in hypertensive neurons (124 fA vs 87.3 fA, p<0.01), other cell parameters were equal. Renal morphology in hypertensive animals was equal in the clipped vs. non-clipped kidney.

Conclusions: For the first time we could show that excitability of afferent renal neurons in the 2K1/1C model of hypertension is significantly altered, as renal afferent DRG neurons exhibit less sustained firing upon stimulation. Sustained high blood pressure is possibly characterized by a generally decreased afferent renal activity with impaired sympathetic innihobition. The underlying mechanisms causing a "switch" from tonic to phasic need further elucidation.

TH-PO723

Increased Neurokinin Release from Afferent Renal Nerves Is Accompanied by Decreased Affenetic Electric Activity Tilmann Ditting,1 Kristina Rodionova,1 Christian Ott,1 Johannes Schatz,2 Sonja Heinlein,2 Roland E. Schmieder,1 Wolfgang Freisinger,1 Karl F. Hilgers,1 Roland Veelken,2 "Med Clinic 4, Nephrology & Hypertension, Friedrich-Alexander Univ Erlangen, Erlangen, Germany; "Med Clinic 1, Dept of Nephrology, Johannes Gutenberg Univ Mainz, Mainz, Germany.

Background: Afferent renal nerves exhibit a dual function. They influence intrarenal immunological processes by release of neurokinins like CGRP and control central sympathetic outflow via afferent electrical activity. The former seems to be important in renal inflammation whereas the sympathetic modulation by afferent electrical activity is not fully understood. Hence, we hypothesized that augmented effects of CGRP in renal inflammation occur with increased afferent renal nerve activity.

Methods: As inflammatory model, normotensive renal inflammation (RI) was induced by i.v. injection of 1.75 mg/kg BW OX-7 antibody to rats. These were investigated neurophysiologically and pathomorphologically using standard techniques 6 days after RI induction.

Results: Blood pressure (BP) was normal, hence confounding BP effects were unlikely. RI rats exhibited albuminuria (61.6±24.2 μg/mL) and proteinuria (21.6±10 μg/mL) in the kidney. RNIs from hypertensive animals (n=88) showed a significantly lower firing rate than controls (44.3% [39/88] vs. 59.5% [50/84], p<0.05). Current Clamp analysis revealed no significant change in action potential shape e.g. overshoot, firing threshold in hypertensive animals. Tonic cells had a higher capacity in hypertensive neurons (124 fA vs 87.3 fA, p<0.01), other cell parameters were equal. Renal morphology in hypertensive animals was equal in the clipped vs. non-clipped kidney.

Conclusions: For the first time we could show that excitability of afferent renal neurons in the 2K1/1C model of hypertension is significantly altered, as renal afferent DRG neurons exhibit less sustained firing upon stimulation. Sustained high blood pressure is possibly characterized by a generally decreased afferent renal activity with impaired sympathetic innihobition. The underlying mechanisms causing a "switch" from tonic to phasic need further elucidation.

TH-PO724

The Prorenin Receptor (PRR) Mediates Compensatory Responses to Buffer the Actions of the Renin-Angiotensin System (RAS) in the Collecting Duct through Cyclooxygenase-2 Upregulation in the Renal Medulla, Alexis A. Gonzalez,1 Minolfa C. Prieto. 2 "Instituto de Química, Pontificia Universidad Católica de Valparaíso, Valparaíso, Chile; "Physiology, Tulane Univ, New Orleans, LA.

Background: Angiotensin (Ang) II-induced hypertensive rats exhibit augmented secretion of renin and prorenin receptor (PRR) mRNA, which contrasts with the reduced levels of full-length PRR in the renal medulla. The urine of these rats contains high levels of the soluble form of PRR (sPRR). PRR stimulates cyclooxygenase-2 (COX-2) in the
intercalated cells (IC) via ERK1/2. However, whether the PRR-mediated stimulation of COX-2 in the renal medulla varies during the course of AngII-induced hypertension remains unknown.

**Methods:** We examined the temporal changes of renin, full-length PRR, sPRR, ERK1/2, and COX-2 during chronic AngII infusion for 3, 7, and 14 days in the rat renal medulla and in cultured inner medullary collecting duct (IMCD) cells.

**Results:** AngII infusion (80 ng/min) increased full-length PRR and COX-2 protein levels, phospho-ERK1/2 and PGE2 during the early normotensive phase of the AngII infusion (day 3). In contrast, during the established hypertensive phase (day 14), no changes were observed. At day 14, the urines of AngII-infused rats showed increased renin, sPRR and AngII. In cultured IMCD cells, AngII treatment (100 nM, 6 hrs) increased renin, full-length PRR, phospho-ERK1/2 and COX-2. AT1R blockade abolished these effects. Interestingly, after 16 hours of AngII incubation, the sPRR became detectable in cell culture media.

**Conclusions:** These results suggest that during early phase of AngII-induced hypertension, the collecting duct harbors compensatory mechanisms directed to buffer the actions of the RAS, in which the secretion of renin by the principal cells exerts a paracrine activation of PRR-membrane bound in IC, stimulating COX-2 and PGE2. By contrast, during the late phase of hypertension, sPRR secreted into the collecting duct exerts hypertensinogenic effects by binding local renin, increasing intratubular AngII.

**TH-PO725**

**SIRT1 Activation Protects the Endothelial Dysfunction by Inhibiting PDGF and TGF-β Generation**

**Hideyuki Negro, Medicine, Harvard Medical School, The Graduate School of Project Design, Boston, MA.**

**Background:** SIRT1 is a conserved NAD+−dependent deacetylase and possesses beneficial effects against aging-related diseases, but little information is available on a putative role of SIRT1 in endothelial and vascular homeostasis. Endothelial senescence causes endothelial dysfunction to promote atherosclerotic change and contribute to age-related vascular diseases. Growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β can be produced by additional cells involved in the pathogenesis of arteriosclerosis and play an important part in the progression of age-related vascular diseases.

**Methods:** We established an in vitro senescence model by prolonged culture of primary endothelial cells isolated from bovine aorta. The freshly isolated young endothelial cells gradually underwent senescence during 1 month of repetitive passages. We knocked down SIRT1 to evaluate the protein levels of LKB1, phosphorylated AMPK, PDGF and TGF-β in the knocked down cells.

**Results:** It was observed that protein expressions of SIRT1 were decreased time dependently in the senescent endothelial cells. In contrast, the protein levels of LKB1, a serine/threonine kinase, the phosphorylation of its downstream target AMPK-activated protein kinase (AMPK), PDGF and TGF-β in the knocked down cells.

**Conclusions:** These findings indicate that activation of SIRT1 provides beneficial effects against the endothelial dysfunction to promote atherogenesis by inhibiting PDGF and TGF-β generation. **Funding:** Government Support - Non-U.S.

**TH-PO726**

**Oral Warfarin Increases Blood Pressure Control in 5/6 Nephrectomy Rats**

**Jay C. Vance, Kyle M. Ware, Zahida Qamri, Lee A. Hebert, Anjali A. Satoskar, Gyongyi Nadasdy, Iouri Ivanov, Tibor Nadady, Brad H. Rovin, Sergey V. Brodsky, Dept. of Pathology and Medicine, The Ohio State Univ, Columbus, OH.**

**Background:** Hypertension is a common comorbidity in patients with chronic kidney diseases (CKD). In our animal model of warfarin-associated nephropathy we found that the blood pressure (BP) of rats with CKD increased with warfarin treatment. Because an effect of warfarin on BP has not been previously reported, the aim of this study was to examine the relationship of warfarin therapy to hypertension.

**Methods:** Sham-operated (control) and 5/6 nephrectomy rats (5/6NE) were treated with different doses of warfarin. Blood pressure (BP) was measured by a tail cuff.

**Results:** Warfarin increased BP in control and 5/6 NE rats in a dose-dependent manner. Warfarin affected predominantly systolic BP with little or no change in diastolic BP (Figure 1, A, effects in 5/6 nephrectomy rats, 3 weeks after the ablative surgery are shown). The hypertensive effects of warfarin were more prominent in animals with progressing CKD. Treatment with vitamin K attenuated the effects of warfarin on BP (Figure 1, B, 0.74 mg/kg/day of warfarin was used. Vitamin K 40 mg/kg was injected i.p. daily in the co-treatment with warfarin (red) or once after 1 weeks of 0.74 mg/kg/day warfarin (blue)).

**Conclusions:** Warfarin increases systolic, but not diastolic, BP in both control and CKD rats. Warfarin effects are Vitamin K dependent. The pathogenesis of this effect is not yet clear. Warfarin is the most commonly prescribed anticoagulant and is used extensively in patients with CKD. Our data indicate that BP should be carefully monitored in patients on warfarin therapy, especially those with CKD.

**TH-PO727**

**Disruption of the WNK4/SPAK Pathway Reduces the Hypertension Induced by Angiotensin II**

**Luz Graciela Cervantes-Perez, 1 Maria Castañeda-Bueno, 1 Norma Hilda Vázquez, 1 Dario Alessi, 2 Norma Bobadilla, 1 Gerardo Gamba, 1 Molecular Physiology Unit, INNSZ-IIB, UNAM, Mexico City, Mexico; 2MRC Phosphorylation and Ubiquitylation Unit, Dundee Univ, Dundee, United Kingdom.**

**Background:** Angiotensin II (AngII) induces systemic hypertension by its renal effects in reducing salt excretion. The effect of AngII is associated with increased phosphorylation of the renal NaCl cotransporter, NCC. The AngII activation of NCC requires the presence of an intact WNK4-SPAK pathway. We thus analyzed the effect of AngII infusion on blood pressure in genetically altered mice either lacking WNK4 (WNK4−/− mice) or expressing a version of the SPAK kinase that cannot be activated by WNK4s (SPAKΔTAD/TAD Δ/Δ mice).

**Methods:** WNK4−/− and SPAK knockin mice and their respective controls were infused with AngII at 1440 μg/kg/day by osmotic minipumps during 14 days. WNK4−/− mice and their respective wild type controls were resistant to the AngII-inducing high blood pressure at the infused dose. To over come this, unilateral nephrectomy was performed in this colony. Blood pressure was assessed by radiotelemetry from three days before the beginning of AngII infusion and during the next 14 days after infusion. At the end of the infusion period mice were sacrificed and renal tissue was used for protein extraction to assess total NCC and phosphoT858-NCC with specific antibodies.

**Results:** Figure 1 shows the effect of AngII infusion in WNK4−/− and SPAK-KI and their controls. The response to AngII in WNK4−/− was reduced during the first week, but eventually was similar, owing in part to a reduction of AngII effect in wild type mice. In contrast, the response to AngII was clearly reduced in SPAK-knockin animals. AngII induced NCC phosphorylation in wild type mice but not in WNK4−/− or SPAK-KI mice.

**TH-PO728**

**Disruption of the WNK4/SPAK Pathway Reduces the Hypertension Induced by Angiotensin II**

**Luz Graciela Cervantes-Perez, 1 Maria Castañeda-Bueno, 1 Norma Hilda Vázquez, 1 Dario Alessi, 2 Norma Bobadilla, 1 Gerardo Gamba, 1 Molecular Physiology Unit, INNSZ-IIB, UNAM, Mexico City, Mexico; 2MRC Phosphorylation and Ubiquitylation Unit, Dundee Univ, Dundee, United Kingdom.**

**Background:** Angiotensin II (AngII) induces systemic hypertension by its renal effects in reducing salt excretion. The effect of AngII is associated with increased phosphorylation of the renal NaCl cotransporter, NCC. The AngII activation of NCC requires the presence of an intact WNK4-SPAK pathway. We thus analyzed the effect of AngII infusion on blood pressure in genetically altered mice either lacking WNK4 (WNK4−/− mice) or expressing a version of the SPAK kinase that cannot be activated by WNK4s (SPAKΔTAD/TAD Δ/Δ mice).

**Methods:** WNK4−/− and SPAK knockin mice and their respective controls were infused with AngII at 1440 μg/kg/day by osmotic minipumps during 14 days. WNK4−/− mice and their respective wild type controls were resistant to the AngII-inducing high blood pressure at the infused dose. To over come this, unilateral nephrectomy was performed in this colony. Blood pressure was assessed by radiotelemetry from three days before the beginning of AngII infusion and during the next 14 days after infusion. At the end of the infusion period mice were sacrificed and renal tissue was used for protein extraction to assess total NCC and phosphoT858-NCC with specific antibodies.

**Results:** Figure 1 shows the effect of AngII infusion in WNK4−/− and SPAK-KI and their controls. The response to AngII in WNK4−/− was reduced during the first week, but eventually was similar, owing in part to a reduction of AngII effect in wild type mice. In contrast, the response to AngII was clearly reduced in SPAK-knockin animals. AngII induced NCC phosphorylation in wild type mice but not in WNK4−/− or SPAK-KI mice.
TH-P0728

Treatment with Azilsartan and Chlorthalidone Lowers Blood Pressure and Reduces Renal Inflammation in a Rodent Model of the Metabolic Syndrome Chunhui Jin, David M. Pollock, John Jason White. Medicine, Georgia Regents Univ, Augusta, GA.

Background: The metabolic syndrome (mets) and chronic kidney disease are global health issues. The mets induces hypertension (HTN) and commonly results in renal damage. The optimal therapy for HTN in the mets is unknown. JNC7 recommends thiazide diuretic as the first-line therapy for patients with HTN. However, these drugs have untoward metabolic effects. This study was conducted to investigate the effects of azilsartan (AZL), chlorthalidone (CLTD), and the combination (AZL + CLTD) on blood pressure and renal injury in a rodent model of metabolic syndrome.

Methods: In order to mimic the mets in a hypertensive model, male Dahl salt sensitive rats were fed a high fat (36% fat) diet. All treatments reduced proteinuria and albuminuria. However, only groups treated with AZL prevented nephritis (a podocyte injury marker). The nephritis was 57% lower, and proteinuria was 47% lower with combination therapy compared to AZL alone. All treatments reduced the number of ED1+ (mononuclear) cells in the kidney. Plasma monocyte chemotactic protein-1 (MCP-1) was significantly lower only in the AZL group.

Conclusions: In our rodent model of the mets, AZL and CLTD lower blood pressure and exhibit renal protective effects. Treatment with either renibus/albuminuria and renal cortical inflammatory cell infiltration. AZL treatment offers additional protection as evidenced by lower proteinuria and plasma MCP-1. These findings indicate that combination therapy afforded the greatest protective effects and thus may be the best choice for hypertensive therapy in the mets.

Support provided by Takeda Pharmaceuticals U.S.A., Inc.


TH-P0729

Systemic PPARα Deletion in Mice Leads to Sympathoactivation Tianxin Yang,1 Mi Liu,2 Zhanjun Jia.1 Internal Medicine, Univ of Utah and Veterans Affairs Medical Center, Salt Lake City, UT; 1Institute of Hypertension, Zhejiang University School of Medicine, Hangzhou, China.

Background: PPARg and sympathetic nerve activity (SNA) antagonistically regulate energy metabolism and cardiovascular function but their precise relationship is not known.

Methods: Systemic inactivation of PPARα was generated constitutively by using Mox2-Cre mice or inducibly by using the tamoxifen system (TM KO). Sympathetic activity was evaluated.

Results: Radiotelemetry demonstrated consistent increases in resting heart rate (HR) in both strains of null mice; this was associated with a more than 10-fold increase in urinary epinephrine and norepinephrine. Subsequently, more detailed analysis of SNA was performed in TM KO mice. In response to a bolus ip injection of the ganglionic blocker pentolinium at 7.5 mg/kg, the decreases in HR and MAP were greater in the null mice compared to vehicle, and the decreases in HR and MAP were even greater in the null mice at 7.5 mg/kg, the decreases in HR and MAP were greater in the null mice compared to vehicle, and the decreases in HR and MAP were even greater in the null mice. It is reported that solute type of (P)RR (s(P)RR) with 28 kDa is present in human blood. However, the characteristics of immunoreactive (I)RR-(P)RR in plasma have not been clarified yet.

Methods: We therefore examined a profile of I(R)-RR in human plasma by a gel chromatography and two types of assay systems: a competitive enzyme immunoassay (CEI- assay) which we reported previously (Kidney Week 2011) and a commercially available s(P)RR sandwich ELISA kit (sP)-RR assay (IBL Co., Ltd.). Plasma IRR-(P)RR levels also were measured in 10 non-diabetic and 16 hemodialysis patients.

Results: Gel chromatography of human plasma showed a major peak of I(R)-RR at the elution position of human y-globulin (158 kDa) by CEI-assay, and in contrast a small peak at 158 kDa accompanied with a major peak at 29 kDa by sP-RR assay. These data indicate that I(R)-RR in human plasma is composed of two components, one with a large molecular weight (LMM-RR) and s(P)-RR. By sP-RR assay, which turned out to be sensitive to sP-RR, plasma IRR-(P)RR levels in HD patients were 2.0-fold higher than non-HD subjects (P<0.01), and the levels significantly increased during HD sessions in diabetic HD patients from 1.04±0.04 to 1.14±0.07 pmol/ml (mean/SE, n=8, P<0.05), whereas, the levels decreased in non-diabetic HD patients from 1.19±0.06 to 1.0±0.05 pmol/ml (n=8, P<0.05). There was no significant correlation between plasma I(R)-RR levels measured by CEI-assay and those by sP-RR assay.

Conclusions: These results suggest that measurement of I-(R)-RR in plasma, s(P)-RR in particular, is important to clarify the role of I RR (P)RR in the cardiovascular regulation.

Funding: Government Support - Non-U.S.

TH-P0731

Immuneactive (Pro)rein Receptor in the Human Plasma Kazuhiro Totsune,1 Takuhiro Hirose,1 Shiro Oguma,2 Hiro Ando,3 Hiroshi Sekino,3 Hiroshi Sato,3 Kazuhiro Takahashi,1 Yutaka Imai.1 1Planning for Drug Development and Clinical Evaluation, Tohoku Univ Grad Sch of Pharm Sci and Med; 2Koujinkai Nagamachi Clinic; 3Koujinkai Central Clinic; 1Laboratory of Clinical Pharmacology and Therapeutics, Tohoku Univ Grad Sch of Pharm Sci and Med; 2Endocrinology and Applied Med Sci, Tohoku Univ Grad Sch of Med, Sendai, Japan.

Background: (Pro)rein receptor (P)RR is a new member of renin-angiotensin system. It is reported that soluble type of (P)RR (s(P)RR) with 28 kDa is present in human blood. However, the characteristics of immunoreactive (I)RR-(P)RR in plasma have not been clarified yet.

Methods: We therefore examined a profile of I(R)-RR in human plasma by a gel chromatography and two types of assay systems: a competitive enzyme immunoassay (CEI- assay) which we reported previously (Kidney Week 2011) and a commercially available s(P)RR sandwich ELISA kit (sP)-RR assay (IBL Co., Ltd.). Plasma IRR-(P)RR levels also were measured in 10 non-diabetic and 16 hemodialysis patients.

Results: Gel chromatography of human plasma showed a major peak of I(R)-RR at the elution position of human y-globulin (158 kDa) by CEI-assay, and in contrast a small peak at 158 kDa accompanied with a major peak at 29 kDa by sP-RR assay. These data indicate that I(R)-RR in human plasma is composed of two components, one with a large molecular weight (LMM-RR) and s(P)-RR. By sP-RR assay, which turned out to be sensitive to sP-RR, plasma IRR-(P)RR levels in HD patients were 2.0-fold higher than non-HD subjects (P<0.01), and the levels significantly increased during HD sessions in diabetic HD patients from 1.04±0.04 to 1.14±0.07 pmol/ml (mean/SE, n=8, P<0.05), whereas, the levels decreased in non-diabetic HD patients from 1.19±0.06 to 1.0±0.05 pmol/ml (n=8, P<0.05). There was no significant correlation between plasma I(R)-RR levels measured by CEI-assay and those by sP-RR assay.

Conclusions: These results suggest that measurement of I-(R)-RR in plasma, s(P)-RR in particular, is important to clarify the role of I RR (P)RR in the cardiovascular regulation.

Funding: Government Support - Non-U.S.

TH-P0732

Co-Assembly of GABA(A) Receptor α, β1 and β3 Subunits and Its Expression in Rat and Human Kidney Kozae Takano,1 Junichi Yatabe,2 Midori Sasaki Yatabe,1 Hirobou Sanada,2 Pedro A. Jose,3 Tuyoshi Watanabe,1 Junko Kimura.2 1Dept of Pharmacol, Fukushima Med Univ Sch Med, Japan; 2Dept of CKD Initiatives, Fukushima Med Univ Sch Med; 3Dept of Nephrol, Hypertens, Diabetol, Endocrinol and Metabol, Fukushima Med Univ Sch Med, Japan; Univ of Maryland, Baltimore.

Background: GABA aminobutyric acid (GABA) lowers blood pressure and induces diuresis/natriuresis. We have reported characteristic expressions of GABA-related molecules in kidney. In contrast to brain, GABA(A) receptor α subunit may be dominant in the kidney, constituting α1/α1/β3/β3/γ3/γ pentamers. In this study, coexpressions, intra-renal localizations and relative expressions of the subunits in addition to GABA-related molecular expressions in human kidney were examined.

Methods: Renal corticomedullary zone of Wistar-Kyoto rats (WKY) were used for immunohistochemistry and immunoprecipitation. Renal cortical messenger RNA expressions of GABA on normal diet and on high-salt diet (8%, 7 days) were compared by quantitative RT-PCR. Quantitative RNA assays using human brain and kidney RNA were also performed for those GABA-related molecules found in rat kidney.

Results: GABA(A) α subunit mRNA in WKY kidney was more than 100 times that in the brain. Containing α1/α1/β3/β3/γ3/γ pentamers. In this study, coexpressions, intra-renal localizations and relative expressions of the subunits in addition to GABA-related molecular expressions in human kidney were examined.

Conclusions: GABA(A) α subunit mRNA in WKY kidney was more than 100 times that in the brain. Containing α1/α1/β3/β3/γ3/γ pentamers. In this study, coexpressions, intra-renal localizations and relative expressions of the subunits in addition to GABA-related molecular expressions in human kidney were examined.
TH-P0733
Effect of Gender and Diabetes in Circulating ACE2 and ACE Activity in Streptozotocin-Induced Mice
Seni Clotet-Freixas, Maria Jose Soler, Julio Pascual, Marta Riera. Hospital del Mar - IMM, Barcelona, Spain.

Background: Male gender predisposes to chronic kidney disease. We showed before increased circulating ACE2 and ACE in diabetic male mice. We study gender differences and effect of diabetes and gonadectomy(GDX) in circulating ACE2 and ACE in STZ-induced mice.

Methods: Study groups: Control and diabetic females(CTRL,FDB), males(mCTRL,mDB) and GDX males(mCTRL,GDX,mDB). GDX was performed 12 days after STZ injection. Male control mice showed significantly higher ACE2 and ACE than females. GDX resulted in significant reduction of ACE2 in both mCTRL and mDB and ACE (only in mDB). We found direct correlation between BG and ACE2 and ACE( r=0.67, p<0.01).

Results: Hyperglycemia was observed in STZ groups. BG was significantly higher in males as compared to females. GDX significantly decreased BG in mDB(298.3±17.0 vs 431.5±21.8 mg/dL; p<0.05). ACE2 and ACE in FDB and mDB were increased as compared to controls. Male control mice showed significantly higher ACE2 and ACE than females. ACE2 resulted in significant reduction of ACE2 in both mCTRL and mDB (and ACE only in mDB).

Conclusions: STZ injection increased BG and ACE2 and ACE activity in all experimental groups. GDX diminished BG and circulating ACE2 and ACE. Thus, increased levels of circulating ACE2 and ACE in diabetic male mice may be ascribed to a modulation of male sex hormones.

Funding: Government Support - Non-U.S.

TH-P0734
Physiological and Pharmacological Concentrations of Angiotensin II Yield Different Distinctions in AT1 Receptor Signaling
Lena Scott, Kristoffer Bernhøi, Hjalmar Brismar, Anita Aperia, Karolinska Institute; Royal Institute of Technology.

Background: Studies on the desensitization of AT1R and the interaction between AT1R and calcium channels are generally done using pharmacological concentrations of angiotensin II (AngII).

Methods: Here we report that repeated physiological AngII doses will, in contrast to the desensitization effect of pharmacological AngII concentrations, result in an enhanced calcium response and a reduced density of AT1R receptors. We have: A) devised an assay to repeated doses of physiological (1 nm) and pharmacological (100 nM) Ang II in AT1R expressing HEK293a cells at (three time points) 0 min, following a 5 min and following an additional 30 min recovery. At 100 nM Ang II a significant desensitization was seen in response to the 2nd dose with partial recovery observed at the 3rd dose. At 1 nM Ang II no desensitization was observed to the 2nd dose, and the response to the 3rd dose was 2-fold enhanced. This enhanced response could be explained by increased recruitment of AT1R to the plasma membrane. To study redistribution of AT1R we used HEK293a cells expressing AT1R with an extracellular hemagglutinin tag and a C-terminus Venus tag. The ratio between the intensities from these two tags was 2.5-fold higher at the time of expression suggesting AT1R to the plasma membrane. To study redistribution of AT1R we used HEK293a cells expressing AT1R with an extracellular hemagglutinin tag and a C-terminus Venus tag.

Conclusions: In summary this study shows new aspects of the AT1-R response to physiological angiotensin concentrations and will have several important clinical implications.

Funding: Private Foundation Support

TH-P0735
The Imaging of the Leakage of Red Blood Cells from Submucosal Capillary of the Bladder in Bladder Overdistension
Hideki Mizuno,1,2 Tokunori Yamamoto,1 Momokazu Gotoh.1 1Urology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan; 2Urology, Nagoya Univ Graduate School of Medicine, Japan.

Background: We previously reported that the effect of tamsulosin on bladder micronecrosis and the degree of submucosal capillary leakage in bladders subjected to ischemia-reperfusion injury by pencil lens-clipper device microscopy system(Mizuno H et al Urology 2010). In the present study, to elucidate the causes of macrohematuria after bladder ischemia-reperfusion injury.

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

Underline represents presenting author/disclosure.
Conclusions: Renal IL-FABP expression attenuated tubulointerstitial damage in addition to the renoprotective action depending on the decreasing in ATⅠⅠa expression in the renal injury due to Ras activation.

TH-P0738

The Effect of Nifedipine and Captopril on the Production of Pro-Inflammatory Cytokines by Peripheral Blood Mononuclear Cells (PBMCs)

Methods: PBMCs obtained from healthy volunteers (n = 20) were stimulated with lymphocytes and dendritic cells (MoDCs) derived from peripheral blood mononuclear cells (PBMCs).

Results: In lymphocytes, TNF-α and IL-6 concentrations were significantly suppressed by nifedipine and captopril and notably the combined treatment of nifedipine plus captopril suppressed TNF-α significantly more than the monotherapy of each drug. In monocytes, similar results as seen in lymphocytes were observed for TNF-α, whereas only the combination treatment was effective in suppressing IL-6 production. In MoDCs, both TNF-α and IL-6 were significantly suppressed by monotherapy of each drug but not by nifedipine. Flow cytometry analysis showed that TNF-α expression in CD4 cells was significantly suppressed by nifedipine but not by captopril. In CD8 cells, TNF-α expression was significantly suppressed only by the combination treatment of both drugs but not by monotherapy of each drug. Western blot showed that p38 activity was significantly decreased by nifedipine but not by captopril.

Conclusions: We first demonstrated that nifedipine and captopril exert differential effects in the suppression of TNF-α and IL-6 depending on the cell types of PBMCs and the combination treatment of both drugs has additive effects on the suppression of these cytokines. We also showed that the effect of nifedipine on these cytokines may be partly mediated by p38 MAPK pathways.

TH-P0739

Loss of Gstm1 Alters Blood Pressure Homeostasis and Augments Angiotensin II-Induced Hypertension

Background: GSTM1 gene encodes an enzyme that belongs to a superfamily of glutathione-S-transferases that metabolize xenobiotic and a broad range of reactive oxygen species and electrophilic compounds formed as secondary metabolites during glutathione-S-conjugation.

Methods: MoDCs, both TNF-α and IL-6 were significantly suppressed by monotherapy of each drug but not by nifedipine. Flow cytometry analysis showed that TNF-α expression in CD4 cells was significantly suppressed by nifedipine but not by captopril. In CD8 cells, TNF-α expression was significantly suppressed only by the combination treatment of both drugs but not by monotherapy of each drug. Western blot showed that p38 activity was significantly decreased by nifedipine but not by captopril.

Conclusions: We first demonstrated that nifedipine and captopril exert differential effects in the suppression of TNF-α and IL-6 depending on the cell types of PBMCs and the combination treatment of both drugs has additive effects on the suppression of these cytokines. We also showed that the effect of nifedipine on these cytokines may be partly mediated by p38 MAPK pathways.

TH-P0740

Kallikrein Kinin System and Blood Pressure Modulation by Aldosterone

Conclusions: Renal IL-FABP expression attenuated tubulointerstitial damage in addition to the renoprotective action depending on the decreasing in ATⅠⅠa expression in the renal injury due to Ras activation.

TH-P0741

The Role of A1AR in Hypertension Induced by Hyperuricemia

Methods: Hyperuricemia in wild type (WT) and A1AR-/- mice was induced by gavage of 250 mg/kg/d oxonic acid. Arterial blood pressure and urine electrolyte excretion were determined. The expression of renin, αSMA, COX2, and nNOS in the juxtaglomerular apparatus (JGA) was assessed by immunohistochemistry and confocal laser microscopy.

Results: Hyperuricemia was successfully induced in WT and A1AR-/- mice. S was increased in hyperuricemic WT mice (106.6 ± 7.4 vs. 114 ± 11 mmHg, P=0.017), accompanied by lower expression of nNOS in macula densa cells and higher expression of αSMA in afferent arterioles. The percentage of renin-positive JGA was increased in hyperuricemic WT mice compared to control and allosporin treated mice (Table 1). Arterial blood pressure and urine electrolyte excretion were determined. The expression of renin, αSMA, COX2, and nNOS in the juxtaglomerular apparatus (JGA) was assessed by immunohistochemistry and confocal laser microscopy.

Conclusions: A1AR may be involved in the hypertension induced by hyperuricemia. The mechanisms underlying this effect need to be studied further.

Funding: Government Support - Non-U.S.

TH-P0742

Exenatide and Human Glucagon-Like Peptide-1 (7-36 Amide) Are Diuretic, Natriuretic, and Positive Inotropes

Methods: Exenatide and human GLP-1 (7-36) amide (GLP-1, 50 nmol/hr) increased excretion of Na+ and clearance of free water. Therefore, GLP-1 and GLP-1 receptor agonists may increase natriuresis and diuresis.

Conclusions: We have developed a comprehensive in vivo screen in the anesthetized rat to simultaneously measure multiple renal, cardiovascular and pharmacokinetic properties of test agents.

Funding: NIH/NIH/NCI/NCATS.

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

268A
mean arterial pressure (MAP) and increased heart rate (HR). Pharmacokinetic analysis showed that exренатine concentrations in plasma substantially increased following renal ligation, affirming predominantly renal clearance of this peptide.

**Conclusions:** This protocol allows collection of over 120 physiological cardioaerial and pharmacokinetic parameters in association with intravenous administration of test agents.

Funding: Pharmaceutical Company Support - GlaxoSmithKline

**TH-PO743**

**Impact of Proton-Pump Inhibitors and Diuretics on the Risk of Hypomagnesemia in Patients Admitted to the Emergency Department**

Spyridon Arampatzis,1,2 Markus Molaht1, Alexander Benedikt Leichtle1, Andreas Paesch1, Aristomenis K. Exadaktylos2, Gregor Lindner1.

1. Dept of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Univ of Bern, Bern, Switzerland; 2. Dept of Emergency Medicine, Inselspital, Univ of Bern, Bern, Switzerland; 3. Center of Laboratory Medicine, Univ of Bern, Bern.

**Background:** The aim of this study was to evaluate the risk of hypomagnesemia under concomitant use of proton pump inhibitors (PPIs) and diuretics and explore the role of hypomagnesemia as a risk factor for adverse outcome in a cohort of emergency department (ED) patients.

**Methods:** Cross-sectional study in 4,919 patients who presented to a large tertiary care ED between 01 January 2009 and 31 December 2010 with measurements of serum magnesium on admission. Hypomagnesemia was defined as serum magnesium concentration of <0.75 mmol/L. Demographic data, electrolyte disorders, data on medication, morbidity and outcome in terms of length of hospital stay and mortality were documented.

**Results:** The mean serum magnesium concentration was 0.81 mmol/L (SD 0.1); 1,195 patients (24%) showed hypomagnesemia on admission. Magnesium levels tended to be lower in patients under diuretic and PPI medication and were significantly lower in subjects taking both drugs (p<0.001). Use of loop diuretics (p=0.002) and thiazide diuretics have previously been shown to cause renal malformations, hypomagnesemia and MODY.

1,195 patients (24%) showed hypomagnesemia on admission. Magnesium levels tended to be lower in patients under diuretic and PPI medication and were signficantly lower in subjects taking both drugs (p<0.001). Use of loop diuretics (p=0.002) and thiazide diuretics have previously been shown to cause renal malformations, hypomagnesemia and MODY.

**Conclusions:** Hypomagnesemia is common in patients presenting to the ED and is associated with use of PPIs, diuretics, and the presence of diabetes. Hypomagnesemia with concomitant hypokalemia was an independent predictor of in-hospital mortality.

**TH-PO744**

**Mutations in PCBD1 Are Associated with Hypomagnesemia, Renal Magnesium Wasting and MODY**

Jeroen H.F. De Baaij, Silvia Ferrè, Joost Hoenderop, René J. Bindels.

Dept of Physiology, Radboud Univ Nijmegen Medical Centre, Nijmegen, Netherlands.

**Background:** Mutations in PCBD1 are causative for transient neonatal hyperparathyroïdism and primary hyperparathyroidism (HPAH4BD). Until now HPAH4BD has been regarded as a transient and benign neonatal syndrome without complications in adulthood.

**Methods:** We assessed 3 patients with PCBD1 for blood magnesium levels and diabetes. Expression levels and localization of PCBD1 in mouse kidney and pancreas were evaluated. Moreover, the ability of PCBD1 wild type and PCBD1 mutants to co-activate the FXYD2 promoter was investigated by luciferase-reporter assays. Additionally, we examined the promoter activity. Furthermore, HNF1B mutations may disturb PCBD1 localization in DCT. Thus, patients with HPABH4D should be monitored for previously unrecognised late complications, such as hypomagnesemia and MODY diabetes.

**Results:** In our study, two adult patients with homozygous mutations in the PCBD1 gene were diagnosed with hypomagnesemia and renal Mg2+ loss. One patient also developed diabetes with characteristics of maturity onset diabetes of the young (MODY). Our results suggest that these clinical findings are related to the function of PCBD1 as a co-regulator for the transcription factor HNF1B. Mutations in the HNF1B gene have previously been shown to cause renal malformations, hypomagnesemia and MODY.

**Conclusions:** Overall, our findings establish PCBD1 as an important co-activator of the HNF1B-mediated transcription necessary for fine-tuning of FXYD2 transcription in DCT. Thus, patients with HPAH4BD should be monitored for previously unrecognised late complications, such as hypomagnesemia and MODY diabetes.

Funding: Government Support - Non-U.S.

**TH-PO745**

**Characterization of Osteoclast-Specific NCX1 Knock-Out Mice**

Daniel G. Fuster,1 Olivier Bonny.2 1. Div of Nephrology, Hypertension and Clinical Pharmacology, Univ of Bern, Bern, Switzerland; 2. Institute of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland.

**Background:** Bone is dissolved by a polarized cell, the osteoclast. Previous studies indicated that sodium/calcium exchanger NCX1 inhibitors decrease bone resorption in a dose dependent manner in vitro. In addition, siRNA-mediated knock-down of NCX1 significantly suppressed osteoclastic bone resorption in vitro, indicating a critical role of NCX1 in osteoclast-mediated bone resorption. To test the role of NCX1 in osteoclasts in vivo, we generated mice with osteoclast-specific deletion of NCX1.

**Methods:** Mice with a floxed exon 11 of NCX1 were crossed with mice expressing Cre recombinase under the influence of the cathepsin K promoter to generate osteoclast-specific NCX1 knock-out mice (herein named NCX1 ΔOC/ΔOC mice).

**Results:** Osteoclasts differentiated from NCX1 ΔOC/ΔOC mice displayed a 80% reduction of NCX1 mRNA and protein compared to wild-type mice. NCX2 was not expressed in osteoclasts. NCX3 was expressed a low levels in osteoclasts but was not upregulated in NCX1 ΔOC/ΔOC osteoclasts. NCX1 expression was unaltered in extracellular tissues in NCX1 ΔOC/ΔOC mice. Structural bone parameters, analyzed by high-resolution microtomography (μCT) were not different in 12 week old male and female wild-type and NCX1 ΔOC/ΔOC mice. Similarly, no differences were observed when we assessed osteoclast differentiation or bone resorption in vitro of cells isolated from wild-type and NCX1 ΔOC/ΔOC mice, respectively. Finally, to stimulate osteoclast-mediated bone resorption, we performed surgical ovariectomy in 12 week old female mice. Ovariectomy-induced bone loss, however, was not different in wild-type and NCX1 ΔOC/ΔOC mice at 3, 6, 9 and 12 weeks after the operation.

**Conclusions:** Thus, our data indicate that genetically induced deficiency of NCX1 in osteoclast-precursors and mature osteoclasts does not affect osteoclast differentiation and bone resorption in vitro. Furthermore, osteoclast-specific deletion of NCX1 seems not to affect bone volume in 12 week ovariectomy or ovariectomy-induced bone loss in female mice until 12 weeks after the operation.

**TH-PO746**

**Angiotensin II and PDGF Decrease the Phosphorus-Induced Calcification in Vascular Smooth Muscle Cells In Vitro**

Carmen Herena1, Maria Encarnacion Rodriguez ortiz1, Juan R. Muñoz-Castañeda2, Julio Manuel Martinez Moreno1, Rocío Canalejo1,2, Addy Rosa Montes de Oca Gonzalez1, Carmen Marin1, Antonio Canalejo1, Mariano Rodriguez1, Yolanda Almaden Peña1.

1. IMIBIC, Spain; 2. Univ of Huelva, Spain; 3.Reina Sofia Univ Hospital.

**Background:** High Phosphorus (HP) plays a key role in the pathogenesis of vascular calcification(VC), which occurs through a Wnt/β-catenin(BCTN) induced osteoblastic differentiation of vascular smooth muscle cells(VSMCs). The involvement of AngiotensinII(AII) and platelet derived growth factor(PDGF) in the development of VC is controversial. We evaluated the effect of AII and PDGF on VC in human VSMCs in vitro.

**Methods:** VSMCs were cultured with HP alone or supplemented with 10mM AII or 20ng/ml PDGF for 9 days. Calcium deposition (spectrofotometry), osteogenic genes expression(RT-PCR) and BCTN nuclear translocation(confocal microscopy) were measured.

**Results:** High Ph induced calcification was associated with BCTN nuclear translocation. An increase in mRNA levels of BMP2,Runx2,Osterix and ALP was produced. AII and PDGF supplementation reduced calcium levels,osteoblastic genes expression and BCTN translocation. *p<0.05 vs control; #p<0.05 vs HP.

**Conclusions:** Calcium salts affect acid-base balance by stimulating differently mineral disease: Ca/Mg/PO4.

**TH-PO747**

**Calcium Salts Affect Acid-Base Balance by Stimulating Differently Type A and B Intercalated Cells in Mouse Kidney Collecting Ducts**

Yukiko Yada1, Yuichi Sato1, Hiroshi Nonoguchi1, Katsumasa Kawahara1,2.


**Background:** Calcium salts (calcium carbonate (CaC) and calcium phosphate (CaP)) are widely used for patients with chronic kidney disease (CKD) and osteoporosis. These salts have the potential to affect acid-base balance via the Ca-sensing receptor (CaSR) expressed on Type A and B intercalated cells (I,IIc cells) and an inhibition in Wnt/BCTN pathway.

**Methods:** We assessed 3 patients with PCBD1 for blood magnesium levels and diabetes. Expression levels and localization of PCBD1 in mouse kidney and pancreas was evaluated. Moreover, the ability of PCBD1 wild type and PCBD1 mutants to co-activate the FXYD2 promoter was investigated by luciferase-reporter assays. Additionally, we examined the subcellular localization of PCBD1 wild type and mutants in HEK293 cells.

**Results:** In our study, two adult patients with homozygous mutations in the PCBD1 gene were diagnosed with hypomagnesemia and renal Mg2+ loss. One patient also developed diabetes with characteristics of maturity onset diabetes of the young (MODY).

**Conclusions:** Overall, our findings establish PCBD1 as an important co-activator of the transcription factor HNF1B. Mutations in the HNF1B gene have previously been shown to cause renal malformations, hypomagnesemia and MODY. Gene expression analysis in the kidney showed that Pebp1 is co-expressed with Hnf1b in the distal convoluted tubule (DCT) where Pebp1 transcript levels are upregulated by a low Mg2+-containing diet. Overexpression in a human kidney cell line demonstrated that wild-type PCBD1 binds HNF1B to co-stimulate the FXYD2-promoter, whose activity is instrumental in Mg2+ reabsorption in DCT. Five out of seven PCBD1 mutations previously reported in HPAH4BD patients caused proteolytic instability leading to a reduced FXYD2 promoter activity. Furthermore, HNF1B mutations may disturb PCBD1 localization in the nucleus, since PCBD1 showed an increased cytosolic localization when co-expressed with HNF1B mutants.

Funding: Government Support - Non-U.S.
of anion exchanger type 1 (AE1), Pendrin (an apical HCO₃⁻/Cl⁻ exchanger), and CaSR along the collecting duct. Blood and urine samples were also analyzed.

Results: Plasma Ca concentration and urinary Ca excretion increased slightly, but not significantly in mice with 2.5% CaC (n=7) and 2.5% CaP diets (n=8). In contrast, these measurements significantly increased from 7.7 to 9.9 (mg/dl) and from 0.12 to 3.21 (mg/d) in mice with 2% CaCl₂, diet (n=12). In addition, urine pH significantly decreased from 6.73 to 5.78 (CaCl₂) increased to 7.25 to 7.5 (CaC), and was unchanged (6.58) in mice with CaP. In IC-A, as expected, the level of the AE1 mRNA expression (an index of acid excretion) increased, decreased, and remained unchanged, respectively, in mice with CaCl₂, CaC, and CaP supplements. On the other hand, in IC-B, the levels of the pendrin (an index of alkaline excretion) and CaSR mRNA expression decreased due to acidosis caused by the CaC, containing diet, whereas they increased in mice showing normal plasma pH consuming CaC and CaP diets.

Conclusions: These data strongly suggest that CaC may work as an alkali as well as a cation transporter, and may increase urinary Ca excretion by stimulation mediated by basolateral CaSR in IC-B. Therefore CaC may be the best Ca supplement for patients with CKD and osteoporosis with regards to Ca metabolism and acid-base balance.

**TH-PO748**

β-Adrenergic Receptor Signaling Activates the Ephitelial Calcium Channel, TRPV5, via the Protein Kinase A Pathway

Kukiat Tudpor, Eline A.E. Van der Hagen, Sjoerd Verkaart, René J. Bindels, Joost Hoenderop. Physiology, Radboud Univ Nijmegen Medical Centre, Nijmegen, Netherlands.

Background: Epinephrine (Epi) and norepinephrine (NE) are present in the proximal tubule. β-adrenergic receptor (β-AR) blockers administered to counteract sympathetic overstimulation in patients with congestive heart failure (CHF). Even though Epi and NE are secreted in the pro-urine no effects of these hormones through signaling via β-ARs on renal active Ca²⁺ transport have been reported. Active Ca²⁺ reabsorption in the late distal convoluted and connecting tubules (DCT2/CNT) is initiated by Ca²⁺ influx through the transient receptor potential vanilloid type 5 (TRPV5) Ca²⁺ channel.

Methods: Expression levels and localization of β-adrenergic receptors was investigated in mouse kidney by immunohistochemistry and DCT2/CNT were isolated using the COPAS technology. TRPV5 was expressed in HEK293 cells and the intracellular Ca²⁺ concentration was assessed by tissue calcium was associated with the tunica media (histology). Increasing the media calcium (Ca) levels and visualized with von Kossa staining.

Results: Delaying 2.5mM magnesium treatment continued to be effective if the increase in CaCl₂, treatment was administered and CaSR expression decreased due to acidosis caused by the CaC, containing diet, whereas they increased in mice showing normal plasma pH consuming CaC and CaP diets.

Conclusions: These data strongly suggest that CaC may work as an alkali as well as a cation transporter, and may increase urinary Ca excretion by stimulation mediated by basolateral CaSR in IC-B. Therefore CaC may be the best Ca supplement for patients with CKD and osteoporosis with regards to Ca metabolism and acid-base balance.

**TH-PO749**

The Pathophysiology of Aortic Calcification in an In Vitro Model: The Role of Mineral Imbalance

Navid Shobeiri, Julie Crujines, Rachel M. Holden, Michael A. Adams. Dept of Biomedical and Molecular Sciences, Queen's Univ, Canada; Medicine, Queen's Univ, Canada.

Background: Vascular calcification (VC) is accelerated in patients with chronic kidney disease (CKD), resulting in increased risk of cardiovascular disease and mortality. Mineral imbalance in CKD contributes to this process, and elevated phosphate is a major risk factor.

Methods: An in vitro model of VC was developed to determine the impact of bone minerals (phosphate, magnesium, calcium). Aortas were incubated in pre-calcification DMEM media with or without elevated magnesium. Calcium was assessed by tissue calcium (Ca) levels and visualized with von Kossa staining.

Results: The degree of calcification was dependent on time-course and phosphate concentration. Aortic rings calcified in media phosphate concentrations above 3.0mM (2.5mM phosphate in Ca, however elevated calcium media did not cause calcification. Aortas in 3.8mM phosphate media demonstrated accumulation of calcium at day 2 (78.2±17.2nmol/mg), but an accelerated accumulation by day 4 (528.9±62.4nmol/mg). This calcification was associated with the tunica media (histology). Increasing the media magnesium levels from 2.5mM CaCl₂, increased to 2.5mM blunted tissue calcification significantly (.933%; p<0.05). Delaying 2.5mM magnesium treatment continued to be effective if the increase occurred prior to day 4 or a 6 day incubation period (addition of magnesium at day 2 .66±14% and day 3 .35±4%tissue Ca). Two day pretreatment with 2.5mM magnesium also prevented phosphate-induced calcification. That is, incubation of these vessels for only 2 days in high magnesium prevented de novo calcification when transferred to pre-calcification media without high magnesium (+4 days) (10.5±1.3nmol/mg vs 175.5±28.9nmol/mg tissue Ca, p<0.05). Consequently, tissue magnesium remained elevated at day 6 (12.6±1.2nmol/mg vs 14±4.6nmol/mg, p<0.05).

Conclusions: Elevated phosphate appears to be a key signal in the development of pathological calcification. This process is blocked by magnesium, but only if calcification has not already begun.

**TH-PO750**

Estrogen Directly Downregulates NaPi-IIa through the Activation of Both Estrogen Receptor Isoforms (ERα and ERβ) in Rat Kidney Proximal Tubule

Hassane Amlal, Rose P. Webster, Rashma Farooqi, Moshe Levi, Sulaiman Sherrif. 1Internal Medicine, Univ of Cincinnati, Cincinnati, OH; 2Internal Medicine, Univ of Colorado, Denver, CO; 3Dept of Surgery, Univ of Cincinnati, Cincinnati, OH.

Background: Estrogen depletion in postmenopausal women is associated with hyperphosphatemia. We have demonstrated that β-estradiol (EST) downregulates NaPi-IIa and causes phosphaturia and hyperphosphatemia in ovx (ORX) rats. However, the signaling mechanism(s) mediating this effect remain unknown.

Methods: The expression of ERα and ERβ in the proximal tubule (PT) was examined using RT-PCR. The respective roles of these receptors in EST-induced downregulation of NaPi-IIa was studied using the EST rats placed in metabolic cages and treated with specific agonists of either ERα (PPT or DPN). A cell line (U2OS) stably expressing ERα or β or both under doxycycline control and transiently transfected with rat NaPi-IIa was also used. In these cells, ERα and β are expressed in a functional ERα/β heterodimers.

Results: RT-PCR data indicate that both ERα and ERβ are expressed in the cortex and PT cells. PT suspensions harvested from EST ovx rats and incubated on a shaker in a cell culture incubator for 24hrs exhibited a significant downregulation of NaPi-IIa expression (RNA + protein) in the presence of EST vs. vehicle. Treatment of OVX rats with either PPT or DPN alone did not affect NaPi-IIa expression and did not cause phosphaturia. However, combined treatment with PPT+DPN mimicked the effect of estrogen and caused a sharp downregulation of NaPi-IIa along with significant phosphaturia. U2OS cells expressing both ERα and ERβ showed a significant downregulation of NaPi-IIa protein in response to EST, vehicle only when pre-treated with doxycycline. Interestingly, NaPi-IIa protein abundance was not altered by EST in U2OS cells bearing either ERα or ERβ alone.

Conclusions: These studies demonstrate that rat PT cells express both ERα and ERβ and that EST downregulates NaPi-IIa by directly acting on PT cells. This effect is mediated via a complex mechanism involving the activation, and likely heterodimerization of ERα and ERβ.

Funding: NIDDK Support

**TH-PO751**

Estrogen Downregulates NaPi-IIa in Mouse Kidney through a Mechanism Involving the Activation of Estrogen Receptor Isoform α (ERα) and 3′UTR Region of NaPi-IIa mRNA Transcript

Hassane Amlal, Sulaiman Sherrif, Rashma Farooqi, Rose P. Webster. 1Internal Medicine, Univ of Cincinnati, Cincinnati, OH; 2Internal Surgery, Univ of Cincinnati, Cincinnati, OH.

Background: 17β-estradiol (EST) downregulates NaPi-IIa mRNA and protein and causes phosphaturia in rats likely by activating both EST receptor isoforms ERα and ERβ (published report and accompanying abstract). To confirm these findings, we sought to study the effect of EST on NaPi-IIa using mice with genetic deletions of ERα or ERβ.

Methods: Females ERα knockout (KO), ERβ KO and their wild-type (WT) mice were placed in metabolic cages with free access to food and water and treated with EST or its vehicle for 3 days. Food and water intake, urine volume and urinary Pi excretion were measured daily. A cell line (U2OS) stably co-expressing both EST and ERα or ERβ under doxycycline control and transiently transfected with different mouse NaPi-IIa constructs (mNaPi-IIa) was also used. Molecular studies examined the expression of NaPi-IIa in the kidney of U2OS cells.

Results: Like rats, EST-treated WT mice exhibited a significant reduction in food intake along with increased renal phosphate wasting. However, unlike rats, the phosphaturic effect of EST resulted from a sharp downregulation of NaPi-IIa protein without affecting its mRNA expression levels. Interestingly, EST-induced phosphaturia and downregulation of NaPi-IIa protein were also observed in ERβ KO but not in ERα KO mice. U2OS cells expressing ERα and ERβ treated with EST for 24hrs showed a significant downregulation of NaPi-IIa protein abundance when transfected with a plasmid containing ORF-3 UTR but not 5′UTR-ORF of mNaPi-IIa transcripts. This effect is observed only when cells were pre-treated with doxycycline.

Conclusions: EST causes phosphaturia in mice despite a reduction in food intake. This effect results from the downregulation of NaPi-IIa protein abundance with no change in mRNA expression levels, and is mediated through the exclusive activation of ERα. A cis-acting element in the 3′UTR region of mNaPi-IIa mRNA likely plays an important role in the inhibition of its translation by EST.

Funding: NIDDK Support

**TH-PO752**

Conditionally Immortalized Human Proximal-Tubular Epithelial Cells Isolated from the Urine of a Healthy Subject Express Functional Calcium-Sensing Receptor (CaSR)

Annamita Di Mise, Grazia Tamura, Marianna Romano, Maria Svelo, Elena N. Levchenko, Giovanna Valenti. 1Dept Biosciences, Biotechnologies and Biopharmaceutics, Univ of Bari, Bari, Italy; 2Dept of Pediatric Nephrology, Univ Hospital Gasthuisberg, Leuven, Belgium.

Background: The calcium-sensing receptor (CaSR) is a G protein coupled receptor, which plays an essential role in regulating Ca²⁺ homeostasis.

Here we show that conditionally immortalized proximal tubular epithelial cell line (cPTuECs) obtained by immortalizing and subcloning cells exfoliated in the urine of a healthy subject expresses functional endogenous CaSR.

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

Underline represents presenting author/disclosure.

270A
PH-0753

**Tissue-Derived Microarrays for Delineation of the Renal Pathway in Calcium Reabsorption**

**Methods:** Kidney tissue from rats with acute renal failure, normal rats, and hyperphosphatemia was collected and snap-frozen. The tissue was dissected into tubular and glomerular fractions and subjected to RNA isolation using TRIzol. The RNA was subsequently reverse-transcribed into cDNA and analyzed using the Affymetrix Mouse GeneChip platform. The expression levels of differentially expressed genes were determined using GeneSpring GX software.

**Results:** A total of 1,234 genes were found to be significantly differentially expressed in the renal tissue of rats with acute renal failure compared to normal rats. Among these genes, those related to calcium reabsorption, such as calbindin-D9k, were found to be upregulated.

**Conclusions:** This study provides a comprehensive view of the renal pathway in calcium reabsorption using tissue-derived microarrays, which can be used to identify potential targets for future therapeutic interventions.

Funding: Supported by the National Institutes of Health (NIH).

---

**PH-0754**

**Nephrotoxicity of Lipid-Mobilizing Agents in Rodents**

**Methods:** Male Sprague-Dawley rats were treated with either a lipase inhibitor or a lipase activator for 14 days. The rats were then sacrificed, and renal tissues were collected for histological analysis.

**Results:** Treatment with the lipase inhibitor resulted in significant histological changes in the renal tissues, including increased inflammation and fibrosis. In comparison, treatment with the lipase activator did not cause any significant histological changes.

**Conclusions:** These findings suggest that the use of lipase inhibitors may be associated with nephrotoxicity in rodents.

Funding: Supported by the National Institutes of Health (NIH).

---

**PH-0755**

**Lanthanum Carbonate: Safety Data after 9 Years**

**Methods:** A retrospective analysis of safety data from a double-blind, placebo-controlled trial of lanthanum carbonate was conducted. The trial included 441 patients who received lanthanum carbonate for 1 year, and safety data were collected for up to 9 years.

**Results:** No significant differences in adverse events were observed between the lanthanum carbonate and placebo groups. The most common adverse events were constipation and diarrhea.

**Conclusions:** Lanthanum carbonate is safe and well-tolerated for up to 9 years of treatment.

Funding: Shire Healthcare.

---

**PH-0756**

**Double-Blind, Dose-Ranging, Study of Lanthanum Dioxycarbonate (SPI-014, Renzor) in Healthy Volunteers Shows High Phosphorus Binding Capacity**

**Methods:** A double-blind, dose-ranging study was conducted in healthy volunteers. The study included three dose levels of SPI-014: 1500, 3000, and 4500 mg/day.

**Results:** All doses of SPI-014 were well tolerated. There were no significant changes in serum phosphorus levels or other laboratory parameters at the end of the study.

**Conclusions:** SPI-014 is safe and effective in healthy volunteers.

Funding: Shire Healthcare.

---

**PH-0757**

**Barriers and Facilitators to Dialysis Patient Self-Management of Phosphate Binders**

**Methods:** A qualitative study was conducted with dialysis patients to identify barriers and facilitators to self-management of phosphate binders. Semi-structured interviews were conducted, and data were analyzed using thematic analysis.

**Results:** Common barriers to self-management included medication complexity, cost, and side effects. FACilitators included patient education, support from healthcare providers, and the availability of convenient medication schedules.

**Conclusions:** Improved education and support for dialysis patients can help improve their self-management of phosphate binders.

Funding: Shire Healthcare.
manage their phosphate binder medications to improve patient outcomes. To achieve this goal, a qualitative study was conducted to pinpoint dialysis patient-centered facilitators and barriers to phosphate binder self-management.

Methods: Primary data were gathered from five, 90-minute, small-group interviews with hemodialysis patients (N = 17) in Atlanta, GA. The majority of patients were female (70%), African American (76%), had a dialysis vintage > 87 months (SD=59), and a daily pill burden of 16 pills (SD=13). A constant comparative method was used to identify themes that emerged from a line-by-line review of the interview transcripts.

Results: Participants identified three facilitators to self-managing their phosphate binders: social support; placing binders in multiple locations; and seeing images that depict health consequences associated with high serum phosphorus. Patients also identified three main barriers to self-management of phosphate binders: financial burden of medications, privacy concerns about taking medications in a public setting, and medication regimen complexity.

Conclusions: The study findings provide the basis for the development of future research and targeted interventions that can improve patient self-management of phosphate binders and improve dialysis patient health outcomes.

TH-PO758
At What Stage of CKD Phosphate Binder Treatment Should Be Started?
Juegeren Bommer,1 Martina Flisser,2 Heinz Juegen Roth,2 Daniel Saure,1 1Medical Univ Hospital Heidelberg, Dialysis Center Heidelberg, Heidelberg, Germany; 2Limbach Laboratory, Heidelberg, Germany; 3Institute of Medical Biometry and Informatics Univ Heidelberg, Heidelberg, Germany.

Background: Disturbed mineral metabolism plays a major role in vascular calcification followed by an increased mortality. The constant serum P concentration until eGFR decreases to about 30 ml/min was explained by increasing phosphaturic effect of increasing PTH and FGF 23 in patients with progressing renal failure. Recently an increased vascular calcification (CAC) score was reported in early CKD (eGFR 90-60ml/min) compared with the group with normal renal function This raises the issue at which point in the evolution of CKD interventions in mineral metabolism should be started.

To address this issue we studied in a large cohort of unselected subjects of the outpatient units the association between eGFR/creatinine clearance and serum concentration as well as 24 hr urinary excretion of Ca and P.

Methods: Serum concentrations of Ca, P and Crea were measured photometrically in 26 097 unselected individuals, 60.4% males, a mean age of 68.8±13.7 years (range 19-99 years). In addition 24 hr urine of 2758 subjects, 59.3% males, mean age of 56.1±14.2 years (range 15-96 years) was collected to quantify excretion of Ca, P and creatinine photometrically. eGFR was estimated by the MDRD formula.

Results: Mean and median of serum Ca and P concentration remained constant at eGFR > 30 ml/min. When eGFR decreased to <30 ml/min serum phosphorus increased (p < 0.0001) and serum Ca decreased (p=0.0001). In parallel with the decrease of eGFR from 120 down to <20 ml/min a continuous decrease was found for Ca excretion [from 5.3±3.0 to 1.16±0.98 mmol/24 hr (p=0.0001)] as well as P excretion [from 27.2±9.5 to 15.4±6.8 mmol/day (p=0.0001)].

Conclusions: Serum Ca and P Premain constant until eGFR is decreased to levels below 30 ml/min. However, 24 hr urinary excretion of Ca and P start to decrease at much earlier stages of CKD. These findings may be related to the early onset of soft tissue calcification in CKD patients. In view of these findings the optimal start of P-binder treatment requires further investigation.

TH-PO759
Effect of High and Low Phosphate Intake on Oxidative Stress Levels
Essam F. Elsayed, Maram Museitif, Makoto Kuroo. UT Southwestern.

Background: High phosphate (Pi) intake has been shown to be associated with premature aging and increase in oxidative stress in animals and many of these abnormalities are rescued by a low phosphate diet. In humans, serum phosphorus levels positively correlate with premature aging and increase in oxidative stress in animals and many of these abnormalities. In humans, serum phosphorus levels positively correlate with premature aging and increase in oxidative stress in animals and many of these abnormalities.

In animal models, induction of high levels of oxidative stress and oxidative DNA damage by fraction excretion of Pi (FePi), was used as the independent predictor and the outcome measure of CKD interventions in mineral metabolism should be started.

Results: Participants identified three facilitators to self-managing their phosphate binders: social support; placing binders in multiple locations; and seeing images that depict health consequences associated with high serum phosphorus. Patients also identified three main barriers to self-management of phosphate binders: financial burden of medications, privacy concerns about taking medications in a public setting, and medication regimen complexity.

Conclusions: The study findings provide the basis for the development of future research and targeted interventions that can improve patient self-management of phosphate binders and improve dialysis patient health outcomes.

TH-PO760
Effects of Dietary Phosphorus Load on the Postprandial Blood Glucose and Glucose-Regulating Hormone Levels
Miehiro Yamasaki, Misaki Katsumoto, Yutaka Taketami, Hisami Okumura, Eiji Takeda. Dept of Clinical Nutrition, Univ of Tokashikina, Japan.

Background: Dietary phosphorus (P) loading implicates bone and mineral disturbance in CKD patients. However, disturbance of P metabolism also affects other nutrient metabolism including glucose and lipid metabolism. In this study, we examined the effects of dietary P loading on the postprandial blood glucose and glucose-regulating hormone levels.

Methods: 24 healthy young men (21 to 27 years old) were alternately served with a high glycemic index (GI) high P meal (HGHp; white rice, P400mg), high GI low P meal (HGLP; white rice, P1200mg), low GI high P meal (LGHp; barley, P 1200mg) or low GI low P meal (LGLP; barley, P 400mg). Blood and urine samples were collected before and at 0, 15, 30, 60 and 120min after the meal ingestion and measured serum levels of P, intact-parathyroid hormone (PTH), glucose, insulin, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), and fractional urinary P excretion.

Results: In the low GI group (LHGP and LGLP), dietary high P loading significantly increased the postprandial blood glucose levels at 15-30min compared to low P loading (P<0.05). Serum insulin and GLP-1 levels tended to increase after high P loading. On the other hand, there was no significant change in serum GIP levels in response to P loading. The area under the curve (AUC) at 0-120min of serum P was positively associated with the change of serum GLP-1 concentration at 0-60min in low GI group (P<0.05). However, these associations were not clearly observed in high GI group (HGHp vs HGLP, P>0.90).

Conclusions: Our study demonstrates that dietary high P loading can affect the blood glucose concentration and the glucose-regulating hormone such as GLP-1 when glucose loading is not so much.

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

TH-PO761
Minute-to-Minute Regulation of Plasma Calcium and Plasma Phosphate after Experimental Induction of Hypercalcaemia and Hyperphosphataemia
Eva Lewin,1 Eva Gravesen,2 Jacob Hofman-Bang,2 Klaus Olgaard,2 1Nephrological Dept B, Herlev Hospital, Univ of Copenhagen, Copenhagen, Denmark; 2Nephrological Dept P, Rigshospitalet, Univ of Copenhagen, Copenhagen, Denmark.

Background: Bone is the main storage of calcium (Ca) and phosphate (P). A ‘labile’ Ca storage pool, which is in equilibrium with blood Ca, exists on the bone surface, which is supposed to serve as a ‘buffer’, temporarily storing excess calcium, hereby keeping plasma ionized Ca (Ca²⁺) very stable on a minute-to-minute basis. Whether a similar rapid regulation of plasma P exists is not known. Our purpose was to evaluate the rapid minute-to-minute regulation of plasma Ca²⁺ and P after induction of acute hypercalcaemia and hyperphosphataemia.

Methods: Acute hypercalcaemia or hyperphosphataemia was induced by intravenous (i.v.) injections, and then the rapid recovery of Ca²⁺ and P were followed for 80 min. in normal rats and acute nephrectomized (NX) rats. The control group had NaCl.

Results: The i.v. bolus of Ca increased p-Ca²⁺ significantly from 1.29±0.03 to 1.64±0.03 mM/L (P < 0.01). Within 40 min p-Ca²⁺ was normalized. Another group of rats had a very large Ca bolus, increasing p-Ca²⁺ to 2.35±0.08 and p-Ca²⁺ became normalized within 80 min. Acute hyperphosphataemia was induced by an i.v. bolus of P, which increased p-P significantly from 2.42±0.19 to 5.54±0.17 mM/L (P < 0.01). Within the 60 min p-P
Hypercalcemia of malignancy (HCM), caused primarily by tumor-induced bone resorption, is often treated with IV bisphosphonates (BPs); BPs may not be appropriate for patients (pts) with renal impairment. Denosumab binds to RANKL to inhibit osteoclast-mediated bone resorption.

Methods: In this single-arm open-label study, pts with HCM (albumin-corrected serum calcium [CSC] ≥12.5 mg/dL) despite IV BP treatment ≥7 and ≤30 days (d) before screening received SC denosumab 120 mg on d 1, 8, 15, and 29, then every 4 weeks. The primary endpoint was rate of response (defined as CSC ≤11.5 mg/dL) within 10 d of denosumab initiation.

Results: The study enrolled 33 pts (64% men, mean age 60 [SD 15] years). At baseline, estimated creatinine clearance (CrCl; Cockcroft-Gault formula) was <60 mL/min for 11 pts (33%), ≥60 mL/min for 17 pts (52%), and missing for 5 pts (15%). By d 10, 10/17 pts (59%) with baseline CrCl ≥60 mL/min had a response. By d 10, 7/17 pts (41%) with baseline CrCl <60 mL/min had a response. By d 10, 7/17 pts (41%) with baseline CrCl <60 mL/min and 3/11 pts (27%) with CrCl <60 mL/min had a complete response. The rate of response was significantly higher in pts with baseline CrCl ≥60 mL/min (p < 0.01).

Conclusions: Denosumab appears effective in pts with baseline CrCl ≥60 mL/min. Further studies in pts with baseline CrCl <60 mL/min are warranted.

Background: Hypercalcemia is a marker of intestinal phosphorus absorption and may be a more reliable marker of phosphate homeostasis. Studies report good correlation between urine phosphorus-excretion ratio (uPiCr) and 24-hour urinary phosphate excretion, but whether uPiCr is associated with risk of CVD or mortality is uncertain. We aimed to assess the association between urinary phosphate excretion measured by uPiCr and outcomes in a large population-based cohort.

Methods: Using the nationally representative Australian Diabetes, Obesity and Lifestyle Study (AusDiab) cohort, uPiCr was determined from available urine samples (n=11,116). Participant baseline characteristics were compared across quartiles of uPiCr and regression analysis was used to determine associations. Relationships between uPiCr and all-cause mortality were determined using Cox proportion hazards regression with uPiCr modelled using fractional polynomials.

Results: Mean age 51±14y, 45% males and 9.6% had chronic kidney disease (CKD). uPiCr was significantly lower in pts with lower GFR, greater prevalence of CVD and hypertension (all p < 0.05). Relationships between uPiCr and all-cause mortality were determined using Cox proportion hazards regression with uPiCr modelled using fractional polynomials.

Results: Mean age 51±14y, 45% males and 9.6% had chronic kidney disease (CKD). uPiCr was significantly lower in pts with lower GFR, greater prevalence of CVD and hypertension (all p < 0.05). Relationships between uPiCr and all-cause mortality were determined using Cox proportion hazards regression with uPiCr modelled using fractional polynomials. Mean age 51±14y, 45% males and 9.6% had chronic kidney disease (CKD). uPiCr was significantly lower in pts with lower GFR, greater prevalence of CVD and hypertension (all p < 0.05). Relationships between uPiCr and all-cause mortality were determined using Cox proportion hazards regression with uPiCr modelled using fractional polynomials.
TH-PO766

Treatment of Hyperphosphatemia with Bixalomer in Hemodialysis Patients with Sevelamer-Associated Gastrointestinal Symptoms Hiroaki Ogata,1 Chiaki Kumata,1 Kae Ito,1 Kanji Shishido,1 Akiko Takeshima,2 Masahide Mizobuchi,3 Erika Kinogasa,1 Tadao Akizawa,2 1Internal Medicine, Kawasaki Clinic, Kawasaki, Japan; 2Dept of Internal Medicine, Showa Univ Northern Yokohama Hospital, Yokohama, Japan; 3Div of Nephrology, Dept of Medicine, Showa Univ School of Medicine, Tokyo, Japan.

Background: Bixalomer (Bix) is an anion-functional polymer, non-calcium (Ca) containing phosphate (P) binder and has been clinically available in Japan recently. Bix is expected to cause fewer gastrointestinal (GI) side effects as compared with sevelamer hydrochloride (SH), because of less expansion of Bix in the GI tract.

Methods: In this retrospective study, we evaluated changes in GI symptoms by the Gastrointestinal Symptom Rating Scale (GSRS) score in long-term hemodialysis outpatients with SH-associated GI symptoms, who switched to Bix from SH. Total 114 patients (age 63.7±10.8 year (mean±SD), female 65.5%, vintage 11.2±8.6 years, diabetes mellitus 27.4%) were enrolled. The GSRS score was checked at 0 and 12 weeks after the start of Bix. Bix was started at the initial dose of 750mg/day, and then was titrated.

Results: Serum albumin, P, Ca, and iPTH levels did not significantly change during Bix treatment period. However, serum LDL-cholesterol and bicarbonate levels significantly increased at 12 w as compared with those at 0w (73.1±20.0 vs 92.4mg/dL±23.9, P<0.0001 in LDL-c; 18.7±2.0 vs 19.5±2.3mEq/L, P<0.0001 in HCO3). In GSRS score, total and each domain scores including constipation, diarrhea, and reflux, heartburn, significantly reduced in 12w after Bix treatment as compared with 0w.

Conclusions: Bix is an effective P binder in long-term hemodialysis patients. In addition, Bix may be less often associated with gastrointestinal symptoms as compared with SH.

TH-PO767

Are Allograft Microcalcifications a Marker of Mineral Bone Disease? Sarah Margaret Moran,1 Kate O’Connor,2 Marek J. Mazur: 1Nephrology, Cork Univ Hospital, Ireland; 2Histopathology, Cork Univ Hospital, Ireland.

Background: Renal allograft calcification has been previously described, however its significance remains unclear. We aim to assess whether renal transplant allograft calcification is associated with mineral bone disease.

Methods: A computerized search of histopathological records was conducted. Data on primary renal diagnosis, allograft biopsy diagnosis, transplant & patient outcome and comorbidities were obtained. Serum calcium, phosphate, bicarbonate and parathyroid hormone (PTH) within 3 months of biopsy and serial creatinine measurements were obtained. Pathological slides were assessed by a Consultant Nephropathologist for calcification using a validated scoring system.

Results: We identified a total of 32 allograft biopsies in 25 patients. Time to biopsy ranged from 1 to 180 months. Calcification was present in 46.9% (15/32). The number of foci ranged from 1 to 42, mean 7.5. Calcifications were located in tubules in 93.3% (14/15), with 0 to 42 foci, mean 6.3 foci. Interstitial calcification was present in 20% (6/30). Randomization order had no effect. Urinary cGMP correlated negatively with serum phosphate (r=0.55, p<0.001).

Conclusions: This is the first study to examine the significance of microcalcifications in non-protocol allograft biopsies up to 180 months. Non-significant trends were observed towards associations with allograft outcome and elevated PTH levels.

Funding: Clinical Revenue Support

TH-PO768

PTH Inhibits Type IIa Sodium Phosphate Cotransporter mRNA Expression through Both Protein Kinase A and Protein Kinase C-Dependent Mechanisms Rebecca Murray,1 Nina W. Lesousky,2 Syed J. Khundmiri,2 Barbara Clark,1 Eleanor D. Lederer,1,2 1Physiology & Biophysics, Univ of Louisville, Louisville, KY; 2Medicine, Univ of Louisville, Louisville, KY; 3Biochemistry & Molecular Biology, Univ of Louisville, Louisville, KY; 4Robley Rex VAMC, Louisville, KY.

Background: We have previously shown that PTH decreases NpT2a mRNA stability through an effect dependent on both transcription and translation. However, little is known about the signaling pathways responsible for destabilization of NpT2a mRNA by PTH. The PTHR receptor activates both cAMP/PKA and PLC/PKC pathways, and both pathways have been shown to decrease proximal tubule phosphate reabsorption. A genome-wide analysis by Zhang et al (PNAS, 2005) identified a half-CRE within the promoter region of the NpT2a gene.

Methods: We hypothesize that PTH produces chronic down-regulation of NpT2a mRNA through activation of the PKA pathway. To address this hypothesis, we treated opossum kidney cells, a proximal tubule cell line featuring PTHR-sensitive sodium-phosphate cotransport, with 8-bromo-cAMP (8-br) or phorbol myristate acetate (PMA) to activate the PKA and PKC pathways, respectively, and measured Np2a mRNA expression by qRT-PCR.

Results: 2h treatment of OK cells with 10 μM 8-br decreased NpT2a mRNA by 45.46 (±12.2), and 8h treatment decreased NpT2a mRNA expression by 55.25 (±46.0%)

Conclusions: We conclude that both PKA and PKC pathways may contribute to regulation of NpT2a mRNA by PTH. Funding provided by VA to EDL.

Funding: Veterans Affairs Support

TH-PO769


Background: Acute phosphate loading with a single meal impairs endothelial function but the effect of sustained phosphate loading has not been studied. We studied the effect of sustained phosphate loading and phosphate binding medication on endothelial function in healthy volunteers.

Methods: Healthy volunteers attended for 3 visits. Prior to each visit a 24 hour urine collection was performed for urinary electrolytes and cGMP. Bloods were drawn for routine biochemistry and FGF-23. Flow mediated dilatation (FMD) was recorded at each visit. Volunteers were randomised at visit 1 to receive phosphate sandoz (PS) or lanthanum carbonate (LC) for two weeks prior to visit 2. After a wash out period, volunteers took the other drug before attending for a final visit.

Results: There were 19 participants. At baseline, mean age was 42±14 years, serum phosphate 1.05±0.18mmol/L and fractional excretion of urinary phosphate (FeP) 14±3%. Median FMD was 8.4% (IQR 6.2-11.6%). After PS, there was a non-significant trend towards a higher serum phosphate within the normal range, FGF-23 and FeP rose significantly compared to baseline (p=0.013, p=0.001) and FMD reduced significantly (3.38% (IQR 2.57-5.26%), p=0.001). With LC, FMD also reduced significantly (p=0.033). Randomization order had no effect. Urinary cGMP correlated negatively with serum phosphate (p<0.001).

Conclusions: This is the first study to show that sustained phosphate loading impairs endothelial function. Serum phosphate was unchanged but the deleterious effect seen with PS may be explained by elevated total body phosphate. Elevated FeP and FGF-23 are likely surrogate markers of higher total body phosphate. Urinary cGMP, as a marker of endothelial dysfunction negatively correlates with serum phosphate. This supports the hypothesis that phosphate increases cardiovascular risk by impairing endothelial function, possibly via the nitric oxide pathway and shows that sustained phosphate loading is directly detrimental to the vasculature even when serum phosphate remains within the normal range.

Funding: Other NIHR Support - British Heart Foundation
TH-PO770

Spurious Hyperphosphatemia due to High Bilirubin Levels


Background: We report a case series of spurious hyperphosphatemia in patients with end-stage liver disease (ESLD) that was associated with highly elevated serum bilirubin levels. Hyperphosphatemia was noted with one type of laboratory analyzer, but the results could not be duplicated utilizing a different analyzer that is based on a different calibration method. As treatment of spurious hyperphosphatemia may lead to complications, awareness of this issue may have important ramifications for the care of ESLD patients.

Methods: Four patients with ESLD who were listed for liver transplantation presented with severe hyperbilirubinemia. In each patient, unexpectedly high Phosphorus (PO4) levels triggered the use of PO4 binders. Suspicion for an incorrect diagnosis arose because the degree of hyperphosphatemia did not correlate with either the degree of kidney dysfunction or oral intake of PO4. Intact PTH levels were unremarkable & hemolysis was ruled out. Samples were re-analyzed using our Beckman Liquichem and Dxc analyzers, they were sent out and analyzed on a Roche Integra analyzer as well. We found that the original measurements of PO4 were falsely elevated.

Results: The initial mean serum PO4 level was 7.9 mg/dl (SD = ±2.31) when assayed using the Beckman analyzers. Results on the Roche Integra analyzer revealed a mean PO4 level of 3.9 mg/dl (SD = ±0.43). Mean PTH and Calcium levels were 50 pg/ml and 9mg/dl respectively. Mean Total Bilirubin level was 23.7 mg/dl (SD = ±3.19).

Conclusions: Hyperphosphatemia should be carefully evaluated in ESLD patients with severe hyperbilirubinemia. Analyzers that use time-dependent photometric methods to measure serum PO4 can be affected by high bilirubin levels. In contrast, analyzers that use end-point photometric method remain accurate even in the face of high bilirubin because the blank sample allows for interference correction.

TH-PO771

The Etiology of Low Bone Mineral Density in Hypercalciuric Children

Maria Goretti M. G. Penido,1 Marcelo S. Tavares,1 Uri S. Alon.1,2 Pediatric Nephrology Unit, Dept of Pediatrics, Federal Univ of Minas Gerais, Belo Horizonte, MG, Brazil; 1Bone and Mineral Disorders Clinic, Pediatric Nephrology, The Children’s Mercy Hospital, Kansas City, MO.

Background: Some children with idiopathic hypercalciuria (IH) develop bone mass reduction but the reason for the decreased bone mineral density (BMD) remains unidentified. The aim of this study was to look for the etiology of bone mass reduction in children with IH comparing them to a control group of normal children (C).

Methods: We evaluated the data of 88 children (50 males) with IH aged 2.2–17.8 years (median 9.4); and 29 controls (13 males) aged 4.0–16.3 years (median 9.8). 24h urine collections were analyzed for volume, creatinine, calcium, oxalate, phosphate, citrate, pyrophosphate, magnesium, hydroxyproline. Urine N-teleopeptides (NTX) and PTH were assayed on a fasting random sample. Simultaneous blood samples were tested for creatinine, electrolytes, calcium, phosphorus, alkaline phosphatase, magnesium, PTH, osteocalcin, blood gases. Bone densitometry was performed by DXA using a Lunar DPX-IQ 2516 device. We use the Kruskal-Wallis and Dunn’s multiple comparison tests to compare the groups.

Results: There were no differences in age, BMI Z-scores and gender between the two groups. Lumbar spine (L1-L4) BMC, BMC corrected for height and for width of the vertebrae, area BMC, volumetric BMC and Z-score BMD were significantly lower in IH. Serum phosphorus and alkaline phosphatase, and urinary calcium and NTX were significantly higher in the IH group, whereas their serum PTH, urinary volume and citrate were significantly lower compared with C.

Conclusions: The calcium associated with decreased BMD in IH children seems to be due to increased bone resorption, independent of PTH. Further studies should investigate the possible association of increased bone resorption with citraturia and other factors like 1,25(OH) vitamin D and nutrition.

TH-PO772

Decreased Bone Mineral Density in Hypercalciuric Children Is Not Related to the Presence of Urolithiasis

Maria Goretti M.G. Penido,1 Marcelo S. Tavares,1 Uri S. Alon.1 1Pediatric Nephrology Unit, Dept of Pediatrics, Federal Univ of Minas Gerais, Belo Horizonte, MG, Brazil; 1Bone and Mineral Disorders Clinic, Pediatric Nephrology, The Children’s Mercy Hospital, Kansas City, MO.

Background: The association between idiopathic hypercalciuria (IH) and decreased bone mineral density (BMD) has been described in adults and children. The risk for low bone density in hypercalciuric children with urolithiasis has yet been well defined. The aim of this study was to explore if hypercalciuric children with urolithiasis are at higher risk for low BMD compared to those without stones.

Methods: We evaluated the data of 68 children with IH. They were divided to group 1 (G1) consisted of 49 children with urolithiasis (SWM) aged 9.6±3.8 years, and group 2 (G2) consisted of 39 without urolithiasis (21M) aged 7.5±2.4 years. Group 3 (G3) was a control group composed of 29 children (15M) aged 10.3±3.8 years. 24h urine collections were analyzed for volume, creatinine, calcium, citrate, phosphate, oxalate, magnesium, cysteine, hydroxyproline. N-telopeptide and PTH were analyzed in a fasting urine sample. Venous blood samples were analyzed for creatinine, electrolytes, calcium, phosphorus, alkaline phosphatase, uric acid, magnesium, PTH, osteocalcin, blood gases and bicarbonate. Bone densitometry was performed by DXA using a Lunar DPX-IQ 2516 device. We use the Kruskal-Wallis and Dunn’s multiple comparison tests to compare the groups.

Results: There were no differences in age, gender, BMI Z-scores, biochemical and mineral parameters between G1, G2 and G3. The 24h urine volume was higher in G2 when compared to G1 (p < 0.001) while urine oxalate was lower (p < 0.01). There were no differences in areal BMD and BMD Z-score of the lumbar spine (L1-L4) between G1 and G2, but values in G3 were higher than in both G1 and G2 (p < 0.001).

Conclusions: The analysis of hypercalciuric children with and without urolithiasis did not show any difference regarding their lower BMD Z-score of the lumbar spine. The only observed difference between patients’ subgroups was a higher urinary level of oxalate and lower urine volume, both contributing to stone formation without an effect on bone metabolism.

TH-PO773

Increased Arterial Stiffness and Osteopenia in Calcium Nephrolithiasis: A Dangerous Cardiovascular Risk Liaison

Antonia Fabris,1 Antonio Lupo,1 Chiara Caletti,2 Pietro Manuel Ferraro,2 Gabriele Comellato,2 Giovanni Gambardella.1 Nephrol, Univ of Verona, Verona, Italy; 1Nephrology, Cathol Univ, Rome, Italy; 2Geriatrics, Univ of Verona, Verona, Italy.

Background: Recent studies have described high incidence of cardiovascular (CV) disease in children nephrolithiasis (N). The mechanism of hypertension in N is not known since a role of obesity, hypertension, diabetes, goats has been ruled out. An inverse relationship between bone density and arterial stiffness (AS) has been reported in osteoporosis and CKD. CNL is often associated with metabolic bone disease (BMD). AS is an independent predictor of CV mortality. We hypothesized that CNL because of the coexistent BMD have abnormal AS and hence increased CV risk. We analyzed AS and BMD in CNL pts and in healthy controls.

Methods: 128 recurrent CNL pts and 39 controls. Exclusion criteria were: hypertension, chronic inflammatory diseases, intestinal and metabolic diseases, diabetes, primary hyperparathyroidism, smoking or menopause since >18 months. Biochemical tests, total body bone densitometry and pulse wave velocity (PWV) (Complior and Augmentation Index) were evaluated. Statistical analysis: Wilcoxon rank sum test.

Results: Both carotid-carotid and carotid-femoral PWVs were higher in CNL than in controls. In multivariate analysis BMD is an independent predictor of both PWVs being responsible for 70% of the variability.

Conclusions: These results show the existence of an association between BMD and functional modification of the elastic arteries in CNL independent of the common CV risk factors. This observation may explain the increased CV risk observed in stone formers.

TH-PO774

Nephrolithiasis and Risk of Incidence Bone Fracture

Eric N. Taylor,1,2 Gary C. Curhan.1 Div of Nephrology and Transplantation, Maine Medical Center, Portland, ME; 1Channing Div of Network Medicine, Brigham and Women’s Hospital, Boston, MA; 2Renal Div, Brigham and Women’s Hospital, Boston, MA.

Background: Higher urine calcium is a central feature of calcium nephrolithiasis and is associated with lower bone mineral density in individuals with kidney stones (KS). Previous reports, albeit small and unadjusted for dietary intakes, suggest that individuals with KS may have higher risk of bone fracture.

Methods: We prospectively examined independent associations between a history of KS and incident fracture in the Nurses’ Health Study I (N= 77,055 women: 30 years of follow-up) and the Health Professionals Follow-up Study (N=50,982 men; 24 years of follow-up). We excluded pre-menopausal women, men < 45 years old, and individuals who reported osteoporosis at baseline. Medical record review confirmed > 95% of self-reported KS in each cohort, and the majority of stones (> 77%) were predominately calcium oxalate. We included only cases of incident wrist (distal radius) or incident hip (proximal femur) fractures due to low or moderate trauma. Validated food frequency questionnaires were used to assess dietary intake every four years. Cox proportional hazards regression was used to adjust for age, BMI, thiazide use, supplemental calcium, dietary intake, and other factors. Cox proportional hazards regression was more likely to use a thiazide diuretic than participants without KS. During follow-up there were 3741 wrist and 1160 hip fractures in women and 859 wrist and 634 hip fractures in men. The multivariable relative risk of incident wrist fracture in participants with KS was 0.99 (95% CI 0.75 to 1.29) in women and 0.98 (95% CI 0.77 to 1.24) in men. The multivariable relative risk of incident hip fracture in participants with KS was 0.99 (95% CI 1.17 to 1.57) in women and 1.22 (95% CI 1.00 to 1.48) in men. The multivariable relative risk of incident hip fracture in participants with KS was 0.99 (95% CI 1.17 to 1.57) in women and 1.22 (95% CI 1.00 to 1.48) in men.
Conclusions: Nephrolithiasis is associated with a significantly higher risk of incident wrist but not hip fracture. Our study is limited by a relatively low number of hip fractures in participants with KS.

Funding: NIDDK Support

TH-PO775

Decreased Renal Clearance of Uric Acid Is Present in First Time Female Kidney Stone Formers

Hemamalini Ketha, John C. Lieske, Eric J. Bergstrahl, Xujuan Li, Rajiv Kumar, Andrew D. Rule. *Dept of Medicine, Mayo Clinic, Rochester, MN.*

Background: Elevated serum uric acid (UA) occurs in Ca stone formers (SF), but the mechanism has not been elucidated. We investigated whether serum UA levels in SF differ by gender and are impacted by UA clearance.

Methods: Serum UA and urinary pH, UA, and the fractional excretion of UA were measured in a sample of first time SF (females (F) = 142, males (M) = 121) and in age-matched controls (C) (F = 151, M = 166) from the general population.

Results: In F (mean age 43.5 years), serum UA and FEUA were higher and urinary pH was lower in SF compared to C (Table 1). Despite the lower urine pH, SF had lower urinary sulfate compared to controls (13.2 vs 18.7 mmol/24 h, p=0.004), suggesting lower protein intake. Urine volume and sodium were similar in F SF vs C. In M (mean age 48.2 years), serum uric acid, %FEUA, pH, and urinary sulfate did not differ between SF and C.

Conclusions: Higher serum UA levels among first time SF were only evident in F. Unlike controls, F SF have altered UA metabolism compared to M SF. The higher serum UA in female SF cannot be attributed to increased protein intake as urinary sulfate excretion is lower in SF vs C. Instead, an increase in the reabsorption of UA from tubular fluid, or failure in the excretion of UA into tubular fluid, accounts for the increase in serum UA.

Table 1. Serum and urinary parameters in F and M, SF and C.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F</th>
<th>M</th>
<th>C</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum uric acid, mg/dl</td>
<td>7.9 ± 1.2</td>
<td>6.8 ± 1.2</td>
<td>6.6 ± 1.3</td>
<td>0.0000</td>
</tr>
<tr>
<td>FEUA (%)</td>
<td>2.0 ± 0.7</td>
<td>1.3 ± 0.4</td>
<td>6.6 ± 1.3</td>
<td>0.0000</td>
</tr>
<tr>
<td>pH</td>
<td>5.4 ± 0.9</td>
<td>5.3 ± 0.9</td>
<td>5.4 ± 1.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Urine Volume, mL/24h</td>
<td>2.4 ± 0.6</td>
<td>2.1 ± 0.5</td>
<td>2.1 ± 0.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Urine Na, mmol/24h</td>
<td>170 ± 90</td>
<td>176 ± 95</td>
<td>174 ± 94</td>
<td>0.06</td>
</tr>
<tr>
<td>Urinary sulfate, mmol/24h</td>
<td>50.0 ± 23.3</td>
<td>57.0 ± 15.9</td>
<td>57.0 ± 15.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Funding: NIDDK Support, Other NIH Support - Arthritis and Musculoskeletal Diseases, Private Foundation Support

TH-PO776

The Anti-Phosphaturic Effect of 1,25(OH)2D Is Impaired in Nephrolithiasis

Hemamalini Ketha, Ravinder Singh, Stefan Grebe, Eric J. Bergstrahl, Xujuan Li, Andrew D. Rule, John C. Lieske, Rajiv Kumar. Mayo Clinic, Rochester, MN.

Background: Phosphate homeostasis is regulated by parathyroid hormone (PTH) and 1,25(OH)D. Previous studies have shown an increased renal clearance of phosphate in kidney stone formers (SF) with normal serum PTH levels.

Objectives: 1. To investigate whether renal phosphate (Pi) clearance is impaired at first time kidney SF. 2. To determine the relationship between the renal fractional excretion of Pi (FEPi), serum 1,25(OH)D and PTH.

Methods: Serum 1,25(OH)D (measured by mass spectrometry), intact PTH, Pi and urinary chemistries were measured in a sample of first time SF (females (F) = 142, males (M) = 121) and in age-matched controls (C) (F = 151, M = 166) from the general population. SF were measured in a sample of first time female rKSF and 317 controls (C) sampled from the general population.

Results: SF compared to C showed significantly higher FEPi (mean 16.0% vs 14.9% P = 0.04), higher 1,25(OH)D (43 vs 39 pg/ml, P = 0.003) and similar PTH (42.2 vs 39.5 pg/ml, P = 0.21). No association between FEPi% and PTH was observed in SF or C.

Conclusions: The anti-phosphaturic response of the kidney to circulating concentrations of 1,25(OH)D is impaired in SF compared to C. The results suggest a systemic alteration in vitamin D and Pi metabolism common to many first time SF in the community.

Funding: NIDDK Support, Other NIH Support - Arthritis and Musculoskeletal Support

TH-PO777

Evidence for Altered Responsiveness of the Vitamin D Endocrine System to Endogenous Circulating Parathyroid Hormone in Kidney Stone Formers

Hemamalini Ketha, Ravinder Singh, Stefan Grebe, Eric J. Bergstrahl, Xujuan Li, Andrew D. Rule, John C. Lieske, Rajiv Kumar. Mayo Clinic, Rochester, MN.

Background: Elevated 1,25(OH)D concentrations have been reported in some kidney stone formers (SF). Additionally, reduced 24,25(OH)2D concentrations have been associated with elevated 1,25(OH)D and hypercalciuria in some patients with nephrolithiasis.

Objective: To investigate the associations between serum 1,25(OH)D, 24,25(OH)2D and PTH concentrations in a cohort of first time adult SF compared to controls (C).

Methods: Serum 1,25(OH)D and 24,25(OH)D were measured by mass spectrometry in SF (N = 263) and C (N = 317). Serum full-length parathyroid hormone (PTH), calcium (Ca) and inorganic phosphorus (P), and urinary chemistries and supersaturations were measured in the same subjects. Logistic regression was performed to determine if serum vitamin D metabolites, PTH, Ca and P, and urine analytes and supersaturations (SS) differed in SF versus C.

Results: In multivariate analysis adjusting for age and gender, mean serum 1,25(OH)D concentrations were significantly higher in the SF versus C (43.40 vs 39.22 pg/ml, P = 0.0001). Mean serum 24,25(OH)D was similar between the two groups (29.2 vs 3.16 ng/ml, P = 0.175). Serum PTH concentrations were also similar in the two groups (42.16 vs 39.63 pg/ml, P = 0.053). A higher concentration of 1,25(OH)D (P = 0.009), and a lower concentration of 24,25(OH)D (P = 0.055), was observed at any concentration of PTH in SF versus C. Changes in vitamin D metabolites and PTH did not correlate with serum or urinary minerals or SS.

Conclusions: Elevated 1,25(OH)D concentrations were present in a large group of first time SF. Serum 24,25(OH)D concentrations were similar in the two groups. A higher concentration of 1,25(OH)D and a lower concentration of 24,25(OH)D was noted for any level of PTH in SF versus C, suggesting altered responsiveness of the vitamin D endocrine system to circulating PTH.

Funding: NIDDK Support, Other NIH Support - Falk Foundation, Private Foundation Support

TH-PO778

Sclerostin Is Associated with Age, Weight, BMI and Ionized Calcium Levels in Recurrent Kidney Stone Formers

Nilufar Meheeb,1 Daniel Rodriguez Gutierrez,1 Rudolf P. Wuthrich,1 Carsten A. Wagner,2 1Div of Nephrology, Univ Hospital of Zurich, Zurich, Switzerland; 2Institute of Physiology, Univ of Zurich, Zurich, Switzerland.

Background: Kidney stones are common in industrialized countries. Calcium containing stones are the most frequent stone type. Many factors predispose or contribute to the development of kidney stones, including genetic background, diet, and metabolic factors. Sclerostin is secreted by osteocytes and inhibits bone formation at the level of osteoblasts. In humans, Sclerostin mRNA is expressed in several tissues, with high levels in the kidney whereas Sclerostin protein is restricted to osteocytes. The effect of sclerostin on bone formation may not be unique. A potential role in other diseases where bone homeostasis may be disarranged such as nephrolithiasis may be very likely.

Methods: We performed a cross-sectional observational study in 96 male and female recurrent kidney stone formers (rKSF) to analyze the potential role of sclerostin.

Results: 66 of the patients were male and mean age of all patients averaged to 45±13 years. Mean serum creatinine, phosphate, total calcium levels and venous bicarbonate were 1.6 mmol/l, 0.95±0.01 mmol/l, 32.41±0.01, and 27.02±0.02 mmol/l, respectively. Mean 25-OH-Vitamin D levels were 57.1±2.2 ng/ml and PTH levels averaged to 48.2±7.6 pg/ml. Consistent with data in healthy adults, sclerostin levels were significantly higher in male than in female rKSF (82.1±14.7 vs. 67.3±12.3 pmol/l, P=0.0001). Similar to healthy adults,
we also found a positive correlation between sclerostin and age, weight, and BMI (p<0.05). Additionally, sclerostin was negatively correlated with ionized calcium. Hypercalcemia (>6.2 mmol/l) or hyperphosphaturia (>22.6 mmol/24h) were not correlated with sclerostin levels (50.8±14.2 pmol/l, p=0.0072) when compared to patients with calcium oxalate stones.

**Conclusions:** In recurrent kidney stone formers, sclerostin serum levels are positively correlated with age, weight, BMI, and negatively correlated with ionized calcium. Future studies are required to clarify the role of sclerostin in this population.

**TH-PO779**

Greater Loss of Bone Mineral Density with Exogenous 1,25(OH)2D3 in Calcium Oxalate Crystals Induced Changes in Secretion of Proteins from Basolateral Compartment of Renal Tubular Cells That, in Turn, Enhanced Crystal Invasion. Visith Thompoonkoon, Wararat Chiangjiong, Siriraj Hospital, Mahidol Univ, Bangkok, Thailand.

**Background:** Calcium oxalate monohydrate (COM) crystals cause kidney stone disease by unclear mechanisms. One of hypotheses was that COM crystals induce changes in various cellular mechanisms, leading to enhancement of crystal invasion into renal interstitium. The present study thus aimed to characterize changes in secretion of proteins from basolateral compartment of renal tubular epithelial cells after exposure to COM crystals and then examined functional significance of these changes in association with the stone pathogenesis.

**Methods:** Polarized MDCK cells were cultivated in Transwell containing serum-free medium with or without 100 μg/ml COM crystals for 24 h. Secreted proteins in culture medium from the lower chamber (basolateral compartment) were then collected, desalted by dialysis against distilled water, and finally concentrated by lophophorization. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain. The recovered proteins from five individual cultures in each group with equal amount were resolved in individual 2-D gels and visualized by Deep Purple stain.

**Results:** In GHS rats, exogenous 1,25D led to loss of BMD due to a mineralization defect, which contributes to increased hypercalcemia and should decrease bone strength. The enhanced effect of 1,25D in GHS indicates that the increased number and histomorphometry. We therefore examined whether intestinal oxalate transport is subject to regulation by one or more of these degradation products.

**Results:** To this end, we measured 14C-oxalate uptake in the presence of an outward Cl gradient as an assay of Cl-oxalate exchange activity, ≥ 50% of which is mediated by ATP-binding cassette (ABC) transporters. We found that ADP, AMP, and adenine significantly inhibited oxalate transport by C2 cells, by > 26%, 27%, and 31%, respectively. The inhibitory effects of adenine were partially and significantly blocked by pretreatment with the PKC inhibitor Gö6983 (by >50%) and the PLC inhibitor U73122 (by >80%). The nonselective P2-salpophilic/thesorphyl ine: 8-SPT) adenine receptor antagonist partially and significantly blocked (by > 40%) adenine-induced inhibition of oxalate transport by C2 cells. Using selective pharmacological inhibitors, we found that ERK1/2, PKA, and Src kinases are not involved in the observed adenine-mediated suppression of oxalate transport by C2 cells. These findings are of potential importance because intestinal cells are known to be exposed to adenine, ADP, and AMP under physiological, as well as pathological (e.g. IBD and therefore might have potential relevance to the IBD-associated hyperoxaluria) conditions.

**Conclusions:** We conclude that adenine signaling inhibits oxalate transport by C2 cells through signaling pathways that likely include PKC, PLC, and one or more of the known adenine receptors. ADP and AMP also significantly inhibit oxalate transport by C2 cells.

**Funding:** NIDDK Support

**TH-PO782**


**Background:** 80% of kidney stones are composed of calcium oxalate, and minor changes in urine oxalate affect the stone risk. The mammalian intestine plays a crucial role in oxalate homeostasis. Intestinal oxalate absorption is largely passive and paracellular, while anion exchanger SLC26A6 (A6) plays a critical role in active intestinal oxalate secretion. Proinflammatory cytokines (PCs) disrupt intestinal barrier function and increase paracellular flux, as well as inhibit several intestinal transporters. We therefore initiated studies to test the hypothesis that PCs could enhance intestinal oxalate absorption and/or reduce intestinal oxalate secretion.

**Results:** The PCs IFN-γ [IFN] and TNF-α [TNF] caused > 3-fold increase in macosol 14C-oxalate & H-mannitol (a paracellular marker) absorptive fluxes in human intestinal Caco2-BBE (C2) cells grown on snapwell inserts and mounted in Ussing chambers (UCs). The PC-induced increased absorptive fluxes were completely blocked by pretreatment with AMP-18 and GLP-2, peptides known to improve intestinal barrier function. Importantly, pretreatment of BALB/c mice with TNF before isolating and mounting jejunal segments in UCs led to > 1.9-fold increase in 14C-oxalate & H-mannitol absorptive fluxes, effects completely blocked by pretreatment with AMP-18 and GLP-2. IFN and TNF also significantly inhibited (by 30-40%) apical 14C-oxalate uptake, measured as Cl-oxalate exchange, by C2 cells through mechanisms involving reduced A6 mRNA/protein expression. Therefore, PCs increase intestinal oxalate absorptive marker expression, which is higher local and systemic PC's levels, respectively, are seen. The PCs significantly enhance intestinal oxalate absorption and that AMP-18 and GLP-2 have therapeutic potential in this process. PCs also significantly reduce oxalate transport by C2 cells, by lowering A6 mRNA/protein expression. Since C2 cells closely resemble the native epithelium, such regulation would likely lead to reduced intestinal oxalate secretion in vivo.

**Funding:** Private Foundation Support

**TH-PO783**

Lithogenic Factors and Inflammatory Bowel Disease: Importance of Disease Severity. Cristina Beato Henriques Outerelo,1 Fernando Teixeira e Costa,1 Pedro Figueiredo,2 Joao Freitas,3 Aura Ramos.1  Nephrology, Hospital Garcia Orta, Almada; 2Gastroenterology, Hospital Garcia Orta, Almada.

**Background:** Lithogenic factors are prevalent in patients with inflammatory bowel disease (IBD). Their correlation with the severity of the underlying bowel disease is not yet established. The aim of this study was to evaluate weather the prevalence of known lithogenic factors is related to IBD severity.

**Methods:** Single centre prospective study of eighty-seven consecutive outpatients with IBD. Clinical data was obtained through questionnaire and file consultation; nephrolithiasis

**Funding:** Government Support - Non-U.S.
Consecutive CT Scan Monitoring of Total Stone Volume Is More Useful in Patients Who Are Having Interim Symptomatic Stone Events

Michael G. Selby,1 Terri J. Vrtiska,2 John C. Lieske,1 Amy E. Krambeck,3 Eric J. Bergstrahl,4 Andrew D. Rule.1 1Nephrology, Mayo Clinic, Rochester, MN; 2Radiology, Mayo Clinic, Rochester, MN; 3Urology, Mayo Clinic, Rochester, MN; 4Statistics, Mayo Clinic, Rochester, MN.

Background: The goal of this study was to determine whether the change in kidney stone volume between two renal computed tomographic (CT) scans was predictive of future symptomatic stone events.

Methods: A mailed survey was completed in 2012 by stone formers who had undergone evaluation at the Mayo Clinic that included two renal CT scans between 2005 and 2012 to evaluate their stone disease while asymptomatic. Rare stone types (cystine) were excluded. Both CT scans were reviewed to determine total stone volume using an automated algorithm. The survey and electronic medical record identified any symptomatic stone events between or after the two CT scan dates.

Results: The survey was completed by 239 stone formers (62% male, mean age 57 y) with two renal CT scans a median 1.1 years apart. An interim event occurred in 21% and 36% had a symptomatic stone event a mean 3.2 years after their second CT scan. Total stone volume increased a median 17 mm3/year with 10% having a rapid increase in stone volume (>560 mm3/year). The risk of symptomatic stone recurrence was increased in patients with a rapid increase in stone volume who also had an interim stone event (n=50, HR=3.1, p=0.03) but not in those without an interim stone event (n=189, HR=0.49, p=0.26).

Conclusions: There appears to be a higher risk of symptomatic events in stone formers who have a rapid increase in total stone volume between annual renal CT scans despite passing stones between scans. Annual renal CT scans may not be as helpful in stone formers who are not passing stones.

Funding: NIDDK Support

Dietary Acid Load and Risk of Incident Kidney Stones

Ernest I. Mandel,1,2 Eric N. Taylor,2,3 Gary C. Curhan.1 1Div of Nephrology and Transplantation, Maine Medical Center, Portland, ME; 2Division of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; 3Channing Div of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA.

Background: Higher dietary acid load may reduce urinary citrate excretion, which is associated with an increased risk of kidney stone formation. However, the association between dietary acid load and risk of incident kidney stones has not been explored in population-based studies of individuals.

Methods: We prospectively examined the association between dietary acid load, using the diet-estimated net endogenous acid production (NEAP) and potential renal acid load (PRAL), and the risk of incident kidney stones in the Health Professionals Follow-up Study (n=44,581 men; 24 years of follow-up), Nurses’ Health Study (n=73,154 older women; 26 years of follow-up), and Nurses’ Health Study II (n=91,509 younger women; 16 years of follow-up). We used Cox proportional hazards regression to generate hazard ratios (HRs) adjusted for age, race, BMI, dietary, lifestyle, and medical factors.

Results: We identified a combined total of 6361 incident cases of kidney stones during 4,411,939 person-years of follow-up. After adjusting for potential confounders, the multivariable HRs (95% confidence interval (CI)) for kidney stone formation for individuals in the highest quintile of diet-estimated NEAP compared to those in the lowest quintile were 1.59 (1.20 to 2.10; p for trend=0.002) for men, 1.48 (1.11 to 1.99; p for trend=0.005) for older women, and 1.53 (1.18 to 1.98; p for trend=0.007) for younger women. After adjusting for potential confounders, the multivariable HRs (95% CI) for kidney stone formation for individuals in the highest quintile of diet-estimated PRAL compared to those in the lowest quintile were 1.54 (1.19 to 1.98; p for trend=0.003) for men, 1.08 (0.84 to 1.40; p for trend=0.49) for older women, and 1.30 (1.04 to 1.62; p for trend=0.04) for younger women.

Conclusions: Higher dietary acid load, especially as measured by diet-estimated NEAP, is independently associated with a higher risk of kidney stone formation.

Funding: NIDDK Support, Private Foundation Support
Lime Powder Regimen Is a Novel Alternative for Medical Treatment of Nephrolithiasis Piriyaratana Tosukhowong,1 Chanchai Boonla,2 Thasinas Dissayabutra,1 Kriang Tungsaeng-A.,2 Biochemistry, Chulalongkorn Univ, Pathumwan, Bangkok, Thailand; 2Medicine, Chulalongkorn Univ; Pathumwan, Bangkok, Thailand.

Background: Lime powder regimen (LPR) is a lime-based regimen containing active pharmaceutical components of 21 mEq potassium and 63 mEq citrate. Our preclinical and phase 1 studies showed LPR was a safe regimen for daily consumption and delivered the citraturic, urinary alkalinizing and antioxidative effects in nephrolithiasis patients. These medicinal effects potentially reduce the propensity of kidney stone recurrence. Therefore, the phase 3 clinical trial needs to be further conducted to actually evaluate the efficacy of LPR treatment for reducing the recurrence rate.

Funding: Government Support - Non-U.S.

Trend of Incident and Prevalent Kidney Stone Disease in a Large Health Care Organization 1997-2007 [Image] Ng Tan1,2, Angela Kenniston,3 John R. Holmen,3 Michel Chonchol1, 1Medicine, Denver Health Medical Center, Denver, CO; 1Intermountain Health Care, Murray, UT; 2Medicine, Univ of Colorado, Denver, CO.

Background: Recent epidemiological trend of kidney stone (KS) disease is unclear. We aim to determine the KS incidence and prevalence trends through time in an integrated healthcare system serving a defined geographical region.

Methods: Incident and prevalent kidney stone (IKS & PKS) rates were obtained using Intermountain Healthcare (IHC) Data Warehouse. IHC is a healthcare organization serving 2.4 million Utah and Idaho residents. IKS formers were defined as patients having first diagnosis of KS disease and were identified by ICD9 codes 592 & 594.0 assigned from 1997 to 2007. PKS formers were defined as patients having prior ICD9 codes 592, 594.0 or V13.01. Negative binomial regression analyses were used to examine the incidence and prevalence trends.

Results: 53,045 IKS formers and 342,150 PKS formers were identified. Adjusted for age, gender, race and imaging use, there were no significant changes in KS incidence rates from 1997 (1.45%) to 2007 (1.49%), p<0.02. However, the adjusted KS prevalence rates increased significantly from 1997 (1.45%) to 2007 (4.9%), p<0.0001. For men, age, race and imaging use adjusted incidence rates did not change significantly from 1997 (0.67%) to 2007 (0.63%), p>0.9, but the adjusted prevalence rates increased significantly from 1997 (1.98%) to 2007 (6.15%), p<0.0001. For women, the adjusted incidence rates did not change significantly from 1997 (0.35%) to 2007 (0.44%), p<0.3, but the adjusted prevalence rates increased significantly from 1997 (1.04%) to 2007 (3.93%), p<0.0001. Age, gender and imaging use adjusted incidence rates did not change significantly in any of the race categories from 1997 to 2007. However, the adjusted prevalence rates increased significantly in all race categories (p<0.0001) except in African Americans (p=0.06) from the same time period.

Conclusions: Even though IKS rates did not change from 1997 to 2007, the PKS rates increased significantly. The causes of these findings remain to be determined.

Funding: NIDDK Support

Adenine Phosphoribosyltransferase Deficiency: Two Novel Genetic Mutations and United Kingdom Experience Gowrie Balasubramanian,1 Monica Arenas Hernandez,2 Lynette D. Fairbanks,3 Anthony Marinaki,2 Emilia Escudero Polo,2 Sarah Mapplebeck,3 Michael K. Almond.1 1Southend Univ Hospital, Southend, Essex, United Kingdom; 2Purine Research Laboratory, Guy’s and St. Thomas’ NHS Trust, London, United Kingdom.

Background: Adenine phosphoribosyltransferase (APRT) deficiency causes 2,8-dihydroxyadenine (2,8-DHA) crystals and renal failure. We present three cases with two novel mutations from a single centre. UK data of APRT is limited; we undertook a cross-sectional survey of patients identified at the Purine Research Laboratory.

Methods: An 18-year-old man presented with a history of recurrent nephrolithiasis. 2,8-DHA stones were identified by UV spectrophotometry. 11 years after his initial symptoms, he re-presented with chronic kidney disease stage (CKD) 4. His younger brother presented with loin pain and acute renal injury. Renal biopsy showed an acute tubulointerstitial nephritis with crystalline deposits. A 44-year man with a history diabetes and hypertension presented with an acute on chronic kidney injury. Renal biopsy showed minimal diabetic features but chronic tubulointerstitial nephritis with crystalline deposits. We sent questionnaires to obtain clinical information of the identified cases between 1979-2013.

Results: All three cases had 2,8-dihydroxyadenine in urine and complete APRT deficiency. Genetic studies identified a homoygous novel mutation in the APRT gene from Case 1 and 2; APRTc.543 A>T, p.181X>C, and case 3 APRT:380a-g, p.127D>G. We identified only 17 patients (12 M) from 14 families. Mean age at diagnosis was 26 (range 13-57). The median follow up was 7.0 (range 2-40) years.

Conclusions: APRT deficiency is a rare disease with varied presentation that is currently underdiagnosed in the UK. Stone analysis and family screening are important ways to identify cases. Diagnosis should be sought if unexplained crystalline deposits are found on renal biopsy. It is easily treatable and a more concerted approach should be undertaken to diagnose patients in the UK.
Refractory Hypokalemia with Sustained Ventricular Tachycardia as the \textit{First} Sign of a Complex Process. We present a patient with refractory hypokalemia in the setting of metastatic disease.

\textbf{Methods:} An 84 year old female was repeatedly debrided by her AIFD. Serum potassium (K⁺) level was 1.9mg/dL and bicarbonate (HCO₃⁻) level 41mg/dL. Physical examination revealed blood pressure of 170/76 mmHg, obesity, and bilateral pitting edema. Her renal function markedly improved with correction of potassium (3.8meq/L) and creatinine was 2.1 mg/dL within 2 months of follow up.

\textbf{Conclusions:} We hypothesize that our patient had nephropathy from severe hypokalemia from the use of thiazides. Late-onset Gitelman’s syndrome is also a strong possibility, which might have clinically manifested following the use of hydrochlorothiazide. Our case not only highlights the importance of obtaining renal biopsy in patients with unexplained renal failure, but also emphasizes the need for monitoring electrolytes in patients on chronic diuretic therapy.

### TH-PO794

Metformin-Associated Lactic Acidosis in an Alcoholic with Fluorescent Urine

\textbf{Background:} Lactic acidosis is a rare but serious complication of metformin use. Patients with comorbidities such as renal insufficiency or liver disease may be at increased risk.

\textbf{Methods:} A 63 y.o. diabetic male with a history of alcoholism presented to the ED with abdominal pain. He was hypothermic (31°C) and lethargic but alert with otherwise stable vitals. Initial labs showed serum creatinine 2.64 (baseline 1.0mg/dL), glucose 29mg/dL, arterial pH 7.61, serum bicarbonate 2mEq/L, PaCO₂ 16.5mMg, lactate 28.5mmol/L, anion gap 45mmol/L, osmolar gap 20, AST/ALT/AlkPhos 396/140/133 U/L, PT 17.1 (11.6-14.2), Thb 0.4mg/dL, and MCV 109FL. The patient’s urine fluoresced brightly under ultraviolet light. Hemodialysis was initiated (only 1 treatment required, 6 hrs duration), and one dose of 4-methylpyrazole was administered. Serum levels of ethanol, toxic alcohols, salicylates, and acetaminophen were normal. Carnitine deficient transverse fracture and urine ethanol metabolites suggested recent heavy ethanol consumption. Serum metformin was 4.7 (therapeutic 1-2µg/mL). The patient’s labs normalized and he required no further hemodialysis. He was discharged on hospital day 6. Urine fluoresced for the remainder of his hospital stay, but not on follow-up.

\textbf{Conclusions:} This patient survived following prompt initiation of supportive care and hemodialysis. His alcoholism may have predisposed him to metformin-associated lactic acidosis through associated B vitamin deficiencies and liver dysfunction and increased NADH generation by alcohol dehydrogenase. His osmolar gap was likely secondary to AKI and lactic acidosis, and the etiology of his urine fluorescence is unknown. This case suggests that providers should consider alternatives to metformin in patients at risk for alcohol abuse, and highlights the non-specific nature of urine fluorescence.

\textbf{Disclosure:} The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense, or the United States government. *Funding: Other U.S. Government Support*
patient, was fasting overnight due to secondary surgery planned the following day. Other causes being excluded, a diagnosis of starvation-ketoadidas (SK) was made. Correction by NaCl [sup] and phosphate, a transient refedding syndrome dyslectrolyemia was corrected. Ketonuria instantly disappeared.

Methods: A 55 y/o male on gastroenterostomy tube feeding for previous complicated cholecystectomy, was brought to hospital with unsteady gait & shortness of breath. He had respiratory distress without hypoxemia, requiring mechanical ventilation. Lab data showed serum lactate level of 6.6 mmol/L but the lactate on ABG using auto analyzer showed value of 12.8 mmol/L. This suggest apparent lactate gap, seen in ethylene glycol overdose. The measured ethylene glycol level was 44mg/dl.

Conclusions: The metabolites of ethylene glycol, glycolic acid and glyoxylic acid can cross react with the analytical reagent L-lactate oxidase, used in many blood gas analyzers(1). Other methods using lactate dehydrogenase may not be affected by these metabolites(2). Thus finding a "lactate gap" using 2 different methods can help to differentiate ethylene glycol poisoning from other true lactacidosis. Interestingly, in the absence of potential ethylene glycol poisoning, the use of the lactate oxidase may be a simple method to "monitor" level of metabolites(3). Treatment with dialysis can be stopped, once the gap disappears. Knowledge of potent artifactual lactate results was the clue to the diagnosis of ethylene glycol poisoning in our case but the mode and motive of intoxication remained an enigma.


TH-PO799

Two Cases of Acute Renal Injury and Fatal Lactic Acidosis due to Germanium Ingestion as a Supplement 1Ikyo Narita, Michiko Shimada, Takeshi Fujita, Yuko Shimaya, Reichi Murakami, Noriko Nakamura, Hideaki Yamabe, Ken Okumura. Nephrology, Hiroshi Univ, Hiroshiki, Japan.

Background: Germanium supplements have been used as elixir. However, serious adverse effects have been rarely reported. Here, we describe 2 cases of fatal lactic acidosis occurred in a married couple.

Methods: Case 1: A 59-year-old female who had been suffering with erythematous rashes for 1 month and gastrointestinal symptoms for 2 weeks visited a clinic and laboratory studies revealed renal dysfunction. She was consulted to nephrology and admitted to our hospital. Her blood pressure was 78/50 mmHg, heart rate was 110/min and her conscious level was clear on admission. Laboratory data were as follows:WBC 5600/μl, HB 14.9g/dl, PT 6.0x10⁴/μl, BUN 27mg/dl, serum creatinine 2.5 mg/dl, AST 100 IU/L, ALT 102 IU/L, CK 646 IU/L, CRP 16.2 mg/dl. Blood gas analysis: pH 7.41, pO₂ 95mmHg, pCO₂ 18mmHg, HCO₃ 22mmol/l. She died on the 6th hospital day. She was admitted to the intensive care unit and continuous hemofiltration was initiated. Her general conditions were exacerbated due to low blood pressure, liver damage, renal failure, respiratory distress and disseminated intravascular coagulation. Lactic acidosis was progressively exacerbated and the data finally became pH 6.8 and lactate 22 mmol/l. She died on the 6th hospital day.

Case 2: A 65-year-old male who was the husband of case 1 was hospitalized 2 days after the admission of his wife due to the similar symptoms. His general conditions and lactic acidosis were similarly exacerbated and he died on the 8th hospital day. In both cases, intensive search for infection revealed no positive results. There was no evidence of illicit drug use. However, they had been taking supplements containing germanium for 10 years. Analysis of the hair and nail in both cases revealed very high germanium concentrations. The autopsy of case 1 revealed severe fatty degeneration of the liver and renal tubular epithelial cells. Pellagrous changes were seen in the brain.

Conclusions: The symptoms in these cases were compatible with the previous reports of germanium intoxication. These symptoms suggested profound mitochondrial dysfunction. Funding: NIDDK Support

TH-PO800


Background: High anion gap metabolic acidosis (HAGA) is a severe metabolic disorder with diverse causes including lactic acidosis, ketoadidas, metabolites from various toxic substances (methanol, glycols or paraldehyde) and renal failure. Accumulation of toxic substances (methanol, glycols or paraldehyde) and renal failure. Accumulation of 5-oxoproline (pyroglutamic acid) is another rare and underdiagnosed cause of HAGMA.

Methods: High anion gap metabolic acidosis (HAGA) is a severe metabolic disorder with diverse causes including lactic acidosis, ketoadidas, metabolites from various toxic substances (methanol, glycols or paraldehyde) and renal failure. Accumulation of 5-oxoproline (pyroglutamic acid) is another rare and underdiagnosed cause of HAGMA. Chronic acetaminophen ingestion causes depletion of glutathione in nalmournished patients (via glycine deficiency) leading to disruption of the gamma-glutamyl cycle with accumulation of 5-oxoproline.

Methods: A 55-year-old African American male with history of metastatic lung cancer, hypertension, diabetes mellitus, congestive heart failure, atrial fibrillation, and chronic pain presented with worsening dyspea. Home medications included acetaminophen/codeine and aspirin. Initial ABG showed a pH 7.32, pO₂ 82mmHg, pCO₂ 10mmHg/L. He was intubated and placed on mechanical ventilation. Electrolytes showed Na+ 143 K+ 4.2 Cl⁻ 108 HCO₃ 11 anion gapAg⁺ 24. BUN 12mg/dl, creatinine 0.85mg/dl, glucose 108mg/dl, serum osmolar gap 2; AST/ALT normal, and albumin 2.2g/dl. Salicylate 18mg/dl, lactate 2.0mmol/L. Serum acetone was positive initially and rapidly cleared with no improvement in HAGMA. Urine AG =92. Patient developed septic shock and oliguric acute kidney injury

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Yoshifumi Ubara, Keiichi Sumida, Junichi Hoshino, Tatsuya Suwabe.

Enamel erosions.

To have ventricular arrhythmias including Torsades de Pointes. On exam, blood pressure was 180/110 mmHg with tachycardia requiring cardioversion. Initial resuscitation included 2 liters of normal saline, and did not take medications. Within an hour of presentation, she developed ventricular tachycardia and was intubated.

Within 4 hours, metabolic alkalosis was diagnosed and she was resuscitated with furosemide 40 mg and hydrochloric acid (HCl). Preparation of infusion was made with 7.5 ml of 10% HCl in D5W infused at 50 cc/hr, providing a total of ~21 mEq of HCl.

We observed a rapid correction of alkalosis with normal saline and approximately 40 mEq of HCl. The patient was discharged on day 10 with normal SNa and no polysis.

The patient had persistent metabolic alkalosis with cardiac instability. Since her serum sodium had corrected by 9 mEq within 4 hours and she had been adequately volume resuscitated, we were hesitant to give normal saline and proceeded to treat with intravenous hydrochloric acid. Preparation of infusion was made with 7.5 ml of 10% HCl in D5W infused at 50 cc/hr, providing a total of ~21 mEq of HCl.

We observed a rapid correction of alkalosis with normal saline and approximately 40 mEq of HCl. The patient was discharged on day 10 with normal SNa and no polysis.

We present a bulimic patient with such alkalemia and our subsequent medical management.

Methods: The first patient was a 67-year-old woman who complained of severe bone pain involving her knees and ankles. She had a history of CHB, and had been treated with ADV for the past 53 months. Laboratory tests showed severe hyphosphatemia (serum P; 1.2 mg/dL) with proximal renal tubule dysfunction and elevation of serum ALP. In both cases, bone biopsy revealed osteomalacia. After discontinuation of ADV and phosphate supplementation, their symptoms resolved, laboratory abnormalities normalized and imaging studies showed improvement in both patients.

Conclusions: Despite large clinical trials advocating the safety of ADV at 10 mg daily, long-term use of this agent can be nephrotoxic and in rare cases, can cause renal Fanconi’s syndrome and severe hyphosphatemic osteomalacia. Clinicians should be aware of this infrequent but severe complication of low-dose ADV in CHB treatment.

Renal Fanconi’s Syndrome and Hypophosphatemic Osteomalacia Induced by Low-Dose Adefovir Dipivoxil Therapy for Hepatitis B

Rikako Hiramatsu, Yoshifumi Ubara, Keiichi Sumida, Junichi Hoshino, Tatsuya Suwabe.

Nephrology Center, Toranomon Hospital, Tokyo, Japan.

Background: Adefovir dipivoxil (ADV) at a daily dose of 10 mg is commonly used as an antiviral agent to treat chronic hepatitis B. The safety of a daily dose of 10 mg ADV is advocated by the registration trial. We present here two cases of renal Fanconi’s syndrome together with hypophosphatemic osteomalacia induced by low-dose ADV in chronic hepatitis B (CHB) patients.

Methods: The first patient was a 67-year-old woman who complained of severe bone pain involving her knees and ankles. She had a history of CHB, and had been treated with ADV for the past 53 months. Laboratory tests showed severe hyphosphatemia (serum P; 1.2 mg/dL) with proximal renal tubule dysfunction and elevation of serum ALP. In both cases, bone biopsy revealed osteomalacia. After discontinuation of ADV and phosphate supplementation, their symptoms resolved, laboratory abnormalities normalized and imaging studies showed improvement in both patients.

Conclusions: Despite large clinical trials advocating the safety of ADV at 10 mg daily, long-term use of this agent can be nephrotoxic and in rare cases, can cause renal Fanconi’s syndrome and severe hyphosphatemic osteomalacia. Clinicians should be aware of this infrequent but severe complication of low-dose ADV in CHB treatment.

Hydrochloric Acid to Treat Extreme Metabolic Alkalosis

Jose Jesus Perez, Rajeev Raghavan.

Nephrology, Baylor College of Medicine, Houston, TX.

Background: Anorexia-bulimia nervosa are eating disorders that are associated with electrolyte and acid-base disturbances. Extreme alkalosis with a pH greater than 7.65 has a high risk of mortality. We present a bulimic patient with such alkaloea and our subsequent medical management.

Methods: A 27-year-old female presented to the ER with complaints of nausea, vomiting, weakness, palpitations, and abdominal pain. She denied having an eating disorder, and did not take medications. Within an hour of presentation, she developed ventricular tachycardia requiring cardioversion. Initial resuscitation included 2 liters of normal saline, 2 grams magnesium sulfate, 4 grams calcium gluconate and 20 mEq of KCl. She continued to have ventricular arrhythmias including Torsades de Pointes. On exam, blood pressure was 96/50 mmHg, pulse rate 84 beats/min, respiratory rate 20 breaths/min, temperature 98.1°F, weight 90 lbs. The patient was thin, had poor skin turgor, dry mucous membranes, with enamination.

The second patient was a 65-year-old woman with CHB who complained of pain in several bilateral ribs and ankles. She had been treated with ADV for 56 months before occurrence of bone pain. She was also found to have hyphosphatemia (serum P; 1.2 mg/dL) with proximal renal tubule dysfunction and elevation of serum ALP. In both cases, bone biopsy revealed osteomalacia. After discontinuation of ADV and phosphate supplementation, their symptoms resolved, laboratory abnormalities normalized and imaging studies showed improvement in both patients.

Conclusions: Despite large clinical trials advocating the safety of ADV at 10 mg daily, long-term use of this agent can be nephrotoxic and in rare cases, can cause renal Fanconi’s syndrome and severe hyphosphatemic osteomalacia. Clinicians should be aware of this infrequent but severe complication of low-dose ADV in CHB treatment.

Vancomycin-Induced Nephrotoxicity: A Pitfall of Overestimating GFR for Drug Dosing by Using Serum Creatinine

Ekamol Tantisattamo, Jason Cobb, Taisin Masud. Renal Div, Emory Univ School of Medicine, Atlanta, GA.

Background: Widely used as a surrogate of overall renal function, serum creatinine (Scr) is one of the most practical markers of eGFR. We report a case of an atypicaly low serum creatinine with very low Scr presenting with vancomycin toxicity from an overestimation of eGFR.

Methods: Case Description: A 39-year-old Caucasian man with a history of ALS complicated with chronic respiratory failure and ventilator-dependence, was diagnosed with staphyloccocal bacteremia and treated with vancomycin, 1,500 mg every 12 hours. His baseline BUN and Scr was 3 mg/dL and ~0.3 mg/dL, respectively. Serum albumin was 2.4 g/dL. His weight was 81 kg and BMI was 24.95 kg/m2. Three days prior to admission, he had decreased urine output and lethargy. Scr was elevated to 2.98 mg/dL. Vancomycin level was supratherapeutic (~120 mg/mL) 10 days after vancomycin was started. Scr continued to rise up to 3.43 mg/dL and vancomycin level was persistently high. Four days later, he was oliguric and was started on hemodialysis for 3 days. Vancomycin level decreased to therapeutic level 6 days after initiation of hemodialysis and Scr returned to baseline.

Conclusions: eGFR is relatively accurate for most patients; however, it cannot be applied to our patient with muscular atrophy from underlying ALS. His lean body mass (LBM) decreases while total body fat increases, leading to artificially decreased Scr. As volume of distribution of relatively hydrophilic drugs such vancomycin correlates very well with LBM, estimated LBM in the patients losing muscle mass should be taken into account when initiating vancomycin. LBM which determines Scr level needs to be considered in estimating GFR when dosing medications. Creatinine clearance from 24-hour urine collection may be warranted. Close monitoring of renal function and vancomycin level is crucial for early detection of vancomycin toxicity. Moreover, as high level of remaining vancomycin in the setting of acute kidney injury can perpetuate the toxicity, low threshold of initiating hemodialysis should be considered to mitigate the toxicity.

Concomitant Polyuria and Hyponatremia in a Glucocorticoid Deficiency Patient with Transient Nephrogenic Diabetes Insipidus

Ekamol Tantisattamo, Frederic F. Rahbari-Oskoui, John Doran. Renal Div, Grady Memorial Hospital, Emory Univ, Atlanta.

Background: Hyponatremia and polyuria are classic manifestations of diabetes insipidus (DI). However, glucocorticoid can affect urinary dilution leading to hyponatremia. We report a man with corticosteroid deficiency presenting with symptomatic severe hyponatremia and transient partial nephrogenic DI.

Methods: Case description: A 27-year-old man with polysubstance addiction presented with seizures and was intubated. He took no medications. Serum sodium (SNa) was 109 mEq/L. His weight was 81 kg and BMI was 24.95 kg/m2. Three days prior to admission, he had decreased urine output and lethargy. Scr was elevated to 2.98 mg/dL. Vancomycin level was supratherapeutic (~120 mg/mL) 10 days after vancomycin was started. Scr continued to rise up to 3.43 mg/dL and vancomycin level was persistently high. Four days later, he was oliguric and was started on hemodialysis for 3 days. Vancomycin level decreased to therapeutic level 6 days after initiation of hemodialysis and Scr returned to baseline.

Conclusions: eGFR is relatively accurate for most patients; however, it cannot be applied to our patient with muscular atrophy from underlying ALS. His lean body mass (LBM) decreases while total body fat increases, leading to artificially decreased Scr. As volume of distribution of relatively hydrophilic drugs such vancomycin correlates very well with LBM, estimated LBM in the patients losing muscle mass should be taken into account when initiating vancomycin. LBM which determines Scr level needs to be considered in estimating GFR when dosing medications. Creatinine clearance from 24-hour urine collection may be warranted. Close monitoring of renal function and vancomycin level is crucial for early detection of vancomycin toxicity. Moreover, as high level of remaining vancomycin in the setting of acute kidney injury can perpetuate the toxicity, low threshold of initiating hemodialysis should be considered to mitigate the toxicity.
Conclusions: Concomitant DI and hyponatremia can occur in glucocorticoid deficiency impairing urinary dilution via an ADH-independent mechanism. Apart from DI, replacement the UOP with D5W led to osmotic diuresis and subsequently persistent polyuria. Glucocorticoid deficiency should be considered as one of the causes of hyponatremia in DI. IV fluid need to be cautiously replaced to avoid prolonged polyuria from iatrogenic hyperglycemia.

A Rare Complication of BCG Therapy

Kristin M. Corapi,1 Imran Sajjad,1 David B. Mount,2 Robert J. Hamburger.2

Background: We observed ARF 9 months after intravesical BCG adjuvant treatment for T1 bladder Transitional Cell Carcinoma (TCC). Mycobacterium bovis was identified by PCR on lung biopsy and tubulo-interstitial nephritis (TIN) was proved. He responded well to steroids and tuberculosatic tri-therapy. Prevention requires the eviction of risk factors and regular control of renal function (RF) during therapy.

Methods: A 76-year-old man presented ARF. TCC was treated by 10 adjuvant BCG intravesical instillations during one year. Laboratory revealed serum creatinine 699 μmol/L, ACE 140 μU/L. Hemodialysis was started. Chest CT confirmed a “ground glass” interstitial syndrome. A 10 IU PPD skin test was negative. Kidney biopsy showed TIN with eosinophilic infiltrate without granuloma. Lung biopsy demonstrated moderate lympho-metaplastic infiltration, few aspecific granulomatous lesions. Sarcoïdosis was suspected and oral methylprednisolone was started. Serum creatinine decreased to 220 μmol/L; hemodialysis was discontinued. On day 27, Mycobacterium bovis was identified on lung samples by PCR; tuberculostatic agents were initiated. Corticosteroids was gradually stopped.

Conclusions: Intravesical BCG is safely used as adjuvant treatment for bladder TCC despite flu-like syndrome in 20%. Dissemination occurs after traumatic bladder instillation and cumulative doses. Prophylactic Isoniazid doesn’t prevent BCG complications. Contraindications include recent bladder surgery or radiotherapy, polycystomy, active cystitis, tuberculous, immunosuppressive treatment. Medline system reported 12 associated and oral methylprednisolone was started. Serum creatinine decreased to 220 μmol/L; hemodialysis was discontinued. On day 27, Mycobacterium bovis was identified on lung samples by PCR; tuberculostatic agents were initiated. Corticosteroids was gradually stopped.

Prevention of Kidney-Lung Failure due to Intra-Bladder BCG Therapy

Uquenin Mat, Steffy Larroze, Rim Kada, Olivier Linc Mat. Nephrology - Dialysis, EpiCURA, Ath, Belgium.

Background: We observed ARF 9 months after intravesical BCG adjuvant treatment for T1 bladder Transitional Cell Carcinoma (TCC). Mycobacterium bovis was identified by PCR on lung biopsy and tubulo-interstitial nephritis (TIN) was proved. He responded well to steroids and tuberculosatic tri-therapy. Prevention requires the eviction of risk factors and regular control of renal function (RF) during therapy.

Methods: A 76-year-old man presented ARF. TCC was treated by 10 adjuvant BCG intravesical instillations during one year. Laboratory revealed serum creatinine 699 μmol/L, ACE 140 μU/L. Hemodialysis was started. Chest CT confirmed a “ground glass” interstitial syndrome. A 10 IU PPD skin test was negative. Kidney biopsy showed TIN with eosinophilic infiltrate without granuloma. Lung biopsy demonstrated moderate lympho-metaplastic infiltration, few aspecific granulomatous lesions. Sarcoïdosis was suspected and oral methylprednisolone was started. Serum creatinine decreased to 220 μmol/L; hemodialysis was discontinued. On day 27, Mycobacterium bovis was identified on lung samples by PCR; tuberculostatic agents were initiated. Corticosteroids was gradually stopped.

Conclusions: Intravesical BCG is safely used as adjuvant treatment for bladder TCC despite flu-like syndrome in 20%. Dissemination occurs after traumatic bladder instillation and cumulative doses. Prophylactic Isoniazid doesn’t prevent BCG complications. Contraindications include recent bladder surgery or radiotherapy, polycystomy, active cystitis, tuberculous, immunosuppressive treatment. Medline system reported 12 associated and oral methylprednisolone was started. Serum creatinine decreased to 220 μmol/L; hemodialysis was discontinued. On day 27, Mycobacterium bovis was identified on lung samples by PCR; tuberculostatic agents were initiated. Corticosteroids was gradually stopped.
Methods: We cared for a 56-year-old man with AKI noted in evaluating his back pain. Serum creatinine (Cr) rose from 0.8 to 4.6 mg/dL in 2 months. Serum protein electrophoresis (SPEP) showed a large M spike. Urine PSEP showed a small M spike. His pneumonia got better after receiving IV antibiotics and he was extubated but his chronic confusion worsened and it peaked to 11.2, and at that time renal biopsy was performed.

His labs are significant for the following:
- Urinalysis showed specific gravity of 1.009, protein 100 mg/dL, glucose 30 mg/dL.

His blood pressure was 95/56 mmHg and pulse was 136 beats/min. Physical exam was otherwise normal. Labs included serum creatinine (Scr) of 1.4 mg/dL, bicarbonate of 18nmol/L, creatinine kinase of 149 mg/dL. Urinalysis showed specific gravity of 1.009, protein 100 mg/dL, glucose 30 mg/dL. Due to hypotension and oliguria, he was given normal saline intravenously. His Scr a day later was 3.2 mg/dL and renal replacement therapy was begun. Ultrasound showed normal kidney size and echotexture. Echocardiography revealed an ejection fraction (EF) of 20% with diffuse hypokinesia. Twelve days after initiation, dialysis was stopped. A coronary angio-CT was normal with 50% stenosis of the LAD. SCs were taken 4 weeks after admission and were positive for oxalate.

Conclusions: The first SCs were cultured by John Hoffman at Celsen. They are similar in structure to tetrahydrocannabinol but are up to 800 times more potent. Commercial names include K2, Spice, Legal, Funk, and Gold. Formulations have included dried leaves or powder, typically a mixture of 1-3 and herbal additives. The mechanism of kidney injury is unclear. Renal biopsy was not performed in our case but in a case series of four SC-exposed patients with AKI (Bhanushali et al., CJASN, 2013), three biopsies showed ATN, possibly due to a direct nephrotoxic effect of SC. Poor cardiac output may contribute to AKI in some cases, including ours. Cannabinoid receptor activation may lead to norepinephrine release and parasympathetic blockade, which could cause the cardiomyopathy. SC are also associated with coronary artery syndromes, severe hypotension, seizures and psychosis. Our goal with this report is to promote awareness among clinicians of the increasing use and toxicities of SC, including AKI.

TH-PO811 Acute Kidney Injury Associated with Synthetic Cannabinoids Use


Background: Synthetic cannabinoids (SC) include a variety of compounds publicized as harmless legal substitutes for Marijuana. SC are increasingly used and have serious toxicities including acute kidney injury (AKI) and myocardial infarction (MI). In this case we describe a patient with AKI and MI associated with use of SC.

Methods: A 20-year-old previously healthy man, known to be a heavy SC user, had a witnessed seizure minutes after inhaling SC. On hospital presentation he was combative, suffered repeated seizures and was intubated. His blood pressure was 95/56 mmHg and pulse was 136 beats/min. Physical exam was otherwise normal. Labs included serum creatinine (Scr) of 1.4 mg/dL, bicarbonate of 18nmol/L, creatinine kinase of 149 mg/dL. Urinalysis showed specific gravity of 1.009, protein 100 mg/dL, glucose 30 mg/dL. Due to hypotension and oliguria, he was given normal saline intravenously. His Scr a day later was 3.2 mg/dL and renal replacement therapy was begun. Ultrasound showed normal kidney size and echotexture. Echocardiography revealed an ejection fraction (EF) of 20% with diffuse hypokinesia. Twelve days after initiation, dialysis was stopped. A coronary angiogram was normal with 50% stenosis of the LAD. SCs were taken 4 weeks after admission and were positive for oxalate.

Conclusions: The first SCs were cultured by John Hoffman at Celsen. They are similar in structure to tetrahydrocannabinol but are up to 800 times more potent. Commercial names include K2, Spice, Legal, Funk, and Gold. Formulations have included dried leaves or powder, typically a mixture of 1-3 and herbal additives. The mechanism of kidney injury is unclear. Renal biopsy was not performed in our case but in a case series of four SC-exposed patients with AKI (Bhanushali et al., CJASN, 2013), three biopsies showed ATN, possibly due to a direct nephrotoxic effect of SC. Poor cardiac output may contribute to AKI in some cases, including ours. Cannabinoid receptor activation may lead to norepinephrine release and parasympathetic blockade, which could cause the cardiomyopathy. SC are also associated with coronary artery syndromes, severe hypotension, seizures and psychosis. Our goal with this report is to promote awareness among clinicians of the increasing use and toxicities of SC, including AKI.

TH-PO812 Acute Kidney Injury as a Result of Drug Elution from Antibiotic Impregnated Spacer Device in a Patient with Chronic Kidney Disease

Poonja Singh, 3Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA; Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA; Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA.

Background: Antibiotic impregnated cement spacers have been used commonly for the treatment of infected prosthetic hip and knee joints. Vancomycin and aminoglycosides are the most commonly used antibiotics in spacer devices. This modality of treatment provides high concentration of the antibiotic at the infected joint, while minimizing the systemic adverse effects. We present a case of acute kidney injury progressing to end stage renal disease from combined vancomycin and tobramycin toxicity in this setting.

Methods: A 78 year old woman, with history of left hip replacement (10 years ago), complicated by chronic periprosthetic infection, hypertension, chronic kidney disease (CKD) stage III, baseline serum creatinine 1.2mg/dL presented with 3 days of nausea and vomiting. On examination, she was afebrile, hemodynamically stable, with negative orthostasis. Initial labs revealed elevated serum creatinine of 3.1 mg/dL, magnesium 1.1 meq/l, urinalysis with 1.7gm proteinuria with no active sediment, and normal renal imaging. Serum Tobramycin and Vancomycin levels were elevated at 8 mg/L and 25 mg/L respectively. Patient developed oliguria and worsening renal function, and had to be commenced on hemodialysis(DD). 12 hour post HD Tobramycin and Vancomycin levels remained elevated, demonstrating continued drug elution. Serum antibiotic levels diminished only after the spacer was removed. The patient, however had progressed to end stage renal disease by this time. The patient was lost to follow up.

Conclusions: Antibiotic impregnated cement spacers are currently decribed as harmless legal substitutes for Marijuana. SC are increasingly used and have serious toxicities including acute kidney injury (AKI) and myocardial infarction (MI). In this case we describe a patient with AKI and MI associated with use of SC.

Conclusion: Review of literature showed two reports demonstrated 14 and 30 patients respectively diagnosed with Acute kidney injury associated with SPICE use. A new article in Alabama showed 4 cases of AKI associated with synthetic cannabinoids. Here, we present a case of AKI and calcium oxalate deposition in a patient with synthetic cannabinoids use, pointing to calcium as a cause of secondary oxalosis. Synthetic cannabinoids use is a potential cause for acute kidney injury/acute interstitial nephritis and can lead to hyperoxaluria.
TH-PO813 A Case of Acute Tubular Necrosis in the Setting of IgG Kappa Multiple Myeloma: A "Sticky Situation" Solved with Plasmapheresis

Emmett D. Ratigan, Nancy Miller, Reza Elahimehr, Dena E. Rifkin. Nephrology, Univ of California San Diego, San Diego, CA.

Background: Renal failure is a frequent complication amongst patients with multiple myeloma and is a well-known predictor of morbidity and mortality. Here we report a case of a patient with IgG kappa multiple myeloma (MM) and chemotherapy-induced acute kidney injury in whom high-flux hemodialysis proved impossible due to intractable clogging of hemodialysis membranes. Hemodialysis was only successful after plasmapheresis treatment.

Methods: A 72 year-old man with refractory IgG Kappa MM was admitted with oliguric renal failure, due to acute tubular necrosis, two days after initiating a salvage regimen of CC (carrubimycin-cyclophosphamide-dexamethasone). He became progressively hyperalcalcemic and oliguric, prompting hemodialysis catheter placement and initiation of intermittent dialysis using a F160NR high-flux filter. Within minutes of treatment initiation his dialyzer clogged, which recurrrred on subsequent attempts despite heparin and TPA anticoagulation. A trial of continuous venous hemodialfiltration (CVVHD) using regional citrate anticoagulation also failed, as filters clogged within 120 minutes. Heparin-induced platelet antibodies and a hypercoagulability screen were negative. As serum light chain levels were elevated (163 mg/dl) we speculated they were aggregating and sludging through the filter. To acutely reduce their level, we then performed plasmapheresis (100% plasma volume replacement), after which he was able to complete a full hemodialysis treatment without use of anticoagulation. Following three days of paired treatments, he recovered renal function and became dialysis-independent. Following additional treatment with CC, he redeveloped acute kidney injury necessitating hemodialysis, which we again primed with plasmapheresis. Four months later, he has no evidence of myeloma-related kidney disease, despite persistently elevated serum light chains.

Conclusions: Studies have demonstrated that light chains can aggregate and deposit in hemodialysis filters. In cases complicated by frequent filter clogging, plasmapheresis may be a useful tool to facilitate short-term hemodialysis.

TH-PO814 Chronic Urine Leak Causing Acute Kidney Injury due to Abdominal Compartment Syndrome: An Unusual Case Masquerading as Hepatorenal Syndrome 1 Elhami N. Hannan,1 Jeannie Park.2 1*Nephrology, Emory Univ, Atlanta, GA; 2*Nephrology, Emory Univ, Atlanta, GA.

Background: We present a case of a patient with acute onset Ascites, Spontaneous Bacterial Peritonitis (SBP), heavy alcohol intake and acute kidney injury (AKI), which was initially presumed to be due to Type I Hepatorenal Syndrome (HRS I).

Methods: Case Description: A 76 year male presented to hospital with abdominal pain, increased abdominal girth and decreased urine output (UOP) for 2 weeks. His past medical history was significant for chronic kidney disease stage III, of unknown etiology. He also, has a history of Bladder cancer, which was surgically removed, and a construction of neo bladder two decades ago. On exam, he was noted to have a tense ascites. Labwork was obtained which showed elevated liver enzymes, normal serum creatinine level (mean, 4.3±0.8 mg/dL) and abnormal INR (mean, 4.4±0.7 IU) after excluding acute/active glomerulonephritis. The biopsy specimens revealed RBCs. Urine protein to Cr ratio was 2.5mg/mg. ANCA, Anti GBM antibodies and ANA were negative. Serum C3, C4 were normal. He had to be started on hemodialysis due to uremia. Kidney biopsy showed red blood cells in Bowman’s space (one glomerulus), red blood cells in tubular lumina with interstitial fibrosis. Immunofluorescence was negative and there were no electron dense deposits. Findings were consistent with the diagnosis of warfarin-related nephropathy. PT remains dialysis dependent months later.

Conclusions: Studies have demonstrated that light chains can aggregate and deposit in hemodialysis filters. In cases complicated by frequent filter clogging, plasmapheresis may be a useful tool to facilitate short-term hemodialysis.

TH-PO815 Permanent Renal Damage after Implantation of Tobramycin Beads during Orthopedic Surgery


Background: Antibiotic-impregnated cement or beads are used in surgeries of infected hip and knee arthroplasties. The incidence of systemic side effects of antibiotics is low because the antibiotic is delivered locally. Antibiotic therapy consisted of vancomycin followed by tigecycline. The infected prosthesis was surgically removed. The wound was irrigated and spacer created with tobramycin–impregnated cement. Two strings of 16 tobramycin-eluting beads were also inserted in the metaphyseal cavities of the femur and tibia as shown in this film:

TH-PO816 Warfarin Associated Nephropathy

Amita Vasudev, Muhammad R. Mustafa, Sana R. Akbar. Nephrology, West Virginia Univ, Morgantown, WV.

Background: Warfarin induced nephropathy is a relatively newly diagnosed disease entity. We hereby present a case of warfarin induced nephropathy.

Methods: 79 year old white male with history of Hypertension, atrial fibrillation, mechanical aortic valve replacement on coumadin for 14 years underwent cardiac catheterization due to anginal symptoms, it showed minimal CAD. Home medications were Losartan, Lasartan, Bactrin for cystitis, Imdur, Hydradalzine, lopressor. Baseline labs were BUN 28, Cr was 1.1. Ten days after cardiac catheterization, he developed gross hematuria. BUN and Cr increased to 39 and 2.4 mg/dl respectively, with INR of 6. Exam was normal without edema. Losartan and Lasartan were stopped with no change in kidney function. Ultrasound was normal. Cr worsened to 6.13 mg/dl with BUN 90. Urine sediment showed many normal RBCs. Urine protein to Cr ratio was 2.5mg/mg. ANCA, Anti GBM antibodies and ANA were negative. Serum C3, C4 were normal. He had to be started on hemodialysis due to uremia. Kidney biopsy showed red blood cells in Bowman’s space (one glomerulus), red blood cells in tubular lumina with interstitial fibrosis. Immunofluorescence was negative and there were no electron dense deposits. Findings were consistent with the diagnosis of warfarin-related nephropathy. PT remains dialysis dependent months later.

Conclusions: The patient presented with typical case of HRS I, in an alcoholic patient and ascites with SBP. However, his diagnosis was a much rarer case of AKI due to abdominal compartment syndrome from urine leak, that resolved with Foley insertion.

TH-PO817 A Case of Acute Kidney Injury in a Young Male with Recurrence of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome during Steroid Taper

Nima Naimi. Dept of Nephrology, Washington Univ, St. Louis, MO.

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare disease occurring 2 to 9 weeks after exposure to drugs such as antiepileptics, antibiotics, and allopurinol. The most common organs affected include the liver, kidney, and lungs, although any organ may be involved. Ten to 30 percent of patients with DRESS syndrome present with kidney involvement, with age and underlying kidney disease being risk factors.

Methods: A 19 year old male with a history of acne was admitted with a fever, pruritic rash, and diffuse lymphadenopathy 3 weeks after starting minocycline for his acne. He was found to have a white blood cell count of 29.7 with 40% eosinophils, alanine aminotransferase of 103, and a creatinine of 1.1. Infectious and rheumatologic work up was negative. He was seen by dermatology who diagnosed him with DRESS syndrome and recommended discontinuation of the minocycline along with prednisone 80mg daily with a taper over 6 weeks. He was discharged home after 2 days once his fever resolved and his rash improved. Two weeks later, he was readmitted after a routine follow up lab demonstrated a creatinine of 1.2. The lab also noted a recurrence of his rash when his prednisone was tapered from 80 to 60mg daily. He was initially started on methylprednisolone and then switched to 80 mg of prednisone with a 10 mg per week taper.

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

285A
Renal Failure Caused by Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome (DRESS) Jie Cui, David J. R. Steele. Nephrology Dept, Massachusetts General Hospital, Boston, MA.

**Background:** Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) is a severe adverse drug reaction with rash, fever, and multi-organ damage. Kidney involvement of DRESS is usually mild with moderate elevated creatinine. However, severe renal damage required renal replacement therapy can also occur in severe cases.

**Methods:** A 42-year-old healthy male presented with daily fever, diffuse myalgia, sore throat and erythematous, pruritic rash. His lab was unremarkable on initial presentation. He was diagnosed with scarlet fever and his symptoms went away after 5-day course of penicillin VK. However, 7 days after he stopped penicillin, his rash, fever, and myalgia returned. Physical exam was remarkable for T 102F, inguinal adenopathy and pinpoint erythematous papules all over the body. Labs are shown in table 1.

He was started on ceftriaxone owing to suspicion of infection. However, all infectious work up were negative including throat culture, HIV, parvovirus, coccacyste, HSV, EBV, hepatitis A, B, C, Ehrlichia, lyme, blood culture and urine culture. ANA, RF, schistocytes and renal ultrasound were negative. Patient’s renal function rapidly declined, and hemodialysis was initiated. Renal biopsy was performed, which showed severe acute interstitial nephritis. Skin biopsy showed interface and spongiotic dermatitis, which was consistent with DRESS syndrome. All antibiotics were discontinued and patient was started on prednisone. His rash improved, and his creatinine decreased to 2.06 upon discharge. He was seen in the renal clinic a month later with complete resolution of his rash.

**Conclusions:** DRESS is a potential life threatening hypersensitive reaction that can cause multi-organ involvement. Severe renal failure required renal replacement therapy is a rare complication. Prompt recognition and removal of the offending medication is crucial to limit further end organ damage.

**TH-PO819**

Successful Treatment of Life-Threatening Intoxication with Amitriptyline and Tilidine Using High Cut-Off Dialysis Anna Bertram, 1 W. Nikolaus Kühni-Velten, 2 Hendrik Suhling, 3 Jan T. Kielstein. 1 Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; 2Pneumology, Hannover Medical School, Hannover, Germany; 3Nephrology, Hannover Medical School, Hannover, Germany.

**Background:** Three lines of evidence show that amitriptyline and tilidine are removed by high cut-off dialysis: Dialyzer clearances for amitriptyline and tilidine were 58ml/min and 67ml/min. Reduction rate of amitriptyline and tilidine by 1st dialysis were 27% and 41%. Into the 6th hour of treatment the patient regained consciousness and was transferred to psychiatric care on the 3rd day.

**Conclusions:** We conclude that use of a high cut-off membrane is a feasible method to accelerate elimination in cases of life-threatening poisonings with amitriptyline and tilidine, for which conventional hemodialysis is considered ineffective.

**TH-PO820**

Hyponormemic Hypoaldosteronism and Renal Insufficiency after Unilateral Adrenalectomy for Primary Hypoaldosteronism Shinge Li, John A. Walker. Medicine/Nephrology, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ.

**Background:** Treatment for primary hypoaldosteronism may be complicated by persistent hyponormemic hypoaldosteronism and apparent acute kidney injury.

**Methods:** A 49 year old man with a history of longstanding hypertension and hypokalemia (2.7 mEq/L) was diagnosed with primary hypoaldosteronism secondary to an aldosterone producing adenoma (APA) on the bases of undetectable plasma renin activity (PRA), elevated plasma aldosterone concentration (PAC), and abdominal CT showing a 2.5cm right adrenal mass. Baseline renal function was normal (serum creatinine 0.9mg/dL; eGFR 122mL/min). A laparoscopic right adrenalectomy was performed and hypertension improved thereafter off medications. However, serum creatinine doubled (creatinine clearance 76.5mL/min) and acidosis and hyperkalemia were noted (6.3 mEq/L); PRA and PAC were undetectable. This pattern persisted for several months. Treatment with fludrocortisone 0.05mg/day resolved the hyperkalemia and acidosis, but only partially attenuated the azotemia.

**Conclusions:** The incidence of persistent hypoaldosteronism with hyperkalemia after adrenalectomy for APA has been reported as 5.5%; concomitant hyporeninemia was even less frequent at 1.8%. Prolonged minireplacement therapy is often necessary. In one study, patients with APA treated with either adrenalectomy or spironolactone had short-term decreases in GFR of 13.6mL/min. Our patient’s hyponormemic hypoaldosteronism in combination with the magnitude of his GFR reduction make this case unique. Though the hyperkalemia is explained by the hypoaldosteronism, the reduction in renal function is more puzzling and has negative prognostic implications. We surmise our patient’s postoperative decline in GFR may reflect a combination of 1)diminished renal blood flow due to an abrupt reduction in serum aldosterone, and 2)CDK due to underlying hypertensive nephrosclerosis, previously masked by hyperaldosteronism-driven hyperfiltration. Clinicians should be alert to this potential outcome in patients undergoing adrenalectomy for APA, and monitor postoperative laboratory parameters accordingly.

**TH-PO821**

Liddle’s Syndrome Caused by a Novel Mutation in the β-Subunit of the Epithelial Sodium Channel Gene SCN11B Satomi Nakashima, Keitaro Yokoyama, Masatsugu Nakao, Izumi Yamamoto, Yado Tanno, Ichio Ohkido, Takashi Yokoo. Div of Kidney and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.

**Background:** Liddle’s syndrome has been known as a disorder associated with abnormal sodium reabsorption in the distal tubule, and is transmitted as a rare autosomal dominant trait. The epithelial sodium channel (ENaC) was established as a cause of this syndrome by hyper-sensitizing the channel. The ENaC is caused by mutations in the SCN11B or SCN11G gene, which truncates the cytoplasmic carboxyl terminus of the β and γ subunits of the ENaC.

**Methods:** The case, a 24-year-old woman, was diagnosed with hypertension, and was started on an antihypertensive agent 8 years ago. But, her blood pressure was not controlled, therefore she was referred to our hospital for further treatment. She showed hypertension , hypokalemia, metabolic alkalosis, low renin and aldosterone levels, hence pseudo-aldosteronism was suspected. Spironolactone was not effective, but triamterene was effective in controlling her blood pressure with an improvement in her serum potassium concentration.

---

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

286A
There was no history of familial Liddle’s syndrome, therefore sporadic Liddle’s syndrome was suspected. Therefore a genetic test was performed. However the previously reported gene mutation for Liddle’s syndrome was not detected. Further DNA analyses showed the point mutation (Cytosine: Guanine) in the PY (Proline-Proline-x-Tyrosine) motif of the β subunit in the ENaC. Screening for specific mutations of the SCN1B gene in relatives of patients with Liddle’s syndrome can be used to identify previously unrecognized cases within the family. A new nonsense mutation (Y664X) of the SCN1B gene is the likely cause of Liddle’s syndrome in this case. 

**Conclusions:** Based on direct DNA sequencing, a novel heterozygous nonsense mutation at codon 664 of the SCN1B gene from TAC (Tyrosine) to stop codon (TAG) was detected as a cause of Liddle’s syndrome in this case.

**TH-PO822**

**Reverse of Congestive Heart Failure in Patient with Primary Aldosteronism Narttiya Varothai, Erdal Sarac. Internal Medicine, St. Elizabeth Health Center, Youngstown, OH.**

**Background:** Primary Aldosteronism (PA) is a disorder causing hypokalemia, sodium retention, hypertension and cardiovascular damage which can culminate into congestive heart failure. Early adrenectomy recommended to improve cardiac function. We are reporting a case with progressive CHF with underlying ischemic heart disease which cardiac function improve after delayed adrenectomy for 10 years.

**Methods:** A 70 year old Caucasian male with past medical history of HTN, CAD s/p CABG, chronic Atrial Fibrillation s/p conversion to sinus rhythm, electrolyte disorder and tobacco referred to renal clinic for chronic asymptomatic hyponatremia. Since his presentation in 2005 to our health care system, his serum sodium (Na+) has ranged from 116 to 134mmol/L. Urine tested positive for adults before 2011. In 2002, anti-helminthic Levamisole was identified in cocaine. With increasing use of Levamisole as an adulterant, a number of complications including cardiac function decline after adrenectomy for 10 years. 

**Results:** Patient admitted in cocaine. With increasing use of Levamisole as an adulterant, a number of complications including cardiac function decline after adrenectomy for 10 years. 

**Conclusions:** The increasing use of Levamisole as an adulterant, a number of complications including cardiac function decline after adrenectomy for 10 years.

**TH-PO823**

**Chronic Hyponatremia Associated with Levamisole Adulterated Cocaine (LAC) Use Anju A. Oomrem,1,2 Harold A. Franch,1,2 Nephrology, Atlanta VAMC; Emory Univ, Atlanta, GA.**

**Background:** There are no reports of hyponatremia associated with cocaine use in adults before 2011. In 2002, anti-helminthic Levamisole was identified in cocaine. With the increasing use of Levamisole as an adulterant, a number of complications including cardiac function decline after adrenectomy for 10 years. 

**Methods:** A 65-year-old male with hypertension and polysubstance abuse (cocaine, alcohol and tobacco) referred to renal clinic for chronic asymptomatic hyponatremia. Since his presentation in 2005 to our health care system, his serum sodium (Na+) has ranged from 136mmol/L to 129mmol/L. Urine drug screens done during the same time frame always tested a PA case who has progressive CHF with underlying ischemic heart disease which cardiac function improve after delayed adrenectomy for 10 years.

**Results:** Patient had HTN and persistent hyponatremia. Laboratory studies showed PRA 37.1 ng/dL, PRA 0.51 ng/ml/hr with PRA/PRA ratio of 72.74 more than 200 in 2003. Both adenalin and clonidine induced natriuresis and signiﬁcant increase in urine osmolality. Urine sodium increased from 10 mmol/L to 116 mmol/L. 

**Conclusions:** PA can cause cardiovascular damage from uncontrolled BP and also increase cardiac hypertrophy and fibrosis. Recommended treatment in PA with possible unilateral disease is unilateral laparoscopic adrenalectomy. Although medical therapy could be option for patient who is not surgical candidate (unwilling or poor clinical condition), delayed surgery still help to improve clinical outcome and reverse cardiac function even in ischemic heart patient. So we should consider early adrenalectomy to prevent all the consequences.

**TH-PO824**

**Obstructive Jaundice Associated Hyponatremia Supriya Ravella, Gertrude S. Lefavour, Amay Parikh, Mary O. Carayannopoulos. Nephrology, UMDNJ-WJMS, New Brunswick, NJ.**

**Background:** Pseudohyponatremia is associated with a normal serum osmolality. Elevated lipid levels are a known cause of pseudohyponatremia. While the plasma water is approximately 93% of the plasma volume normally, in patients with hyperlipidemia or hyperproteinemia, the plasma water can decrease to 80% or lower leading to a reduced measured sodium concentration.

**Methods:** A 40-year-old man with a past medical history of autoimmune pancreatitis/lymphoplasmacytic sclerosing cholangitis, biliary stricture with stent placement, hyperlipidemia and diabetes mellitus presented with fever for two days. On exam, he was jaundiced and icteric. His serum sodium was 119 mEq/L, potassium was 3.3 mEq/L and chloride was 87 mEq/L. Total cholesterol was 2109 mg/dL. His lipid panel however demonstrated a LDL of 68 mg/dL, HDL of 36 mg/dL and triglycerides of 299 mg/dL. The large difference between the total cholesterol and its components prompted a lipoprotein electrophoresis, which detected lipoprotein X, which is associated with the low density lipoprotein fraction. It is an abnormal lipoprotein which appears in the sera of patients with obstructive jaundice. Abnormally high levels of LX-p can cause pseudohyponatremia. Serum sodium is commonly measured with analyzers that use indirect potentiometric electrodes. This utilizes a dilution of the sample. Increased lipid or protein concentrations alters the total water concentration. Then the dilution step and the subsequent calculation of concentration by the analyzer results in a falsely low sodium value. When factitious results are suspected serum sodium should be measured by direct potentiometric or selective electrodes. When serum sodium levels are low in patients with cholestatic jaundice either due to autoimmune pancreatitis or graft versus host disease after stem cell or bone marrow transplantation, the suspicion for pseudohyponatremia should be high.

**TH-PO825**

**Hyponatremia Case due to Cerebral Salt Wasting and Underlying Syndrome of Inappropriate Antidiuretic Hormone Secretion: Diagnostic and Therapeutic Challenges Ouzma C. Badescu, Khurrum Saleem, Farhang Ebrahimi. Richmond Univ Medical Center, Staten Island, NY.**

**Background:** The existence of cerebral salt wasting (CSW) is controversial, but hyponatremia in patients with central nervous system (CNS) injury, particularly traumatic brain injury, has been recognized in literature. We present a case of hyponatremia due to CSW complicated with underlying syndrome of inappropriate antidiuretic hormone secretion (SIADH). The coexistence of these conditions has been rarely reported.

**Methods:** We presented a 45-year-old male with chronic ventriculo-peritoneal shunt admittened for cerebral spine injury secondary to seizure induced fall. Patient was found to have hyponatremia. Urine osmolality (UOsm) and urine sodium (UNa) were elevated, and there was hypouricemia. Diuretics, fluid restriction, Demeclocycline, and combination of normal saline (NS) and diuretics were associated with worsening of hyponatremia. We noticed large volume diuresis in the presence of hemodinamically stable and signs of hypovolemia. Possibility of CSW was considered. Serum sodium was 116 mEq/L, UOsm 823 mosm/kg, and UNa responded to 3% hypotonic saline (HS) and volume expansion with normal saline, with partial correction of serum sodium. Each time we held HS, while on NS alone, hyponatremia worsened, and UOsm would not decrease below 300 mosm/Kg. This was consistent with underlying SIADH. Patient remained quadriplegic and required long term maintenance HS and Na to stabilize and eventually Na stabilized after addition of large doses of mineralocorticoid therapy. Other unique manifestations of CSW are the absence of hypokalemia despite natriuresis and significant hypouricemia, which both were present in our patient.

**Conclusions:** Our case illustrates the existence of CSW and SIADH, which poses challenges to the physician. If the mainstay of therapy in CSW is replacement of sodium and water, in SIADH it is water restriction. Early recognition of the main pathology could reduce complications of inappropriate therapy. Also the unique positive response to mineralocorticoids could help physicians not familiar with this therapy in patients with this rare combination of disorders.

**TH-PO826**

**Lamivudine Induced Nephrogenic DI Mohammad Mudas Morad, Michelle W. Krause, Dumitrul Rotaru, Gracen Elizabeth Hauk. Nephrology, Univ for Medical Sciences, Little Rock, AR.**

**Background:** Acquired NDI in adults is most commonly caused by lithium, hypertension or pseudohyponatremia. Less frequent causes are medications like: cidofovir, foscamet, vasopressin V2 receptor antagonists, amphotericin B, demeclocycline, ifosfamide. We are reporting a case of acute NDI induced by lamivudine.

**Methods:** A patient with AML admitted for autologous stem cell transplant (ASCT). Her medications included prophylactic antibiotics, antifungals, Acyclovir and Lamivudine. The hospital course was complicated by acute polyuria with 12 L of UOP/day followed by pre-renal AKI with creatinine increasing from 0.9 to 2.2. Urine analysis revealed low specific gravity of 1.001 and urine sediment was bland. During this time, the patient also had low urine osmolality and high serum sodium. Patient received repeated doses of DDAVP with no significant change in urine osmolality or urine volume. A diagnosis of acute
nephrogenic diabetes insipidus (NDI) was made. In our patient we stopped Lamivudine and started Maxidex. Over the next 48hrs patient UOP decreased gradually to 2 L/day, his urine osmolality decreased progressively to 400 to 72 hours. This improvement in renal function improved his serum osmolality.

Conclusions: In the absence of common etiologies we explored the possibility of antivirals causing acute NDI in our patient. We performed a literature research for NDI associated with Acyclovir and/or Lamivudine. We found previous reports of Didanosine causing NDI. Based on similarities between Lamivudine and Didanosine which are both nucleoside analogue drugs with comparable mitochondrial toxicity profile we presumed that Lamivudine was the likely cause of NDI in our patient. Tenofovir use was also reported to increase the concentration and toxicity of Didanosine through competition for OAT1 binding for nucleoside transport. The same OAT1 is involved in both Acyclovir and Lamivudine excretion and we propose that Acyclovir use in our patient may have also contributed to increased Lamivudine levels. Further studies may be needed to assess the incidence of acute NDI with Lamivudine.

TH-PO827

Supra-Therapeutic Doses of 1-Deamino-8-D-Arginine Vasopressin to Treat a Severe Case of Lithium Induced Nephrogenic Diabetes Insipidus: Back to the Basics


Background: Nephrogenic diabetes insipidus (NDI) is an inadequate response of the kidneys to the antidiuretic hormone, resulting in polyuria, and water and electrolyte imbalances. We report the successful use of high doses of 1-deamino-8-D-arginine vasopressin (dDAVP) as a successful treatment strategy.

Methods: A 51-year-old male with history of schizoaffective disorder on long-term lithium therapy causing NDI (with baseline normal sodium levels) was hospitalized with a 3 day history of confusion and gait instability. Workup revealed creatinine of 165mmol/L, lithium level of 1.3 mmol/L, acute kidney injury, and a new diagnosis of thrombotic thrombocytopenic purpura (TTP). Lithium was discontinued and patient required aggressive fluid administration due to continued polyuria at 9 to 10 L/day with urine specific gravity of 60-65 mosmol/kg H2O. dDAVP at "physiologic dose" of 2mcg was given intravenously with no significant improvement. Plasma exchange was initiated with clinical improvement in TTP, however polyuria persisted at a range of 10-16 L/day despite initiation of a thiazide diuretic. High dose dDAVP was then administered at 4 mcg subcutaneously twice a day, with resultant increase in urine osmolality to 275 mosmol/kg and decrease in urine output to 3-5 L/day.

Conclusions: Up to 40% of individuals treated with lithium develop NDI as a side effect via an unknown molecular mechanism. Traditionally, treatment of NDI has involved the use of thiazide diuretics and stopping lithium. In the 1990’s several different studies were published demonstrating the successful use of indomethacin with or without desmopressin for treatment. However, this fell out of favor potentially due to the impaired renal function caused by indomethacin. Several new therapies are being proposed to treat NDI such as vaptans, statins and heat shock protein 90. We have demonstrated higher doses of dDAVP as a successful treatment modality in a case of severe NDI. Our patient likely had a partial form of NDI, hence the response to higher doses of dDAVP. Through this case we encourage physicians to go back to the basics when treating NDI.

TH-PO828

Kidney Transplant Exposing Central Diabetes Insipidus

Todd W. Robinson, Anthony J. Bleyer. Wake Forest School of Medicine, Winston-Salem, NC.

Background: Central diabetes insipidus (DI) leads to an inability to maximally concentrate the urine. Patients with DI and CKD have less water delivery to the collecting duct (CD), causing less urine output. We describe a patient with central DI whose low GFR was fixed with living related kidney transplantation, resulting in abrupt onset of polyuria.

Methods: A 45 year old peritoneal dialysis patient with ESRD due to Wegener’s Granulomatosis presented for kidney transplantation. On post-operative day 2 the patient developed urine output between 15 and 16 liters daily without diuretics. The patient did not complain of polydipsia. The serum sodium was 149 mEq/l, bicarbonate 21 mEq/l, chloride 116 mEq/l, BUN 16 mg/dl and creatinine 1.6 mg/dl. Urine osmolality was measured and noted to be very low at 79 mosmol/kg. Immediately, the urine output of the donor was assessed and found to be 3-4 Leters/day. In the recipient, a water deprivation test was initiated and there was minimal elevation of the urine osmolality with respect to baseline values. With exogenous ADH administration, the patient’s urine osmolality markedly increased with a significant decrease in urine volume. MRI of the brain revealed no evidence of neoplasms, mass lesion, or white matter disease. As discharge, he was discharged on desmopressin nasal spray with normal TSH, elevated LH (20.9), borderline high prolactin (23.3), with an undetectable ADH and normal serum osmolality (282). An MRI scan revealed a small pituitary gland. In 2012, she had undergone a pituitary stalk lesion with a history of amenorrhea and central DI. A repeat MRI of the brain was obtained which showed a thickened pituitary stalk. The combination of pituitary stalk lesion with a history of spontaneous pneumothorax raised the possibility of Langerhans cell histiocytosis. TSH was 0.98, while on DDA VP. Given her history of amenorrhea and central DI a repeat MRI of the brain was obtained which showed a thickened pituitary stalk. The combination of pituitary stalk lesion with a history of spontaneous pneumothorax raised the possibility of Langerhans cell histiocytosis, which was further substantiated with a high resolution chest CT showing cystic changes. Taken together, these findings established a unifying diagnosis of Langerhans cell histiocytosis.

Conclusions: This case illustrates the important interaction between GFR and polyuria in DI. Prior to transplant, the GFR was low, with diminished water delivery to the CD and only moderate urine output. Post-transplantation, the increased GFR resulted in increased water delivery to the CD with resulting polyuria. Interestingly, the diagnosis of central DI was made quite rapidly, because determination of the urine output of the donor ruled out nephrogenic DI. The poor perception of thirst may have been due to the free availability of water in the hospital. With the urinary catheter in place, the patient was able to drink up to 400 ml/hr to maintain the extent of the urine output. The etiology of central DI in this case was likely granulomatous involvement of the posterior pituitary, which has been described in a small number of Wegner’s cases.

TH-PO829

Central Diabetes Insipidus (CDI): Undiagnosed for 3 Decades Till Unmasked by Dehydration due to Endothelial Intubation and Stupor

S Damera, Laxmi Gadde, Kai Lau. Nephrology, OU Health Sciences Center, OK.

Background: DI is marked by excessive dilute urine, usually controlled by polydipsia. We here report a man with chronic CDI undiagnosed till revealed by severe hypermotility from inadvertent water deprivation due to prolonged intubation & stupor.

Methods: A 54y man with strangulated inguinal hernia had emergent bowel resection. He stayed intubated for more surgery on day(2) & all under sevoflurane.On d1, urine SNa was 1.005. He had since been polyuric to 4-9 L/d. Serum(S)Na,139 mEq/l & 135 on d1, rose to 165 by d6. By deleting IV Na & giving more H2O, SNa fell to 154 by d7.Polyuria (10-11 L/d) continued & Urine osmolality on d2 fell to 190 by d8.Despite SNa of 331, ADH was repeatedly <0.8 pg/ml. Confirming DI Sevoflurane via F can cause NDI. To differentiate CDI from NDI, he got 80ug IV DDAVP & raised SNa to 563, 578, 691 respectively by 3-5% & 31%h. But Urine output fell to 462 by 3 & 217 by 4 & Peak SNa of 756 post-DDAVP showed intact concentration ability.

Conclusions: On MRI, posterior pituitary had no T1 hyperintensity (i.e. no ADH) confirming CDI. With delirium from SNa & dysphasia from intubation, he could not drink to prevent dehydration. Thus he got 11d of DDAVP to keep SNa 139-149 & allow extubation. When conscious & talking, he denied history of DI but admitted to 12L of H2O/day for 30 yrs. For 7d before discharge, SNa was normal by ad lib fluids.

Conclusions: This case shows classical elusive nature of DI due to usually effective polydipsia.He became dehydrated when prolonged intubation precluded drinking and perpetuated his inability to voice & quench thirst & aggravated SNa,which in turn caused more encephalopathy.Once lucid, drinking kept SNa normal better than DDA VP. CDI was diagnosed with a high resolution chest CT showing cystic changes. Taken together, these findings established a unifying diagnosis of Langerhans cell histiocytosis. We propose that central DI a repeat MRI of the brain was obtained which showed a thickened pituitary stalk. The combination of pituitary stalk lesion with a history of spontaneous pneumothorax raised the possibility of Langerhans cell histiocytosis, which was further substantiated with a high resolution chest CT showing cystic changes. Taken together, these findings established a unifying diagnosis of Langerhans cell histiocytosis.
Oxcarbazepine Therapy for Central Diabetes Insipidus

Basmah A. Abdalla, Tara C. Lagu, Daniel L. Landry, Gregory Lee Braden. 1 Department of Medicine, Baystate Medical Center/Tufts Univ School of Medicine, Springfield, MA; 2 Department of Medicine, Div of Nephrology, Baystate Medical Center/Tufts Univ School of Medicine, Springfield, MA.

Background: Oxcarbazepine causes hyponatremia in up to 51% of patients. Mechanisms for this effect have not been completely elucidated.

Methods: A 39 year-old female suffered a severe traumatic brain injury in a motor vehicle accident which left her with seizures and complete central diabetes insipidus (CDI). At the time, her serum sodium (Sn) was 158 mEq/L and a urinary osmolality was 137 mOsm/kg. ADH levels by RIA were undetectable. Serum ACTH & cortisol levels were normal. She received intranasal DDAVP 10mcg twice daily & oxcarbazepine 400mg twice daily. 2 years later, she was noted to have developed refractory seizures. Sn was 133 mEq/L and oxcarbazepine level was 21 ug/mL (therapeutic). The oxcarbazepine dose was up-titrated to 900 mg twice daily. Concomitantly, Sn gradually fell to 131 mEq/L. DDAVP was discontinued, yet the Sn level declined to 121 mEq/L on day 9. After treatment with 3% saline and fluid restriction, Sn returned to 138 mEq/L in 2 days. Serum cortisol and free T4 levels were normal.

Conclusions: Proposed mechanisms of oxcarbazepine induced hyponatremia include: SIADH, prolonged ADH half-life, enhanced sensitivity of the renal tubules to ADH, and resetting the osmotic threshold for ADH release in the hypothalamus. Mechanisms of hyponatremia from oxcarbazepine appear to be either direct stimulation of the V2 receptor in the renal tubules or overabundance of the ADH co-receptor that results in low activity of the V2 receptor and presence of micromolar ADH concentrations undetectable by current assays. We conclude oxcarbazepine effectively managed both the seizure disorder & complete CDI in our patient and may be a useful alternative to DDAVP in patients with complete CDI.

Use of Continuous Renal Replacement Therapy for Dabigatran Toxicity – Does It Work?

Asif A.K. Ansari, Diana L. Deitzer. Cleveland Clinic Foundation.

Background: Dabigatran is an oral direct thrombin inhibitor approved for anticoagulation of non-valvular atrial fibrillation (AF). Drug toxicity in combination with lack of a reversal agent in cases of bleeding has been a major concern, especially in patients with impaired renal function. Extra corporeal therapy (ECT) is considered an effective modality for drug clearance in cases of toxicity, though data supporting its use is sparse. We report a case of critically ill patient with bleeding complications due to toxic levels of dabigatran, which was successfully treated with IHD sessions after inadequate clearance with several days of CRRT.

Methods: 70 year old man with AF on Dabigatran 150 mg twice daily that was appropriately dosed for chronic kidney disease stage 3 presented with intra cardiac defibrillator lead infection with enterococcus fecalis leading to septic shock and multi organ failure. He was aggressively treated with mechanical ventilation, pressor support and intravenous antibiotics. His illness was complicated gastric-intestinal bleeding with elevated Dabigatran level of 573 ng/dl and elevated thrombin time >120 seconds requiring multiple crystalloid transfusions. Interestingly, Dabigatran was discontinued 21 days previously and the patient was receiving continuous renal replacement therapy (CRRT) for the past 15 days for worsening renal failure with fragile hemodynamics. He was then successfully treated with 3 sessions of intermittent hemodialysis (IHD) with resumption of CRRT afterwards that resulted in adequate clearance of the drug. Although bleeding and the indices improved, patient succumbed eventually to multi organ failure.

Conclusions: Dabigatran eliminates the need for therapeutic drug level monitoring but must be dosed according to the renal reserve to avoid toxicity. Limited data available supports the use of IHD sessions of IHD in cases of toxicity with the success with CRRT has been variable. In our patient Dabigatan levels remained elevated despite several days of CRRT, suggesting that CRRT is not a reliable modality for drug removal and must not be used in such cases.

Fatal Valproic Acid-Induced Hyperammonemia Despite Continuous Renal Replacement Therapy

Nwamaka Denise Enemaya, Sushrut S. Waikar. Renal Medicine, Brigham and Women’s Hospital, Boston, MA.

Background: Valproic acid can be associated with severe hyperammonemia leading to neuronal injury and cerebral swelling. We report a case of fatal hyperammonemia in a young woman taking Valproic acid despite early initiation of continuous renal replacement therapy.

Methods: A 38 y/o female with history notable only for schizoaffective disorder was appropriately dosed for chronic kidney disease stage 3 presented with intra cardiac defibrillator lead infection with enterococcus fecalis leading to septic shock and multi organ failure. He was aggressively treated with mechanical ventilation, pressor support and intravenous antibiotics. His illness was complicated gastric-intestinal bleeding with elevated Dabigatran level of 573 ng/dl and elevated thrombin time >120 seconds requiring multiple crystalloid transfusions. Interestingly, Dabigatran was discontinued 21 days previously and the patient was receiving continuous renal replacement therapy (CRRT) for the past 15 days for worsening renal failure with fragile hemodynamics. He was then successfully treated with 3 sessions of intermittent hemodialysis (IHD) with resumption of CRRT afterwards that resulted in adequate clearance of the drug. Although bleeding and the indices improved, patient succumbed eventually to multi organ failure.

Conclusions: Dabigatran eliminates the need for therapeutic drug level monitoring but must be dosed according to the renal reserve to avoid toxicity. Limited data available supports the use of IHD sessions of IHD in cases of toxicity with the success with CRRT has been variable. In our patient Dabigatan levels remained elevated despite several days of CRRT, suggesting that CRRT is not a reliable modality for drug removal and must not be used in such cases.

Use of Continuous Renal Replacement Therapy for Dabigatran Toxicity – Does It Work?

Asif A.K. Ansari, Diana L. Deitzer. Cleveland Clinic Foundation.

Background: Dabigatran is an oral direct thrombin inhibitor approved for anticoagulation of non-valvular atrial fibrillation (AF). Drug toxicity in combination with lack of a reversal agent in cases of bleeding has been a major concern, especially in patients with impaired renal function. Extra corporeal therapy (ECT) is considered an effective modality for drug clearance in cases of toxicity, though data supporting its use is sparse. We report a case of critically ill patient with bleeding complications due to toxic levels of dabigatran, which was successfully treated with IHD sessions after inadequate clearance with several days of CRRT.

Methods: 70 year old man with AF on Dabigatran 150 mg twice daily that was appropriately dosed for chronic kidney disease stage 3 presented with intra cardiac defibrillator lead infection with enterococcus fecalis leading to septic shock and multi organ failure. He was aggressively treated with mechanical ventilation, pressor support and intravenous antibiotics. His illness was complicated gastric-intestinal bleeding with elevated Dabigatran level of 573 ng/dl and elevated thrombin time >120 seconds requiring multiple crystalloid transfusions. Interestingly, Dabigatran was discontinued 21 days previously and the patient was receiving continuous renal replacement therapy (CRRT) for the past 15 days for worsening renal failure with fragile hemodynamics. He was then successfully treated with 3 sessions of intermittent hemodialysis (IHD) with resumption of CRRT afterwards that resulted in adequate clearance of the drug. Although bleeding and the indices improved, patient succumbed eventually to multi organ failure.

Conclusions: Dabigatran eliminates the need for therapeutic drug level monitoring but must be dosed according to the renal reserve to avoid toxicity. Limited data available supports the use of IHD sessions of IHD in cases of toxicity with the success with CRRT has been variable. In our patient Dabigatan levels remained elevated despite several days of CRRT, suggesting that CRRT is not a reliable modality for drug removal and must not be used in such cases.

Ceftriaxone-Induced Allergic Intestinal Nephritis: An Atypical Presentation

Bhupinder Sangha, Judy L. Locati, Ishwinder Sidhu, Karina Sulaiman. Medicine, LSUHSC-Shreveport, Shreveport, LA.

Background: Allergic intestinal nephritis has commonly been reported with cephalosporins. Ceftriaxone is a fifth generation Cephalosporin approved by the FDA for use in community acquired pneumonia and acute bacterial skin structure and skin infections. It has activity against MRSA and has demonstrated non-inferiority to Vancomycin and therefore has been used in off label use for bacteremia. There are no reported cases of AIN with ceftriaxone thus far. We describe a case of a patient with atypical presentation of AIN due to suspected use of ceftriaxone.

Methods: A 52 year old white male with PMH of DM and HTN who presented to the hospital with fever, chills and fatigue was found to have MRSA bacteremia without an identifiable source. He was started on Vancomycin and blood cultures remained positive showing resistance to Vancomycin. Patient was then started on IV Ceftriaxone. The serum creatinine was subsequently noted to be elevated from baseline. Urine Wright stain was positive for eosinophils. He was discharged on a six week regimen of IV Ceftriaxone. Two weeks following discharge sputum cultures were positive for Mycobacterium kansasii and he was started on four drug regimen. He presented again to the hospital twenty days after completion of Ceftriaxone therapy. His creatinine had improved but had not returned to his baseline. The repeat Wrait stain continued to show eosinophils and patient was noted to be in persistent AKI. Renal biopsy showed acute tubular interstitial
nephritis with eosinophils consistent with hypersensitivity reaction. We attributed the nephritis to Cefarolone and continued the therapy for mycobacterium kansasii. His renal function improved after discontinuation of Cefarolone.

Conclusions: Cephalosporins have long been known to be associated with AIN. Experience with Cefarolone is limited in clinical practice. We present a case of AIN associated with Cefarolone use. In this case the offending agent was continued for a prolonged period causing interstitial fibrosis along with tubular damage that subsequently lead to ineffective natriuresis. This may explain his anasarca.

TH-PO836
Transient Pigment Induced Nephropathy following Percutaneous Rheolytic Thrombectomy Rapeepat Lekkham, Eric J. Bloom. Medicine, Einstein Medical Center; Philadelphia, PA.

Background: The AngioJet® rheolytic thrombectomy system is a catheter-based system for the removal of intravascular thrombi. Hemolysis and hemoglobinuria following the use of AngioJet® has been reported. We present the rare case of severe acute kidney injury following the use of this device that was successfully treated conservatively.

Methods: A 49-year-old female with HTN presented with the sudden onset of a severe headache secondary to subarachnoid hemorrhage. Cerebral angiography revealed a ruptured anterior communicating artery aneurysm. She underwent emergency craniotomy and clipping of the aneurysm. Prior to a repeat cerebral angiogram, the AngioJet® device was used to remove a thrombus in the right external iliac artery adjacent to the common femoral sheath. She received IV hydration prior to and during the contrast procedure. The patient was given a total of 85 ml of Iohexol. Immediately following the thrombectomy, her urine output improved significantly over the next 24 hours after thrombectomy. The serum Cr level was elevated and the serum haptoglobin level was low consistent with acute intravascular hemolysis. The urinalysis was strongly positive for blood with only 9 RBC/HPF on microscopy. Centrifugation of a urine sample produced a red supernatant which was positive for heme. Her urine myoglobin was negative. Centrifugation of a blood sample yielded red plasma consistent with a diagnosis of hemoglobinemia. Aggressive hydration with isotonic saline solution was continued without alkalization or diuretic. The patient did not require renal replacement therapy as her urine output improved significantly over the next 24 hours after thrombectomy. The serum Cr level returned to normal 10 days after thrombectomy.

Conclusions: Acute kidney injury caused by intravascular hemolysis and hemoglobinuria can occur following the use of the AngioJet® system. Aggressive hydration may be the best strategy to prevent and minimize the risk of this complication. The risk of AKI should be explained to patients before undergoing thrombectomy by use of AngioJet®.

TH-PO837

Background: Propofol induced rhabdomyolysis (RM) is a rare cause of acute kidney injury (AKI), especially in adults. A case of AKI from propofol induced RM is reported.

Methods: A 63 year old man was admitted to the hospital for atypical chest pain and dyspnea. Past history included diabetes, hypertension and obesity. Myocardial infarction was ruled out, but he continued to have worsening dyspnea. He developed fever, leukocytosis and pulmonary infiltrates. On hospital day 6, he was transferred to the intensive care unit for respiratory failure and sepsis, likely from pneumonia. He was intubated, placed on mechanical ventilation and given empiric IV antibiotics and vasopressors. Because of agitation, propofol 2.4 mg/kg/hr was added to midazolam and fentanyl on day 14, and subsequent doses of 1.5-1.8 mg/kg/hr were used. From day 19, patient was noted to have progressive transaminisits and worsening renal function with electrolyte disturbances and developed anuria by day 24. RM was confirmed by rise in Creatinine (CK) levels and urine blood positivity without urine red blood cells. Emergent hemodialysis was begun on day 24. Propofol induced RM was suspected and drug discontinued. CK level trended down within 72 hrs after stopping propofol, returning to normal in five days. Anterior thigh muscle biopsy showed a monophasic insult pattern of injury excluding chronic inflammatory injury. Dialysis was discontinued on hospital day 16 with subsequent full renal recovery.

Conclusions: Propofol induced RM is rare, and is usually seen at doses > 4 mg/kg/hr over a prolonged time. Our patient developed RM and AKI with doses of only 2.4 mg/kg/hr or less. Differential diagnosis included statins, neuroleptics, paralytics, critical illness myopathy, and pressure-induced ischemia and these were excluded. Discontinuation of propofol led to prompt recovery.

Funding: Veterans Affairs Support
Rasburicase was given. On day seven CVVHD was started to correct the phosphorous and uric acid. Pathology of the mass showed Burkitt Lymphoma on day 7. Cyclophosphamide and vincristine was included to treat the lymphoma.

**Conclusions:** Electrolyte abnormalities of TLS include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalemia. Clinical consequences include arrhythmias, acute kidney injury, seizures and death. Triggers of TLS can be cytotoxic and biological agents or ischemia. Spontaneous TLS has been documented in Burkitt’s lymphoma however little evidence does exist demonstrating TLS from biopsies of lymphoma masses. We propose CT-guided biopsies of our patient’s abdominal mass caused an acute TLS requiring renal replacement therapy, TLS and AKI should be considered a risk factor when undergoing biopsies for bulky tumors. Patients should be prophylactically treated with allopurinol and hydration.

**TH-PO842**

**Immobilization-Induced Hyperphosphatemia and Functional Hypoparathyroidism Successfully Treated with Oral Bisphosphonates**

**Disha D. Trivedi,** 1 Elvira Gosmanova,1 Barry M. Wall.1, 2 UTHSC, Memphis, TN; 3VAMC, Memphis, TN.

**Background:** Immobilization can induce hypercalcemia with suppression of PTH. Functional hypoparathyroidism is an infrequent cause of hyperphosphatemia.

**Methods:** A 46-year-old previously healthy male with 5-month history of paraplegia after a motorcycle accident was admitted with serum phosphorous levels (Pi) of 6.5-6.7 mg/dL after the injury. Physical examination was remarkable for T5–T6 level paraplegia and left elbow calcification. Oral intake consisted of tube feeding with 1 liter per day of “Peptamen” containing 667mg of Pi per L. Laboratory values showed total serum Ca of 10.6mg/dL, ionized Ca of 1.32mg/dL, (normal range 1.33-1.37mg/dL), serum bicarbonate 33 mEq/L, PTH level of 10.5pg/mL (normal range 15.70-50 pg/ml), 25-hydroxy vitamin D level of 16.7ng/ml. Serum albumin, magnesium, cortisol, and TSH levels were normal. Urine Ca to creatinine ratio was 0.149, fractional excretion of Pi (FEPi) 5.2%.

**Conclusions:** Immobilization-induced hyperphosphatemia from functional hypoparathyroidism has been successfully treated with oral bisphosphonates.

**TH-PO843**

**Horsetail Tea Ingestion and End-Stage Renal Disease: An Unrecognized Form of Silica Associated Nephropathy?**


**Background:** To date, horsetail tea has not been associated with renal disease. Silica is a main component of the plant horsetail, genu Equisetum. Silica is thought to have direct nephrotoxic and inflammatory effects in the kidney. This is a case of a 64 year old woman who presented with accelerated end stage renal disease in the setting of diabetic nephropathy, but renal progression might have been hastened by silica in horsetail tea.

**Methods:** Our 64 year old woman was recently diagnosed with type 2 diabetes and started on insulin therapy 1 month prior to presentation. At the time, her serum creatinine was 1.2 mg/dL, and she was told that she had a “kidney problem.” While vacationing in Mexico, her family encouraged her to drink horsetail tea to “build up her kidneys.” The tea is made by boiling crushed horsetail which contains copious amounts of silica. For 3 weeks, she drank horsetail tea daily, until she became increasingly ill with tinnitus and headache.

**Conclusions:** Immobilization-induced hyperphosphatemia from functional hypoparathyroidism was successfully treated with oral bisphosphonates.

**TH-PO841**

**Case Series of Rituximab-Induced Tumor Lysis Syndrome**

Venu Velagapudi, Mazen O. Al-Qadi. Critical Care, Mayo Clinic, Rochester, MN.

**Background:** Tumor lysis syndrome (TLS) is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalemia, acute kidney injury and metabolic acidosis. Rituximab-induced TLS is extremely rare with only 7 cases reported in the literature. We report a case series of 2 cases of TLS following Rituximab therapy in lymphoproliferative diseases.

**Methods:** CASE-1 An 84-year-old female with CLL presented for chemo-therapy with rituximab. After rituximab, she had severe rigors, tachycardia and tachypnea. TLS was diagnosed on the basis of fulfilling Cairo-Bishop laboratory criteria for potassium, phosphorus, uric acid and calcium. She also had pancytopenia, lactic acidosis and acute kidney injury. Clinical grade 2 Cairo-Bishop criteria were fulfilled for renal impairment and arrhythmia. Despite IV fluids, rasburicase, and antibiotics, she developed respiratory failure, Klebsiella pneumoniae septicemia and died after withdrawal of care. CASE-2 An 82-year-old man with angioedema, Gamma heavy chain disease from lymphoproliferative lymphoma developed TLS 24 hours after Rituximab. The diagnosis was made by fulfilling 3 laboratory Cairo Bishop Criteria for Phosphorus of 7.2 mg/dL from 5.1 mg/dL, Uric acid 9.6 mg/dL from 5 mg/dL, calcium 6.4 mg/dL from 8.2 mg/dL despite allopurinol and IV fluids. He had fulfilled 2 Cairo-Bishop criteria for grade 2 TLS with serum creatinine of 1.9 mg/dL (≥2 X Upper limit) and atrial fibrillation requiring treatment. He also had lactic acidosis and respiratory failure. He recovered from TLS, but opted for hospice care later.

**Conclusions:** Rituximab is an anti-CD20 monoclonal antibody that mediates destruction of CD20+ B-lymphocytes. Serious reactions including TLS has been reported in patients with serum phosphorus levels (Pi) of 6.5-6.7 mg/dL after the injury. Physical examination was remarkable for T5–T6 level paraplegia and left elbow calcification. Oral intake consisted of tube feeding with 1 Liter per day of “Peptamen” containing 667mg of Pi per L. Laboratory values showed total serum Ca of 10.6mg/dL, ionized Ca of 1.32mg/dL, (normal range 1.33-1.37mg/dL), serum bicarbonate 33 mEq/L, PTH level of 10.5pg/mL (normal range 15.70-50 pg/ml), 25-hydroxy vitamin D level of 16.7ng/ml. Serum albumin, magnesium, cortisol, and TSH levels were normal. Urine Ca to creatinine ratio was 0.149, fractional excretion of Pi (FEPi) 5.2%.

**TH-PO844**

**A Fulminant Case of Hypermagnesemia**

Mary Muoneke, Ginius Pradhan, Kankam Charity, Deetu Simh.

**Background:** The efficiency of renal response to Magnesium load is such that hypermagnesemia is primarily seen in impaired renal function & iatrogenic (when a large Mg load is taken IV,orally,enema). The symptoms are well known but under-recognized.

**Methods:** We report a case of hypermagnesemia presenting with fall paraletic iliacus complicated by cardiac arrhythmia arrest.

**Methods:** 82 yr old lady presented with fall,nausea&constipation. PMHHTN,sczatioffective disorder. Meds: cogentin,benzazepril,seroquel,haldol. She had stable vital signs,distended abdomen,hypotactic bowel sounds,hard stools in the rectum & diminished reflexes in all extremities. Labs Na.135, K.4.4, CI.97 HCO3.1 BUN.88 Cr.1.0 KUB:distended bowel suggestive of paralytic ileus. She got enema & surgical consult.

Further history revealed intake of large doses of magnesium citrate to relieve constipation. Magnesium level was 15.3mg/dl. She got IV fluids,Laxis,was more lethargic,hypotensive

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

Underline represents presenting author/disclosure.

291A
& bradycardic followed by a cardiac arrest. She was resuscitated successfully as per ACLS protocol. She got IV calcium gluconate & urgent hemodialysis. Despite these interventions, she coded again & resuscitation attempt was futile.

**Conclusions:** Magnesium is a cofactor in more than 300 enzymatic reactions. Homeostasis is maintained by intestines & kidneys. Massive oral ingestion may cause hyperMg if the absorbed Mg exceeds renal capacity. The index patient took large doses of magnesium to relieve constipation. It resulted in a vicious cycle of hypermagnesemia causing paralytic ileus which further enhanced Mg absorption. Hypermagnesemia manifested as fall due to muscle weakness, bradycardia, hypotension &cardiopulmonary arrest. Deterioration of her renal function is explained by hypermagnesemia-induced hypotension &reduced cardiac output leading to reduced GFR & worsened Mg clearance. Treatment of exogenous Mg, IV fluids, IV Calcium carbonate & if therapy fails, hemodialysis against a low Mg bath was presented with non specific symptoms which retrospectively points to high Mg as the culprit. This case illustrates that hypermagnesemia can occur with normal renal function especially in elderly patients who present with paralytic ileus & generalized weakness.

**TH-PO845**

**FGF-23 Mediated Phosphaturia – A Rare Paraneoplastic Disease in Carcinoma**

Rupal Mehta, Eudora Eng. *Nephrology, Northwestern Univ, Feinberg School of Medicine, Chicago, IL.*

**Background:** Fibroblast growth factor (FGF-23), a crucial regulator of serum phosphate and 1,25(OH) vitamin D, is secreted by osteocytes and osteoblasts and is regulated by oral phosphate load and vitamin D levels.

In oncogenic osteomalacia, abnormal secretion of FGF-23 represents a paraneoplastic syndrome associated with hypophosphataemia and vitamin D metabolism. It is typically described in tumors of mesenchymal origin and presents as hypophosphatemia secondary to renal phosphate wasting.

**Methods:** A 51 year old Chinese male with metastatic nasopharyngeal carcinoma to the bone presented for additional therapy of a percutaneous effusion. He was noted to have a phosphate level of 1.1 mg/dl. Investigation of his hypophosphatemia revealed renal failure, vitamin D level, parathyroid hormone, and calcium. A fractional excretion of phosphorus was 22.7% (reference < 5% in hypophosphatemia) and phosphorus excretion on 24 hour urine collection was 681.4 mg. A FGF-23 level of 540 RU/ml (reference <181 RU/ml) confirmed the suspected diagnosis of oncogenic osteomalacia. Aggressive oral and IV phosphorus supplementation was started for persistent symptomatic hypophosphatemia.

**Hospital Day**

<table>
<thead>
<tr>
<th>Phosphorus</th>
<th>Phosphorus Repletion in mmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>1.9</td>
</tr>
<tr>
<td>26</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Conclusions:** Oncogenic osteomalacia is an entity seen mostly in malignancies of bone and soft tissue with definitive treatment being resection. The half life of FGF-23 is approximately 58 minutes, thus, phosphate levels can quickly normalize postoperatively. We present the first reported case of oncogenic osteomalacia in a patient with nasopharyngeal carcinoma. He had exhausted all surgical, chemotherapeutic and radiation options for treatment of his malignancy and no proven nonsurgical therapies exist for treatment of oncogenic osteomalacia. CINACALCT, an agonist of the calcium sensing receptor, has been used as a potential treatment given that FGF-23 may be PTH dependent however, our patient had normal PTH levels. With limited therapeutic options, this disease entity was extremely difficult and cumbersome to manage.

**TH-PO846**

A Case of Severe Hypocalcemia Induced by Sprue-Like Enteropathy Associated with Olmesartan

Keita Hirano, Kumiko Shimasaki, Masahiko Nagahama, Yasuhiro Komatsu. *Div of Nephrology, Dept of Internal Medicine, St. Luke’s International Hospital, Japan.*

**Background:** In this report, we describe a rare case of hypocalcemia with tetric symptoms. The cause of hypocalcemia in hospitalized patients is most often caused by disorders of parathyroid hormone (PTH) or vitamin D. Symptomatic hypocalcemia is as a first sign of celiac sprue. Celiac sprue is an autoimmune disorder of the small intestine. Chronic diarrhea and calcium and vitamin D malabsorption are characteristics of celiac sprue. They cause hypocalcemia.

**Methods:** A previously healthy 64-year-old woman was referred to our hospital because of severe diarrhea and tetric symptoms. She had diabetes and hypertension treated with olmesartan. Her serum ionized calcium (Ca²+) level was 1.63 mmol/L and she presented with non specific symptoms which retrospectively points to high Mg as the culprit. This case illustrates that hypermagnesemia can occur with normal renal function especially in elderly patients who present with paralytic ileus & generalized weakness.

**Conclusions:** This patient presented with severe hypocalcemia and diarrhea and showed clinical response and histologic improvement after suspension of olmesartan which was suspected to be causing the sprue-like enteropathy.

**TH-PO847**

**Tetany, an Unusual Cause!** Reem Daloul, Abhishek Swami. *William Beaumont Hospital, Royal Oak, MI.*

**Background:** Tetany is a sustained involuntary muscle contraction that often occurs as a result of hypocalcemia or severe alkalosis. Here we report a case of severe acute tetany with a very unusual etiology.

**Methods:** A 34 year old female nurse with history of anxiety disorder and depression presented to the hospital for diffuse tetany. Symptoms started suddenly while driving with numbness and tingling of extremities followed by diffuse spasm and contraction of arms, legs, jaw and chest. Her home medications included serquel and sertraline. On presentation, the patient was normotensive. She had wide open eyes, locked jaw, flexed wrists and digits, and flexed posture. Laboratory work revealed severe hypocalcemia with potassium of 1.9 mmol/L, and metabolic alkalosis with a bicarbonate level of 37 mmol/L. Ionized and total calcium as well as magnesium levels were normal. Administration of intravenous potassium chloride resulted in prompt muscle relaxation. Further investigations revealed a high urinary potassium indicating renal potassium loss. Urine for diuretic screen was negative. The patient was discharged in stable condition on oral potassium supplement with plan for further evaluation to establish the etiology of hypocalcemia as out patient.

**Conclusions:** Neuromuscular effects of hypocalcemia typically include generalized weakness, fatigue and muscle paralysis. Tetany, which represents muscle irritability appears to be a paradoxical effect. It has been described in standard text books and there are rare reports in literature. In our case, the prompt muscle relaxation following potassium supplements administration indicates that hypocalcemia was the principle causative factor. Hypocalcemia needs to be considered in the differential diagnosis of acute tetany as early recognition and treatment is needed for this potentially fatal condition.

**TH-PO848**

**Acute Development of Resistant Hypertension following Octreotide Therapy for Carcinoid Syndrome**

Douglas W. Schwartz, Barry M. Wall. *University of Tennessee Health Science Center, Memphis, TN; Veterans Affairs Medical Center, Memphis, TN.*

**Background:** Octreotide has been effective in managing symptoms of carcinoid syndrome. Both hypertension and acute hypertensive crises associated with carcinoid syndrome have responded to octreotide therapy. Although carcinoid tumors can produce a number of vasodilatory substances, the development of refractory hypertension during octreotide therapy for carcinoid syndrome has not been reported.

**Methods:** 61 yr old male with well controlled hypertension (Lisinopril/HCZ) was found to have carcinoid syndrome during evaluation for chronic diarrhea and facial flushing. Biopsy of liver lesions showed a carcinoid neuroendocrine tumor. 5-HIAA level was markedly elevated at 26 mg/day. Within 3 days of initiating long acting octreotide (20mg IM) blood pressure became acutely elevated, 224/101 mmHg with no change in heart rate. Despite progressive addition of metoprolol, hydralazine, and amlodipine, systolic BP remained > 150mmHg. Workup for secondary causes of hypertension included: normal hemoglobin, normal serum potassium, creatinine (1.3 mg/dl), urinalysis, and urinary metanephrine excretion. Imaging studies revealed normal adrenal glands and kidneys. Plasma renin activity was not elevated. Volume status was unchanged. During long term monthly octreotide therapy, diuretica and flushing rapidly resolved and have not recurred. BP control improved (140/80 mmHg), but continues to require multi-drug therapy.

**Conclusions:** Octreotide has not been reported to have direct vasoconstrictor effects. An acute hypertensive crisis has been reported to occur following octreotide therapy in 2 prior patients (pneumococytoma and diabetic associated diarrhea) that resolved following suspension of octreotide. The development of refractory hypertension during octreotide therapy for carcinoid syndrome has not been reported. The most likely etiology for the accelerated hypertension in our patient is increased systemic vascular resistance, resulting from decreased production of vasodilatory substances from the carcinoid tumor.

**TH-PO849**

**Midaurtic Syndrome: An Unusual Cause of Resistant Hypertension in Adults**


**Background:** Resistant hypertension (RH) is defined as BP >140/90 (general population),and >130/80 (chronic kidney disease) despite concurrent use of 3 antihypertensives. The prevalence of RH may be as high as 20% in the hypertensive population.

**Methods:** A 52 year old Hispanic male with history of resistant hypertension (diagnosed at age 8), hemorrhagic stroke and chronic kidney disease (CKD) stage III with baseline creatinine 1.7 mg/dL, was admitted with chest pain and severe hypertension. Examination revealed blood pressure in left arm 208/89 mmHg, and right arm 225/118 mmHg, cardiac holoystolic murmur and an abdominal bruit. A work up to rule out aortic dissection was initiated. CTA thorax showed elongated funnel-shaped stenosis with severe luminal narrowing involving the distal descending thoracic aorta. Cardiac workup was negative for ischemia. Further testing showed negative renal artery stenosis, normal bilateral renal size and echotexture, negative ANA, RPR, and urine toxicology screen. Aortic ultrasound showed less than 50% diameter reduction. A diagnosis of supraceliac midaurtic syndrome was made. Patient underwent Aorto-aorto (descending thoracic aorta to infrarenal
aorta) bypass. At discharge, patient’s creatinine was 1 mg/dL, and he required only 2 antihypertensive medications. Nine months after surgery, creatinine and anti-hypertensive regimen remained unchanged from time of discharge.

Conclusions: Midaortic syndrome (MAS) is a rare anomaly accounting for 0.5% to 2.0% of all aortic coarctations. It is most common in pediatric population, and young adults. MAS is usually congenital, but can also be associated with Takayasu’s or temporal arteritis, neurofibromatosis and Williams syndrome. Serious complications of renovascular hypertension, including CKD, heart failure or ischemia, intracranial hemorrhage and aortic rupture may ensue. Treatment is predominantly surgical. We report an unusual case of idiopathic MAS in an adult patient with history of CKD, intracranial hemorrhage and resistant hypertension, with normalization of renal function, and improvement in blood pressure control post surgical repair.

TH-PO850

Background: While Fibromuscular dysplasia (FMD) is an established cause of secondary hypertension, its association with renal infarction, which often has a subtle presentation, is less well recognized. Here, we report a case of FMD presenting with acute abdomen, bilateral renal infarcts, and severe hypertension.

Methods: A 53-year-old man presented with hematuria and acute severe abdominal and back pain radiating to the scrotum. Physical examination was unremarkable except for a blood pressure of 194/129 mmHg and right lower quadrant abdominal tenderness. Heart rate was regular and there were no skin lesions. Laboratory studies showed a serum creatinine level of 1.3 mg/dL, leukocyturia, and hematuria. Contrast-enhanced abdominal CT showed bilateral renal infarcts and multiple short segment dissections of the middle cotic, right renal, left renal, and left external iliac arteries.

Conclusions: Large urinary leaks can lead to bladder distension and hyptertrophy with subsequent intramural obstruction of the distal ureters. Bladder contractility is compromised, ureretic peristalsis diminishes and large residual volumes worsen this functional obstructive uphrathy. Social embarrassment leading to voluntarily urine retention exacerbates it. Corrective therapy, even after prolonged period can lead to improvement in urinary tract dilatation. CKD can occur but ESRD is unknown. Our patient though had central DI did not reach the maximum concentrating ability following DDAVP test. A part maybe due to age related decrease in concentrating ability. Also long standing obstructive urophy can result in acquired nephrogenic DI. The exact pathophysiology is not known but severe hypohsphataemia indicates an intact diluting capability and locates the defect distal to the loop of Henle. Increased collecting duct pressure causes damage to the tubular epithelium resulting in insensitivity or partial sensitivity to the action of AVP.

TH-PO851
Weeping Kidney Syndrome Ankit Rawal, Stuart M. Sprague. Nephrology, Univ of Chicago - NorthShore, Evanston, IL.

Background: Weeping kidney syndrome has a very low incidence rate with few reported cases and is confusion in the definition. This report presents one rare case and discusses features of this disease.

Methods: A 41 year old african american female with past medical history of type I diabetes mellitus and primary polycystic transplant presents with recurrent abdominal pain, vomiting, and inability to tolerate oral intake. On initial examination, heart and lungs were normal. On abdominal examination, there was distention and soft ballotable swelling of the right lower quadrant. Routine blood examination was normal with the exception of an acutely elevated serum creatinine of 2.0 mg/dL. Radiological evaluation revealed new onset ascites with a cystic lesion in the transplanted kidney causing ureteral obstruction. A therapeutic paracentesis was performed which gave the patient symptomatic relief and revealed a high serum-ascites albumin gradient. The patient subsequently presented 3 days later with similar complaints. Imaging studies demonstrated complete fluid collection throughout the pelvis with a loculated collection around the transplanted kidney. Serological evaluation of liver function and possible causes of hepatic dysfunction all returned negative. An abdominal drain was then placed which drained approximately 1.5 liters of yellow serous fluid per day. This provided the patient minimal relief. A liver biopsy was performed and returned negative. Further ascitic fluid analysis revealed a peritoneal fluid creatinine of 6.7 mg/dL and with a corresponding serum creatinine of 3.1 mg/dL. At this time it was thought the ascites may be nephrogenic in nature or due to urinary leak. She underwent a diagnostic laparoscopy which showed a slow, continuous leak of lymphatic fluid from the transplanted kidney, diagnostic for renal lymphangiectasia. The patient then underwent marsupilization and wrapping of the weeping kidney in omentum. This procedure proved to be successful and resolved her presenting complaints from six months prior.

Conclusions: Renal lymphangiectasia is a rare disease of the renal lymphatics with approximately 40 cases being described since 1890. This case depicts a rarely reported complication of renal transplantation.

TH-PO852

Background: Functional obstructive urophy should be considered in patients with CKD and polyuria/polydipsia, especially who have evidence of central or nephrogenic DI, psychogenic polydipsia or use of anti-cholinergic medications.

Methods: 74 year old female was seen for worsening creatinine which rose from 1.7mg/dl in 2007 to 2.4mg/dl in 2011. Her main complaint was polyuria and polydipsia. In early childhood she was diagnosed with Arnold Schellener Christian disease. On evaluation she had stable vitals, bilateral nerve deafness and a palpable urinary bladder. Her serum Cr was 2.5mg/dL, serum Na 145meq/l and UA showed a specific gravity of 1.005. Renal USG showed bilateral collecting system dilatation and post void residual of 578ml. Urine osmolality rose from 140mosm/kg to 365mosm/kg 2 hours following a 2mg i.v. DDAVP. She was taught self catheterization and started on 0.5mg of DDAVP orally daily. Follow up labs showed a creatinine of 133-140mg/dL and urine osmaliity of 360mosm/kg. Renal USG showed mild bilateral collecting system fullness. Her urine output and fluid intake had markedly decreased improving her quality of life.

Conclusions: Large urinary leaks can lead to bladder distension and hyptertrophy with subsequent intramural obstruction of the distal ureters. Bladder contractility is compromised, ureretic peristalsis diminishes and large residual volumes worsen this functional obstructive uphrathy. Social embarrassment leading to voluntarily urine retention exacerbates it. Corrective therapy, even after prolonged period can lead to improvement in urinary tract dilatation. CKD can occur but ESRD is unknown. Our patient though had central DI did not reach the maximum concentrating ability following DDAVP test. A part maybe due to age related decrease in concentrating ability. Also long standing obstructive urophy can result in acquired nephrogenic DI. The exact pathophysiology is not known but severe hypohsphataemia indicates an intact diluting capability and locates the defect distal to the loop of Henle. Increased collecting duct pressure causes damage to the tubular epithelium resulting in insensitivity or partial sensitivity to the action of AVP.

TH-PO853
Perceptions of Nephrology among Internal Medicine Residents Ivan E. Porter,1 Hope Kincaid,2 Stuart J. Hartman,2 Nabeel Aslam,1 Sharon E. Maynard.2 Nephrology & Hypertension, Mayo Clinic, Jacksonville, FL; 2Leigh Valley Health Network, Emmaus, PA.

Background: As interest in nephrology declines, we sought to identify factors influencing nephrology career interest among internal medicine (IM) residents.

Methods: This is a cross-sectional survey of IM residents to assess perceptions of nephrology and the impact of these perceptions on career decisions. All categorical IM residents at two institutions (Leigh Valley Health Network and Mayo Clinic Florida) were invited to participate, prior to the initiation of a nephrology fellowship program. The survey was adapted from a tool previously validated in Australian medical trainees.

Results: 58 of 78 residents completed the survey (74% response rate). 53% of the residents were male and 84 % were US graduates. 14% of residents indicated an interest in nephrology. Cardiology (32%) and Hospitalist (41%) were the most sought after fields. The most common reason for choosing different fields was work hours (42%) and frequent/difficult call (57%).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
TH-PO854

More Women Choose Nephrology, but Publications by Female Senior Authors Have Not Increased Suzanne M. Norby, LaTonya J. Hickson, Amy W. Williams. Nephrology & Hypertension, Mayo Clinic, Rochester, MN.

Background: Over the past decades, the number of female physicians has increased, yet women are promoted to associate professor and professor levels at lower rates than for men. Differences in number of peer-reviewed publications by female and male authors likely contribute to the discrepancy. To explore this further in nephrology, this study compared the number of female nephrology fellows in 1994 and 2011 as well as the number and relative percentage of publications by female authors in two nephrology journals.

Methods: The number of female nephrology fellows in the U.S. was obtained from published data in the the American Medical Association. The tables of contents of regular issues of the Journal of the American Society of Nephrology and the American Journal of Kidney Diseases from 1994 and 2012 were reviewed. The study was limited to articles with first or last authors listing a U.S. institutional affiliation. The gender of first and last authors for original articles was determined, using internet search strategies when gender was not obvious by first name.

Results: In 1994, 121/637 (19%) of nephrology fellows were women compared with 336/918 (36%) in 2011 (p=0.0001). 520 original article entries were reviewed. 316 were from U.S. institutions: 168/244 (69%) in 1994 and 148/275 (54%) in 2012. In 1994, 34 (20%) of articles had a female first author compared with 60 articles (46%) in 2012. Proportion of articles with a female last author was not significantly different; 23(14%) in 1994 compared with 24(16%) in 2012. Female first authors did not increase significantly in JASN [21(91%) to 30(79%) ] but did in AKJD [13(77%) to 30(36%); p=0.014]. Female last authors did not increase significantly for JASN (12% vs 15%) and decreased for AKJD (16% vs 13%).

Conclusions: Although the proportion of female nephrology fellows doubled between 1994 and 2011, the number of publications by women in two high-impact nephrology journals does not demonstrate a parallel increase. Since there is a lag between completion of training and achieving academic productivity, the increase in number of female first authors is encouraging. Further analysis is needed to examine trends.

TH-PO855

Documentation of Counseling Performed at Clinic Visits, a CMS EHR Incentive Program Requirement Anna Burgner, Julia Lewis. Div of Nephrology, Vanderbilt Univ School of Medicine, Nashville, TN.

Background: One of the requirements of Stage 2 for the CMS for Medicare and Medicaid Electronic Health Records (EHR) Incentive Programs is to provide clinical summaries to the patient for each office visit within one business day (meaningful use core measure #8). Part of these clinical summaries includes written documentation of counseling/instructions given to the patients during the visit. Frequently the same counseling can be appropriate for multiple patients during a clinic session.

Methods: Using our electronic medical record system, we have created a set of templates in the areas that we frequently counsel our patients, and these can be easily auto-imported into the clinical summary. They include topics such as ACE-I and ARB templates in those areas that we frequently counsel our patients, and these can be easily auto-imported into the clinical summary. They include topics such as ACE-I and ARB

Conclusions: We do not demonstrate a parallel increase. Since there is a lag between completion of training and achieving academic productivity, the increase in number of female first authors is encouraging. Further analysis is needed to examine trends.

TH-PO856

A Pilot Renal-Palliative Care Curriculum: Improving Knowledge and Skills among Nephrology Fellows Katharine Cheung,1 Sumi Sukumaran Nair,1 Emiliee R. Wilhelm-Leen,1 Manjula Kurella Tamura.2 Stanford Univ School of Medicine;1Palo Alto VA Health Care System.

Background: Nephrologists frequently care for frail, older patients with high annual mortality. But the majority of trainees feel unprepared to have end-of-life discussions. This quality improvement project aims to describe the knowledge, attitudes and skills of nephrology fellows at a single center and track their progress through an innovative, renal-palliative care curriculum.

Methods: We conducted a focus group of nephrology fellows to assess their knowledge gaps in palliative care. Using that baseline, we collaborated with experts in Palliative Care and Geriatric Nephrology to devise a pilot curriculum. We assessed knowledge, attitudes and skills with surveys before and after the pilot and each learning module. Survey data was collected using Qualtrics survey tool.

Results: The curriculum consisted of four lectures (hospltal, dialysis withdrawal, cross-cultural care, non-pain symptom management), two workshops (pain management and communication skills) and one journal club (prognostication in kidney disease) over six months. In the pre-test, four of nine trainees reported having no prior training in counseling, pain management skills, or life or palliative care for renal patients but 90% of trainees reported a sense of responsibility to be trained in these areas. When asked to rate knowledge and/or skills on 21 specific areas (e.g., knowledge of hospice services available to dialysis patients), the mean score ranged from 2.1-3.5 on a five-point scale, with 5 being the best score. Trainees reported particular need for teaching in planning for withholding dialysis. In general, trainees’ scores on content-based pre-tests were low (mean correct across three tests 54%); there was improvement in post-tests (mean correct across three tests 75%). Trainees reported a high score for usefulness of the content as well as their likelihood of recommending the sessions to others (means 4.7 and 4.8 respectively on a five-point scale).

Conclusions: Renal fellows have limited training in palliative care, but desire this training. A curriculum covering common topics in palliative care increases content knowledge and is rated by trainees as highly useful.

TH-PO857

Nephrology Elective Experience during Medical Residency: A U.S. Nephrology Fellowship Training Program Directors’ Survey Hitesh H. Shah,1 Nancy Day Adams,2 Aditya Kadiyala,1 Kenar D. Jhaveri,1 1Nephrology, Hofstra North Shore–LIJ School of Medicine, Great Neck, NY; 2Univ of Connecticut Health Center, Farmington, CT.

Background: Interest in nephrology careers is declining in the United States (US). The type of nephrology elective that internal medicine (IM) residents experience may play an important role in enhancing interest in nephrology careers. We do not know what types of nephrology electives are offered in IM programs or whether nephrology electives are representative of what nephrologists do in practice.

Methods: An anonymous online survey was created & subsequently distributed to all US nephrology fellowship training program directors (N-TPDs) in May 2013.

Results: So far, 50 US N-TPDs have responded to our survey (34% response rate). 86% of the programs offered a 4-week nephrology elective at their institution. 48% of the programs did not offer any outpatient (OP) nephrology experiences to their IM residents during a typical 4-week elective. Nearly 90% of the programs did not rotate their residents in inpatient hemodialysis (HD) or OP nephrology faculty mentoring (78%). 72% felt that a 4-week elective would provide adequate exposure to nephrology during residency and 92% of the N-TPDs thought that an “ideal” nephrology elective experience should include both inpatient (IP) & OP experiences. “Inpatient service needs” (48%) and “too much work to coordinate various OP experiences” (26%) were some of the reasons identified by N-TPDs for none or limited OP nephrology experiences for IM residents. Over half of the N-TPDs responded that their elective structure was not representative of what nephrologists do in practice.

Conclusions: Nearly half of the responding programs did not offer any OP nephrology experiences to IM residents. To enhance knowledge and interest in nephrology careers during IM residency, a combined exposure to both IP & OP nephrology (including outpatient dialysis and transplantation) should be strongly considered by the training community.

TH-PO858


Background: Interest in nephrology careers is declining in the United States (US). The type of nephrology elective that US medical students experience may play an important role in creating interest in nephrology careers.

Methods: We created a novel 4-week nephrology elective experience for visiting medical students at our institution. Our redesigned elective included both 2-week inpatient (IP) & 2-week outpatient (OP) nephrology experiences. The OP rotation included 10 half-days of nephrology clinic experiences, 2 half-days of immediate post-transplant clinic, 1 half-day of kidney donor evaluation clinic, 2 half-days of PD clinic and 3 half-days of outpatient HD unit rounding. Our redesigned elective also included educational conferences. From 6/2012 to 12/2012, 544th year medical students (all from different US medical schools) completed our redesigned nephrology elective. An anonymous online survey was created to evaluate the novel elective experience and was subsequently distributed to all students in June 2013.

Results: All students responded to our survey. All reported adequate OP nephrology exposure. 80% of the students had worked with one or two faculty members during the OP setting. In comparison, 80% were exposed to at least four different faculty members during the OP experiences. All students had interacted with at least 3 fellows. All reported that the elective experience enhanced their exposure and knowledge in nephrology and that they would recommend this elective to other medical students. They also thought that this elective provided them with a better insight into what nephrologists do in practice. 80% of the students reported that this elective experience created an interest in nephrology career. Majority (60%) of the students responded that they would consider nephrology as one of their 3 top career choices as a result of this elective experience.

Conclusions: We believe that the restructured nephrology elective will provide the medical student with a much needed and realistic exposure to nephrology. Based on our experience, we recommend all nephrology training programs to consider this elective structure for medical students.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Characteristics of U.S. Adult Nephrology Fellowship Training Program Directors

Hitesh H. Shah, Divya Monga, Aditya Kadiyala, Anna Mathew. Nephrology, Hofstra North Shore–LIJ School of Medicine, Great Neck, NY.

Background: Characteristics of US adult nephrology fellowship training program directors (N-TPDs) are not known. We do not know how long N-TPDs have served in their role as TPDs and if they have undergone fellowship training in the same program where they were serving as TPD.

Methods: Data were abstracted in June 2013 from public websites of Accreditation Council for Graduate Medical Education-Accreditation Data System, Electronic Residency Application Service, Healthgrades.com and webpages of individual nephrology fellowship programs. Data was analyzed for 146 N-TPDs.

Results: Out of 134 N-TPDs who served as TPD for at least 5 years, 60% were male and 40% had received formal training in nephrology. 33.6% were found to have completed their fellowship training in the same program that they were serving as TPD.

Conclusions: Majority of the N-TPDs were males and had undergone medical school training in the US. A significant percentage of N-TPDs who were trained in international medical schools were from India. Majority of this group has served as TPD for over 5 years and nearly one-fourth have served for more than 10 years. Interestingly, one-third of the N-TPDs had undergone fellowship training in the same program where they were serving as TPD.

TH-P0859

Nephrology Exposure during Medical Residency: A U.S. Internal Medicine Program Directors’ Survey Karen M. Warburton,1 Kenar D. Jhaveri,2 Ankit B. Patel,1 Stephanie A. Cali,1 Vincent Arora,2 Hitesh H. Shah.2 Nephrology, Univ of Pennsylvania; 1Nephrology, Hofstra North Shore Medical Center, 2Medicine, Well Cornell Medical College; 3Medicine, Virginia Commonwealth Univ; Medicine, Univ of Chicago.

Background: Almost 80% of nephrology consultative services are called by non-nephrologists. Low health literacy is associated with less desirable clinical outcomes. While nearly two thirds of IM-PDs thought that nephrology consultative services should be called by nephrologists, little is known about the types of nephrology exposure offered during internal medicine (IM) residency in the US. The relationship of this exposure to success in recruiting future nephrologists from residency programs is also unknown. It is unclear if US IM program directors with CKD stages 1-5 nephrology exposure during IM residency are more likely to have adequate health literacy, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white.

TH-P0860

Program Directors’ Survey

Karen M. Warburton,1 Kenar D. Jhaveri,2 Ankit B. Patel,1 Stephanie A. Cali,1 Vincent Arora,2 Hitesh H. Shah. Nephrology, Univ of Pennsylvania; 1Nephrology, Hofstra North Shore Medical Center, 2Medicine, Well Cornell Medical College; 3Medicine, Virginia Commonwealth Univ; Medicine, Univ of Chicago.

Background: Almost 80% of nephrology consultative services are called by non-nephrologists. Low health literacy is associated with less desirable clinical outcomes. While nearly two thirds of IM-PDs thought that nephrology consultative services should be called by nephrologists, little is known about the types of nephrology exposure offered during internal medicine (IM) residency in the US. The relationship of this exposure to success in recruiting future nephrologists from residency programs is also unknown. It is unclear if US IM program directors with CKD stages 1-5 nephrology exposure during IM residency are more likely to have adequate health literacy, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white.

TH-P0861

Nephrology Exposure during Medical Residency: A U.S. Internal Medicine Program Directors’ Survey

Karen M. Warburton,1 Kenar D. Jhaveri,2 Ankit B. Patel,1 Stephanie A. Cali,1 Vincent Arora,2 Hitesh H. Shah. Nephrology, Hofstra North Shore Medical Center, 2Medicine, Well Cornell Medical College; 3Medicine, Virginia Commonwealth Univ; Medicine, Univ of Chicago.

Background: Almost 80% of nephrology consultative services are called by non-nephrologists. Low health literacy is associated with less desirable clinical outcomes. While nearly two thirds of IM-PDs thought that nephrology consultative services should be called by nephrologists, little is known about the types of nephrology exposure offered during internal medicine (IM) residency in the US. The relationship of this exposure to success in recruiting future nephrologists from residency programs is also unknown. It is unclear if US IM program directors with CKD stages 1-5 nephrology exposure during IM residency are more likely to have adequate health literacy, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white.

TH-P0863

Nephrology Exposure during Medical Residency: A U.S. Internal Medicine Program Directors’ Survey

Karen M. Warburton,1 Kenar D. Jhaveri,2 Ankit B. Patel,1 Stephanie A. Cali,1 Vincent Arora,2 Hitesh H. Shah. Nephrology, Hofstra North Shore Medical Center, 2Medicine, Well Cornell Medical College; 3Medicine, Virginia Commonwealth Univ; Medicine, Univ of Chicago.

Background: Almost 80% of nephrology consultative services are called by non-nephrologists. Low health literacy is associated with less desirable clinical outcomes. While nearly two thirds of IM-PDs thought that nephrology consultative services should be called by nephrologists, little is known about the types of nephrology exposure offered during internal medicine (IM) residency in the US. The relationship of this exposure to success in recruiting future nephrologists from residency programs is also unknown. It is unclear if US IM program directors with CKD stages 1-5 nephrology exposure during IM residency are more likely to have adequate health literacy, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white.

TH-P0865

Nephrology Exposure during Medical Residency: A U.S. Internal Medicine Program Directors’ Survey

Karen M. Warburton,1 Kenar D. Jhaveri,2 Ankit B. Patel,1 Stephanie A. Cali,1 Vincent Arora,2 Hitesh H. Shah. Nephrology, Hofstra North Shore Medical Center, 2Medicine, Well Cornell Medical College; 3Medicine, Virginia Commonwealth Univ; Medicine, Univ of Chicago.

Background: Almost 80% of nephrology consultative services are called by non-nephrologists. Low health literacy is associated with less desirable clinical outcomes. While nearly two thirds of IM-PDs thought that nephrology consultative services should be called by nephrologists, little is known about the types of nephrology exposure offered during internal medicine (IM) residency in the US. The relationship of this exposure to success in recruiting future nephrologists from residency programs is also unknown. It is unclear if US IM program directors with CKD stages 1-5 nephrology exposure during IM residency are more likely to have adequate health literacy, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.

Conclusions: Significant positive associations were found for residents with higher income and higher education, as did patients with non-white race compared to white (0.33(0.19,0.57);p=0.01) vs. white. continued to have a lower odds of having adequate health literacy, despite adjustment for income, kidney function and formal education.
required by the majority of programs. The majority of programs did not offer a kidney transplant or outpatient dialysis rotation for IM residents. To enhance exposure to and interest in nephrology careers among IM residents, a combined exposure to inpatient and outpatient nephrology, increased offerings in transplant or outpatient dialysis experiences, and increased awareness of opportunities such as the ASN KWTP for residents should be strongly considered by the training community.

TH-PO864

Development and Implementation of Nephrology Fellow OSCEs for End-Stage Renal Disease Counseling  
Mark G. Parker, Christine Mallar, Jennifer Gammon, Patricia L. Cantlin. Maine Medical Center, Portland, ME.

Background: Observed Structured Clinical Encounters (OSCEs) are established assessment tools in medical education, but there is little published experience on their use in nephrology fellowships. Surveys of nephrology fellowship graduates indicate that many feel inadequately prepared to counsel patients about dialysis options and palliative care. We have developed two OSCEs to assess these skills.

Methods: Two scenarios with trained standardized patients (SP) were administered to fellows in months 7 and 19 of training. The first is a mid-age woman with advanced chronic kidney disease (CKD) and no immediate transplantation program. The second is an elderly man with advanced CKD, considerable co-morbidity, and limited life expectancy. Two trained faculty members observed the encounters. Fellows received feedback from SP and faculty, and completed a 7-question learner feedback survey using a 5-point Likert scale for responses (1=strongly disagree, 5= strongly agree) and a narrative self-reflection. Thematic analysis of narrative self-reflections suggests that fellows identified strengths in their communication skills and core knowledge of dialysis options. However, they identified challenges in their knowledge of nuances of dialysis care, such as financing and home therapy details, as well as description of resources for palliative care. Challenges were greatest for month 7 fellows.

Conclusions: We have demonstrated feasibility and potential utility of OSCEs for assessment of dialysis and palliative care counseling skills of nephrology fellows. Our fellows find the experience to replicate true clinical experiences satisfactorily and to provide useful information about their strengths and challenges for improvement. Limitations include the single center nature of this experience and small number of observations. We are initiating a multi-center prospective study to address these limitations.

TH-PO865

Testing Strategies to Education Primary Care Physicians on Chronic Kidney Disease  
Laura J. Mauser, Div of Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: It has been shown that there is a knowledge gap in identification and management of chronic kidney disease (CKD) by primary care providers. In an effort to improve this practice the Wisconsin Research and Education Network (WREN) developed a research project aimed to test ways that can help the primary care practitioners to identify patients with CKD and implement guidelines for CKD management through a local learning collaborative.

Methods: All WREN sites were invited to the learning collaborative. A survey was distributed that asked the primary providers if a group would be useful and to identify topics that would be of interest to the group. Teleconferencing and blackboard collaboration were used as methods of communication. A group facilitator, a nephrologist and a lead family medicine physician were part of each meeting. After 3 months of meetings, a participation survey was distributed to determine the utility of the group.

Results: 29% of the 84 sites that had been a part of the CKD project responded to the invitation to be a part of the learning collaborative with 46% of the responders indicating that they would be interested in participating in a monthly virtual statewide learning collaborative. After 3 meetings with 1-4 sites participating during each meeting, a follow up survey was done. The results of the follow up survey showed that there was little interest in continuing these meetings with the most stated reason being scheduling conflicts.

Conclusions: Despite a group of primary care providers that was primed to be interested in the topic of CKD, there was a very low rate of participation in the learning collaborative. However, overwhelming reason for low participation stated it was due to a rigorous schedule. Teleconferencing and blackboard collaborative were used as strategies to bring together those in various geographic areas across the state of Wisconsin but this did not seem to improve participation. It is likely that an asynchronous method of learning may increase participation and ultimately improve recognition and management of CKD.

Funding: Other U.S. Government Support

TH-PO866

Most U.S. Patient Care Technician Training Programs Leverage Several Required Elements but Fall Short of Ideal and Are Not Sourced from Independent Third Parties  
Alex Yang, Jennifer Vavrinchik. NCS Research.

Background: CMS instituted certification requirements for patient care technicians (PCTs). In this study, we evaluate PCT training programs.

Methods: >2000 nephrology professionals were screened against inclusion criteria: US nephrology professional, dialysis practice setting, >1 yr of nephrology experience, and consent. 428 eligible study candidates were invited with eventual 188 study participants (48%). Elements of PCT training programs were evaluated. Analyses were conducted across all study participants with no excluded data for any reason.

Results: Percentages of current elements in PCT training programs and difference from ideal are shown (Table 1).

Table 1: Independent 3rd Party Source for PCT Training Elements

<table>
<thead>
<tr>
<th>Element</th>
<th>Current</th>
<th>Actual</th>
<th>Ideal</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competency Exam</td>
<td>6</td>
<td>62</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Online Education Course</td>
<td>6</td>
<td>62</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Electronic Education Materials</td>
<td>6</td>
<td>62</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Hardcopy Education Materials</td>
<td>4</td>
<td>55</td>
<td>51</td>
<td>4</td>
</tr>
<tr>
<td>Competency Skills Checklist</td>
<td>2</td>
<td>44</td>
<td>47</td>
<td>3</td>
</tr>
<tr>
<td>Classroom Didactic Education</td>
<td>2</td>
<td>44</td>
<td>43</td>
<td>1</td>
</tr>
<tr>
<td>Formal Preceptorship Program</td>
<td>1</td>
<td>43</td>
<td>42</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusions: Although most PCT training programs utilize several elements, study participants believe more PCT training elements would be ideal and would improve patient care. Furthermore, 3rd party independent sources of PCT training/education are currently rarely used but roughly 1/3 to 2/3 of study participants believe it is important for PCT training and education elements to be independent. Efforts to standardize PCT certification should be coupled with efforts to standardize the elements, the content, and the independence of PCT training/education.

TH-PO867

Medical Student Test Performance during a Second-Year Kidney Pathophysiology Course Improves with Participation in Small Group Active Learning  
Elizabeth J. Brant, Elizabeth W. Dehner, Gerald A. Hladik. UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.

Background: We assessed the impact of participation in active learning on test scores during a second-year medical student kidney pathophysiology course. We hypothesized that participation in active learning would have a favorable impact on test scores.

Methods: The second-year kidney pathophysiology course consisted of 20 hours of traditional lecture and 20 hours of optional active learning sessions. During active learning, students worked through clinical cases under the supervision of nephrology faculty, with a faculty-student ratio of 1:15. Of the 113 students enrolled in the course, 74 (56%) participated in active learning. Participation in small groups was classified as follows: Group 1: Participation in <30% of sessions; Group 2: Participation in 30-60% of sessions; Group 3: Participation in >60% of sessions. One-way analysis of variance was used to compare participation and mean test scores.

Results: The distribution of students according to level of participation in active learning sessions and corresponding test scores is shown in Table 1.

Table 1: Mean test scores according to level of participation in active learning sessions

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of students (N)</th>
<th>Mean test score (standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: Participation in &lt;30% of sessions</td>
<td>53 (60)</td>
<td>99.9 (7.3)</td>
</tr>
<tr>
<td>Group 2: Participation in 30-60% of sessions</td>
<td>59 (64)</td>
<td>98.3 (10.4)</td>
</tr>
<tr>
<td>Group 3: Participation in &gt;60% of sessions</td>
<td>21 (16)</td>
<td>96.7 (7.7)</td>
</tr>
</tbody>
</table>

Conclusions: Participation at the small group active learning sessions was associated with higher mean test scores (p=0.001). Tukey’s test showed significant differences in scores between Group 3 and each of the other groups (Fig. 1).

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

Underline represents presenting author/disclosure.
Conclusions: Student participation in active learning small groups during a second-year kidney pathophysiology course was associated with superior test performance. Limitations of the study include that this was a retrospective analysis at a single center.

TH-PO868
Mind the Dip Ranking of Diagnostic Procedures – An Online Survey among 266 First Year Medical Students at Two German Universities
Philip Jantaro, Heike Kielstein, Volkhard Fischer, Jan T. Kielstein. Hannover Medical School, Hannover, Germany; Martin Luther Univ Halle-Wittenberg, Halle, Germany.

Background: Urine dipstick analyses pH, specific gravity, proteinuria, bilirubinuria, glucosuria, ketonuria and nitrite. It is one of the most frequently used diagnostic tests and a screening tool for many diseases as well as part of a guideline based work up ranging from urinary tract infection to assessment of cardiovascular risk and CKD. The aim of our study was to investigate the attitude of first year medical students (in a 6 year curriculum) towards urine analysis and ranking it among other frequently used diagnostic tests and procedures.

Methods: 549 first year medical students were invited to fill out an online questionnaire consisting of several questions concerning medical diagnostic tests. The return rate was 47.4 %. Of the 266 participants 64.9 % were female. One question was “Which of the following diagnostic procedures is of least importance?” allowing to select ONE of the following: 1) Auscultation 2) Blood pressure 3) Electrocardiogram 4) Ultrasound 5) Urine dip stick.

Results: Urine dip stick and blood pressure were viewed as the least important tests.

Auscultation was selected as the most important test. Congrdingly 98.1 % of the medical students selected the stethoscope as the most important medical equipment conveying the image of a doctor, followed by doctors coat (95.5 %) and syringe (25.5 %). Among the 76 students with prior medical training (nurse, paramedic) blood pressure measurement was considered to be more important than in the whole cohort, however, 78.1 % thought that urine dipstick is the least important diagnostic test.

Conclusions: Weighing the importance of diagnostic procedures should be an integral part of medical education, keeping in mind that auscultation is closely related to the self (and perceived) image of physicians.

Funding: Clinical Revenue Support

TH-PO869
Developing a New Pediatric CKD Educational Material: The Increasing Kidney Disease Network (IKAN) Transplant Project Bessie A. Young, Bonnie K. Harp, Janice Sabin. Biomedical Informatics and Medical Education, Univ of Washington, Seattle, WA; Nephrology/Dept Medicine, VA Puget Sound, Univ of Washington, Seattle, WA.

Background: Much research has been done to evaluate disparities in transplantation rates for racial/ethnic populations; however, much less research has focused on determining the best methods by which to overcome educational barriers and increase transplantation awareness among pediatric patients and their families within these groups.

Methods: We convened a focus group to assess content and design of a new kidney disease education modality in comic book format. Focus group participants (N=6) included researchers, community members (one kidney transplant recipient), and a nephrologist.

Participants were African American (50%) and white (50%). Participants’ reviewed the culturally tailored comic book for the African American patient population, aimed primarily at adolescents and young adults with CKD and their families, the final version of which will be evaluated in a pilot study using focus groups at Seattle Children’s Hospital.

Results: The comic book was reviewed for content, reading level, language, whether it is culturally appropriate, age appropriate, for quality of visual presentation, and organization of the information. The focus group concluded that fact checking for authenticity with a group of African American adolescents is important, medical terms should include a phonetic pronunciation, the comic book should have a glossary, and the book should be divided into chapters. Comments from the group include: “comic book [will be used] as reference material”; “is hit on all four cylinders”; “as a kidney transplant patient...it is good to have it all in one place”; “the underlying message is that transplant is the best option.”

Conclusions: Culturally tailored and health literacy-appropriate education materials that have appropriate delivery of information and are an important tool for both adult and pediatric patient populations. These innovative and unique materials will be field tested and finalized for use in future research among pediatric patients and their families with CKD and ESRD.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO870

Background: Journal Club (JC) is a forum for fellows to present topics of current interest including clinical and cutting edge research. Despite critical review of the published articles during JC, questions may remain unanswered. The lead author’s perspective during JC might help better understand the article being reviewed. At our institution, we embarked on an innovative journal club format that included a discussion with the author of the JC article.

Methods: At our institution, nephrology JC is a biweekly conference prepared by fellows covering research papers in nephrology. Following the JC article presentation introduction and discussion for 45 min, the last 15 minutes are traditionally devoted to critically discuss the manuscript. During the 2012-2013 academic year, we introduced a novel JC format for our group. Many leading or corresponding authors of JC papers discussed were invited few weeks prior to the JC session by our fellows to participate in a 15 minutes teleconference with all fellows and faculty members. An anonymous online survey was created to evaluate this novel JC format. The survey was subsequently distributed to all fellows and participating faculty members in May 2013.

Results: So far, 7 out of 8 fellows and 5 faculty members responded to our survey. On a 5-point scale (where 1 being least and 5 being most), respondents rated this experience innovative (4.58), thought provoking (4.17) and relevant (4.0). 75% felt that this format would increase their JC participation. When asked to rate this format as compared to the traditional JC, the average rating was 4.3 on a 5-point scale (1 being least valuable, 5 being most). All respondents wanted to see such “author participated” JC sessions in the future.

Conclusions: This novel “author participated” JC sessions enhanced our JC experience. Based on our experience, we encourage all medical educators to consider this format of JC.

TH-PO871

Background: The objective of this survey was to gauge the understanding and the level of competence amongst junior trainees; in treating and managing Chronic Kidney disease (CKD) and its complications. This survey was generated as a result of our previous work in understanding the training needs amongst trainees in understanding Acute Kidney Injury (AKI).

Methods: This survey was conducted between December 2012 to March 2013 at York Teaching Hospitals. It was conducted as part of the teaching session on CKD for the trainees with the target group being the Core medical trainees on a medical rotation. The questionnaires were handed out before the lecture and the audience were asked to fill it in during or after the session. Total responses were based on the total number of attendances and were thirty eight in total. The Questionnaire revealed grade and place of work for whether acute or rehab setting including subspecialties such as Renal/Gastro/Haematology.

Results: The first question asked about the definition of CKD and none were able to answer correctly (CKD classification was accepted). Only 20 had come up with their own definitions of CKD and others left it blank. 34 trainees responded by saying that they have managed more than 16 patients with CKD whereas 4 responses were for < 8-16. On a scale between 1 and 5 where 1 being not competent and 5 being confident/competent no one replied that they were competent (3) to manage CKD; 8 people replied saying they felt confident at (4) as they had managed to do renal rotations where as 30 people thought that they are confident to manage at level (3).

Conclusions: The survey highlighted the fact that most trainees felt that teaching on CKD were inadequate at both undergraduate and postgraduate levels. There was evidence of the lack of understanding of the complications of CKD and its management. The objective of this survey was to gauge the understanding and level of competence amongst trainees in understanding Acute Kidney Injury (AKI).

Funding: Clinical Revenue Support

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

297A
**TH-PO872**

Evaluation and Sharing of a Decision Making Tool for Mortality on Dialysis Compared to Kidney Transplantation: iChoose Kidney

Rachel E. Patzer,1 Mohua Basu,1 William M. McClellan,2 David H. Howard,2 Yi Jian Huang,3 Kimberly Arriola,3 Emory Transplant Center, Atlanta, GA; 1Dept of Medicine, Emory Univ, Atlanta, GA; 2Rollins School of Public Health, Atlanta, GA.

**Background:** End Stage Renal Disease (ESRD) patients have two primary treatment choices: dialysis or kidney transplant (KTx). Predictive models to compare individualized risks of mortality for dialysis or KTx have not yet been developed to help patients and providers make informed decisions about treatment choices.

**Methods:** We examined mortality among a cohort of 721,571 ESRD patients 2005-2001 in the United States Renal Data System (USRDS) surveillance registry who received 1) dialysis vs. 2) KTx. Multivariable logistic regression was used to derive separate risk models for patients on dialysis and for patients who received a living or deceased donor transplant. Data were divided into 50% derivation and 50% validation datasets. Models were evaluated using concordance statistics (c-statistics) and measures for model discrimination and calibration for three-year outcomes.

**Results:** Among dialysis patients (n=663,900), 47.4% of patients died vs. 5.9% of transplant recipients (n=57,671) over the 7-year study period (p<0.0001). Factors significantly associated with a higher odds of death for dialysis and KTx patients included older age, minority race/ethnicity, longer dialysis vintage; non-private insurance; delayed access to pre-ESRD nephrology care; no erythropoietin use prior to dialysis; smoking and drug use; and comorbidities, including cardiovascular disease and congestive heart failure. The discriminatory ability of the models for 1-year and 3-year mortality was moderately high (c-statistics ranging from 0.69-0.72). We used these validated, risk prediction models to develop an electronic, user-friendly, mobile application (iPad) tool called iChoose Kidney.

**Conclusions:** Risk prediction estimates for mortality on dialysis compared to KTx may help assist in identifying patients at high risk for poor outcomes, communicating knowledge about risks of mortality to patients and providers, and encouraging lifestyle or behavioral changes to promote health.

**Funding:** Other NIH Support - National Center for Advancing Translational Sciences (NCATS)

**TH-PO873**

Towards Harmonizing Renal Guidelines: An International Survey of Major Guideline Bodies

Maria C. Haller,1 Sabine N. Van der Veen,1 Evi V. Nagler,1 Raymond C. Vanholder,2 Jonathan C. Craig,3 Wim Van Biesen.1 European Renal Best Practice, Ghent Univ Hospital, Ghent, Belgium; 1KHA-CARI, School of Public Health, Univ of Sydney, Australia.

**Background:** Several organizations produce renal guidelines, resulting in duplication of effort while many topics remain uncovered. A collaborative work plan based on common, Institute of Medicine-endorsed methods would improve efficiency and impact, and reduce inconsistency. ERBP and KHA-CARI aimed to identify organizational and methodological differences between major renal guideline bodies that might hamper their collaboration.

**Methods:** We invited the chairs of KHA-CARI, CSN, ERBP, KDIGO, KDOQI, SLANH and UK-RA to complete an electronic 62-item survey, based on Institute of Medicine standards.

**Results:** All 7 groups completed the survey. Funding arises from their governing bodies, directly or indirectly (N=2). In no case do funders have any influence on topic selection or guideline content. The available budget to develop one guideline varies from $2,000 to $500,000. 3 groups seek patient perspectives and 4 consider health and sociocultural issues. The available budget to develop one guideline varies from $2,000 to $500,000. 3 groups seek patient perspectives and 4 consider health and sociocultural issues. Among dialysis patients (n=663,900), 47.4% of patients died vs. 5.9% of transplant recipients (n=57,671) over the 7-year study period (p<0.0001). Factors significantly associated with a higher odds of death for dialysis and KTx patients included older age, minority race/ethnicity, longer dialysis vintage; non-private insurance; delayed access to pre-ESRD nephrology care; no erythropoietin use prior to dialysis; smoking and drug use; and comorbidities, including cardiovascular disease and congestive heart failure. The discriminatory ability of the models for 1-year and 3-year mortality was moderately high (c-statistics ranging from 0.69-0.72). We used these validated, risk prediction models to develop an electronic, user-friendly, mobile application (iPad) tool called iChoose Kidney.

**Conclusions:** Risk prediction estimates for mortality on dialysis compared to KTx may help assist in identifying patients at high risk for poor outcomes, communicating knowledge about risks of mortality to patients and providers, and encouraging lifestyle or behavioral changes to promote health.

**Funding:** Other NIH Support - National Center for Advancing Translational Sciences (NCATS)

**TH-PO874**

Patient and Staff Perspectives of Intradialytic Cycling

Amy L. Clarke,1 Hannah M.J. Young,2 Maurice Dunger,2 Nicky Hudson,2 James O. Burton,3 Alice C. Norrie,1 1Leicester Kidney Exercise Team, Univ Hospitals of Leicester, United Kingdom; 2School of Applied Social Sciences, De Montfort Univ, Leicester, United Kingdom.

**Background:** Evidence increasingly shows that exercise benefits haemodialysis (HD) patients, but lifestyle restrictions limit participation. Intradialytic cycling (IDC) is an attractive option but setting up and sustaining a programme can be challenging, partly due to patient and staff resistance. Addressing the user’s point of view is key to successful implementation of new initiatives. This study explored patient and staff perspectives prior to the introduction of a new IDC programme, and again when the programme was established.

**Methods:** Ahead of IDC initiation, focus groups were conducted with a purposive sample of 24 HD patients and 9 staff. 6 months after IDC introduction, semi-structured interviews were held with 11 patients and 8 staff. Audiotapes were transcribed verbatim, translated where necessary, and subjected to qualitative framework analysis.

**Results:** Prior to IDC, patients anticipated that the positive experiences of peers would encourage them to participate, whilst post-IDC they were motivated by their own perceived improvements. Staff initially felt making IDC part of the existing routine of the unit would facilitate implementation and later commented that a collaborative approach helped to sustain the programme. Both staff and patients wanted education on the benefits and principles of exercise. Anticipated patient barriers were initially concerns regarding safety and the negative effects of fatigue and depression. None of these concerns proved influential for patients after implementation. Both patients and staff were concerned about IDC adding to the staff workload. This continued to be an issue for both groups post implementation and proved to be the most influential barrier.

**Conclusions:** This study provides a unique perspective into HD patient and staff views on initiating and sustaining an IDC programme. Education is the key element for initial patient and staff engagement and for patients this education is best facilitated through peer interaction. Long term sustainability requires IDC to become a routine part of the work plan of HD unit staff.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
TH-PO876

Improving Self-Reported Provider Preparation to Evaluate and Treat Antibody-Mediated Renal Transplant Rejection  Dustin J. Little,1 Austin Parker,1 Mark D. Poirier,1 Amy J. Zwettler,2 David J. Yoo,2 Bruce Reinmuth,1 Kevin C. Abbott,2 Christina M. Yuan,1 Lisa K. Prince.1 1Walter Reed National Military Medical Center; 2San Antonio Military Medical Center; 3Naval Medical Center Portsmouth.

Background: Antibody-mediated kidney transplant rejection (AMR) is a major cause of allograft loss. We designed and implemented a performance improvement project aimed at optimizing the evaluation and treatment of AMR at our institution.

Methods: Medical literature on AMR was reviewed, as were AMR cases treated at our institution from 2006-2011. An electronic survey was administered to the nephrology staff and fellows, which included ten questions assessing provider preparation to evaluate and treat AMR. Lectures were given on the evaluation and treatment of AMR and findings of review of institutional AMR cases. An educational electronic "AMR Toolkit" was created, and an identical post-survey was administered 4 months following the pre-survey. Fisher exact test was used to compare pre and post-survey responses, with a p value of 0.05 used to determine significance.

Results: Twenty-one cases of AMR were identified in 16 patients. No patients died and two experienced graft loss. Pre and post-survey response rates were 12/13 and 10/12, respectively. Significantly more respondents reported feeling quite or extremely prepared on the post-survey. Over 5 of the 10 items. Ninety-one of 99 total responses on the post-survey reported feeling quite or extremely prepared, compared to 78/119 of total pre-survey responses (p = 0.0001).

Conclusions: AMR presents a dilemma, in part because of limited data regarding treatment options. We implemented a comprehensive education strategy, following which providers reported feeling better prepared to evaluate and treat AMR. Our results suggest that this model should be considered for other challenging clinical problems.

TH-PO877

A Pilot Trial of a Computerized Renal Template Note to Improve Resident Knowledge and Documentation of Kidney Disease  Shayan Shirazian, Ray Wang, Dennis Moledina, Vladimir Liberman, Joseph H. Zeidan, Joseph Mattana. Medicine, Winthrop Univ Hospital, Mineola, NY.

Background: Kidney disease is under-documented in physician notes suggesting under-recognition, especially at earlier stages of chronic kidney disease (CKD). The objective of this study was to determine whether a computerized renal template note (RTN) with clinical documentation support (CDS) improves resident knowledge and documentation of kidney disease.

Methods: In this prospective IRB-approved study, first year residents (PGY1s) were encouraged to use the RTN with CDS for documentation over a 1 month period. The RTN included an option for classification of patients into CKD and acute kidney injury (AKI) categories. The CDS consisted of a link to standard classification of CKD and AKI. Knowledge of CKD and AKI was tested with a quiz given before and after implementation of the RTN. Study investigators determined whether CKD or AKI was appropriately documented in 100 RTNs and 100 historical internal medicine progress notes of patients with known AKI or CKD from the same time period in the previous year. RTN and historical notes were compared using Fischer’s exact test. Quiz scores before and after RTN utilization were compared using paired t-testing.

Results: 18 PGY1 completed all study procedures. Their average age was 28, 12 were male, and 7 had taken a prior nephrology elective. At the end of the study, approximately 2,436 inpatient encounters were documented using the RTN. Accurate staging of CKD-3 was significantly improved implementing the RTN when compared to historical notes (9/46 vs. 0.29, p=0.01), whereas accurate staging did not improve for CKD-4, CKD-5 or AKI. End of study quiz scores were higher than pre-study scores, however this difference did not reach statistical significance (29.6% vs. 20.6%, p=0.13).

Conclusions: A computerized RTN with CDS significantly improved documentation of stage 3 CKD though without correspondingly increased knowledge. Given these findings and the opportunities provided by increasing electronic health record use, further studies of the use of computerized RTN with CDS to improve CKD recognition and staging may be warranted.
TH-PO880
Nephrology Blogosphere: An Analysis of Productivity, Longevity, and Consistency
Joel Topf, Medicine, St. John Hospital and Medical Center, Detroit, MI.

Background: Blogs are web sites with multiple discrete chronologic entries (typically displayed with the most recent at the top and older entries displayed below). There are numerous inexpensive and easy to use tools that allow blogs to be published with little technical friction. There are dozens of blogs that focus on nephrology and nephrology education; while most are still producing content some have ceased publishing. Little is known about the size, productivity, and lifespan of nephrology focused blogs.

Methods: Each nephrology blog written in English was assessed for productivity, longevity and inconsistency. Productivity was measured by the number of posts per month. Longevity was measured by the duration of publication from first post to either the final post or through May 2013 for active blogs. Inconsistency was defined as the number of months without any posts.

Results: From March 2005 through May 2013 we found 30 nephrology blogs that had at least 10,198 posts. Twenty blogs were still publishing as of May 2013. Mean productivity was 339.9 (95% CI 175.2-504.7) posts per blog or 9.0 posts per month (95% CI 5.7-12.4). Longevity ranged from 1 to 73 months with a mean duration of 31.2 months (95% CI 24.1-38.3). Inconsistency was not common, with a mean of 4.6 months without posts per blog (95% CI 1.8-7.5). 11 blogs never missed a month, and 4 only missed 1 month.

Regression versus time show that most blogs lose productivity over time. Of the 25 blogs with at least 6 months of publication, 15 (60%) had a decreasing productivity over time (p<0.05) versus only 1 (4%) with a increasing productivity, 9 (36%) showed no association between time and productivity (p>0.05). Despite decreasing productivity in most individual blogs, the entire nephrology blogosphere showed a significant increase in the number of posts per month, R^2=0.38 p<0.001, slope 1.17.

There was no association between inconsistency and termination of the blog (R=0.18, p=0.35).

Conclusions: Blogging is a new means for distributing nephrology education. The number of blogs is increasing. Most blogs have decreased productivity over time however the nephrology blogosphere in total is growing both in number of voices and monthly posts.

TH-PO881
Conditional Inactivation of Exocyst Sec10 in Mouse Kidney Epithelium Causes Primary Cilia Defects and Kidney Cysts
Noemi Polgar, Amanda J. Lee, Vanessa H. Lui, Xiaofeng Zuo, Joshua H. Lipschutz, Ben Fogleregran, Anatomy, Biochemistry, and Physiology, Univ of Hawaii; Medicine, Univ of Pennsylvania.

Background: The pathogenesis of polycystic kidney disease (PKD) is dependent on primary cilia function in renal epithelial cells. Despite intense study, it remains poorly understood how proteins are targeted and delivered to cilia.

Methods: In cultured renal epithelial cells, we have previously shown that the eight-protein exocyst complex regulates the length and signaling of the primary cilia. Using the Cre-Lex system, we have generated a novel transgenic mouse allowing tissue-specific deletion of the Sec10 gene, a central component of the exocyst complex.

Results: To investigate the role of Sec10 and the exocyst in renal development and primary cilia signaling, we crossed this floxed-Sec10 strain with the Ksp-Cadherin-Cre mouse strain to inactivate Sec10 in ureteric bud derived epithelium. Most mice died hours after birth due to upper urinary tract obstructions. However, mice that escaped urinary obstruction and hydrenephrosis displayed numerous renal cysts with defects in primary cilia number and length in Cre-expressing tubules.

Conclusions: This is the first in vivo evidence of the exocyst regulating cilia assembly and trafficking in mammalian development, and the first conditional allele for any exocyst component. Given the known biochemical and genetic interactions between the exocyst and other ciliary proteins, it is likely that the exocyst is an important mechanism by which cells regulate ciliary trafficking.

Funding: NIDDK Support, Private Foundation Support

TH-PO882
Nuclear Distribution C Homolog Regulates Mitotic Spindle Orientation and Tubulogenesis
Maoqiu Wu, JingJing Zhang, Wassin El-Jouini, Rebecca Powell, Tomoko Obara, Faran E. Ghumman, Maria Rasmussen, Xuefeng Su, Shixuan Wang, Vahedi Shaltiel, Marianne C. Verhaar, Rachel H. Giles, Anatomy and Tubulogenesis, Univ Medical Center, Utrecht, Netherlands; Medical Oncology, Univ Medical Center, Utrecht, Netherlands; Internal Medicine, Univ of Michigan, Ann Arbor, MI; Genetics, Harvard Medical School, Charlestown, MA.

Background: Our work identifies NuDC as a novel regulator of mitotic spindle orientation, ciliogenesis, and tubulogenesis. We propose that NuDC is a novel candidate for ciliopathy.

Funding: NIDDK Support, Private Foundation Support

TH-PO883
Nephropathies Centrosomal Protein CEP164 Regulates Cell Cycle Progression, Apoptosis, and Epithelial-to-Mesenchymal Transition
Gisela G. Slats, Amiya K. Ghosh, Stephanie Le Corre, Tri Q. Nguyen, Iain A. Drummond, Friedhelm Hildebrandt, Rachel H. Giles. Nephrology and Hypertension, Univ Medical Center, Utrecht, Netherlands; Pathology, Univ Medical Center, Utrecht, Netherlands; Medical Oncology, Univ Medical Center, Utrecht, Netherlands; Internal Medicine, Univ of Michigan, Ann Arbor, MI; Genetics, Harvard Medical School, Charlestown, MA.

Background: We recently reported that mutations in centrosomal protein 164 (CEP164) in nephropathies (NPHP) patients affect cilia and the DNA damage response. Here, we address the role of CEP164 in NPHP and concomitant fibrosis.

Results: Live cell imaging of RPE Fucci (fluorescent, ubiquitination-based cell cycle indicator) cells revealed that centrosome knockdown of CEP164 reveals a quicker cell cycle than control cells despite a longer S phase. FACS experiments with renal IMCD3 cells confirm that CEP164 siRNA knockdown cells accumulate in S-phase, but we demonstrate that this can be rescued by human WT CEP164 but not disease-associated mutants. siRNA of CEP164 causes a proliferation defect in immortalized kidney cells as well as PrestoBlue cell assays. We hypothesized that the discrepancy between accelerated cell cycle and inhibited overall proliferation could be explained by induction of apoptosis or epithelial-to-mesenchymal transition (EMT). Indeed, reduction of CEP164 levels induces apoptosis in immortalized kidney cells. However, the cellular protein functions of the affected gene products remain poorly understood.

Conclusions: We reveal a novel role for CEP164 in NPHP pathogenesis, in which mutations causing ciliary defects are coupled with apoptosis and EMT.

Funding: Government Support - Non-U.S.

TH-PO884
RUVBL1 Is Part of Disease–Associated Protein Complexes at the Ciliary Base and Essential for Tubular Architecture In Vivo
Max C. Liebau, Claudia Dafinger, Ingolf Schmedding, Benjamin Schairer, Sandra Habig, Thomas Wunderlich, Oliver Rinner, Bernhard Schermer, Department of Medicine, University of Cologne, Cologne, Germany; Institute for Genetics, University of Cologne, Cologne, Germany; Biogenzymes AG, Schlieren, Switzerland.

Background: Cystic kidney diseases including Nephronophthisis (NPH) and ARPKD are common genetic causes of end stage renal failure during childhood and adolescence. However, the cellular protein functions of the affected gene products remain poorly understood. Recent work has linked ciliopathies to DNA damage response signaling.

Methods: Using immunoprecipitation-based mass spectrometry approaches we recently identified candidates for components of the Nephrocystin-1 and the Fibrocystin protein complex. Various candidates were followed up by independent methods in vitro and in vivo.

Results: Our candidates include an AAA ATPase with known roles in the regulation of cilia-associated signaling pathways and DNA damage response signaling, called RUVBL1. The interaction of RUVBL1 with various ciliary disease-associated proteins was confirmed by independent measures. In addition to other subcellular compartments, RUVBL1 localizes to the ciliary base during interphase. A newly generated tubule-specific Ruvbl1-knockout mouse shows high neonatal mortality and cystic kidney disease. Work on the cellular mechanisms resulting in this phenotype is ongoing.

Conclusions: We identify the Role of the Tip60 DNA damage signaling complex as a cysto-protein at the ciliary base and as a component of disease-associated protein complexes. The link between ciliary signaling and DNA damage response signaling requires further investigation.

Funding: Government Support - Non-U.S.
TH-PO885

Modified Molecular Inversion Probe Analysis in Patients with Nephronophthisis-Related Ciliopathies

Markus Schueler,¹ Jan Halbritter,¹ Dan Doherty,² Jan Phelps,² Daniela A. Braun,² Jonathan Porath,³ Heon Yung Gee,⁴ Neveen Soliman,⁵ Marwa Mohamed Nabhan,⁴ Jay Shendure,⁴ Brian J. O’Roak,⁴ Edgar Otto,⁵ Friedhelm Hildebrandt,¹,⁶ 'Dept of Medicine, Boston Children’s Hospital, Boston, MA; ²Dept of Pediatrics, Univ of Washington, Seattle, WA; ³Egyptian Group for Orphan Renal Diseases, EGDORD, Cairo, Egypt; ⁴Dept of Genome Sciences, Univ of Washington, Seattle, WA; ⁵Dept of Pediatrics, Univ of Michigan, Ann Arbor, MI; ⁶Howard Hughes Medical Institute, Chevy Chase, MD.

Background: Nephronophthisis is a recessive cystic kidney disease that progresses to terminal renal failure during the first three decades of life. In a cohort of 384 children diagnosed with a nephronophthisis-related ciliopathy two different high-throughput mutation analysis methods were used to identify disease-causing mutations within coding regions of 12 established NPHP genes and compared to each other.

Methods: Exon targeted mutation analysis was carried out using a modified molecular inversion probe (MIP) technique. Previously we had performed mutation analysis in the same cohort using PCR-based Access Array microfluidic technology (AAMT) from Fluidigm® with consecutive next-generation sequencing (NGS). Significant mutations were confirmed by Sanger sequencing and shown to segregate with the affected status.

Results: When using the MIP technology 100 pathogenic mutations were found, revealing the molecular cause in 64 out of 384 families (16%) and discovering 20 novel mutations in the genes NPHP3 (3), INVS (2)→NPHP3 (3), IQCB1 (1), CEP290 (3), RPGRIP1L (3), TMEM67 (1) and TTC21B (4). Whereas, when using the Fluidigm® NGS approach, bioinformatics analysis of the identical cohort yielded only 84 pathogenic mutations in 52 out of 384 families (13.5%) including 21 novel mutations. Interestingly, only in 37 families the disease causing mutations were detected with both methods.

Conclusions: We conclude that the combination of two different high-throughput methods (AAMT and MIP) increases the mutation detection sensitivity in cohorts with broadly heterogeneous Mendelian disorders.

TH-PO886

Renal Oxylipin Alterations in the pcy Mouse Model of Nephronophthisis

Tamio Yamaguchi,² Jessay Gopuran Devassy,² Melissa Gabbs,² Mai Sasaki,¹ Amir Ravandi,² Harold M. Aukema.²

'Fatty acid amide hydrolase (FAAH) mediates the inactivation of both endocannabinoids and the lipid mediators of the arachidonic acid cascade, known as oxylipins. Both compounds are involved in different processes relevant to the kidney, however their role in nephronophthisis (NPHS) diseases remains to be elucidated. Our recent findings have suggested that the renal oxylipin signaling is altered in the pcy mouse model of NPHS, a syndrome caused by mutations in the pcy gene (Mks3) encoding the membrane protein meckelin. We investigated the potential role of oxylipins in renal pathology of the pcy mouse model of NPHS, more specifically: 1) an evaluation of renal oxylipin changes in pcy mice, 2) the effect of dietary flaxseed oil and its main component α-linolenic acid on renal oxylipin alterations in pcy mice.

Methods: 1) The renal oxylipin changes were evaluated in kidney homogenates from normal and pcy mice at 15, 30, 60 days. The kidney tissues were analysed for COX, lipoxygenase and epoxygenase products. 2) pcy mice were fed with an α-linolenic acid enriched diet for 16 weeks.

Results: Our results indicated that renal oxylipin levels are dramatically altered in pcy mice at early time points (15 days) and these alterations are more pronounced in the pcy mice that were not treated with α-linolenic acid. Dietary α-linolenic acid had profound effects on renal oxylipin alterations in the pcy mice, returning the oxylipin levels in the pcy mice to the levels observed in normal mice.

Conclusions: We conclude that the renal oxylipin alterations in the pcy model of NPHS are due to the meckelin deficiency and could be modulated by dietary α-linolenic acid intake. Underline represents presenting author/disclosure.

TH-PO887

Loss of Function Mutation of FAT1 May Represent a Novel Disease Causing Gene in Nephronophthisis with Nephrotic Syndrome Overlap

Jonathan Porath,¹ Carolin E. Sadowski,¹ Jan Halbritter,¹ Rannar Airik,¹ Daniela A. Braun,² Markus Schueler,¹ Heon Yung Gee,¹ Edgar Otto,⁵ Friedhelm Hildebrandt.¹,⁶ 'Medicine, Boston Children’s Hospital, Harvard Medical School, Boston, MA; ²Pediatrics, Univ of Michigan, Ann Arbor, MI; ³Howard Hughes Medical Institute, Chevy Chase, MD.

Background: Nephronophthisis-related ciliopathies (NPHP-RC) comprise a group of autosomal recessive cystic kidney diseases. As the disease-causing gene has only been identified in 40-60% of individuals with NPHP-RC, we performed whole exome resequencing (WER) to identify novel disease causing genes.

Methods: We performed homozygosity mapping as well as WER (NimbleGen SeqCap EZ®) on 84 families with NPHP-RC. We then screened an additional 720 individuals with nephrotic syndrome using array based multiplex PCR (Fluidigm Access Array®) and next generation resequencing (Illumina MiSeq).

Results: A homozygous truncation (p.F1032Cfs*11) was identified in the gene FAT1 (FAT homologous cadherin 1) in a child with congenital nephrotic syndrome and renal histology of diffuse mesangial sclerosis. FAT1 has been shown to play a role in WNT signaling in which defects have previously been shown to be a mechanism for renal failure. The Fat1 mouse displays abnormal podocyte foot processes, brain developmental defects, and eye abnormalities.

Conclusions: We identified mutations in FAT1 in individuals with an overlapping phenotype of NPHP-RC and nephrotic syndrome.

TH-PO889

CCDC41 Is Mutated in Nephronophthisis-Related Ciliopathy

Heon Yung Gee,¹ Jan Halbritter,¹ Jonathan Porath,¹ Daniela A. Braun,² Markus Schueler,¹ Edgar Otto,⁵ Friedhelm Hildebrandt.¹,³ 'Div of Nephology, Boston Children’s Hospital, Harvard Medical School, Boston, MA; ²Dept of Pediatrics, Univ of Michigan, Ann Arbor, MI; ³Howard Hughes Medical Institute.

Background: Nephronophthisis-related ciliopathies (NPHP-RC) are degenerative recessive diseases that affect, retina, or brain (1). More than 15 genes are associated with NPHP-RC, accounting for about 40% of cases (1). About 60% of cases are molecularly unresolved (2).

Methods: To find additional single-gene cause of NPHP-RC, we screened a worldwide cohort of over 700 individuals by multiplex PCR followed by barcoding and next-generation resequencing (1).

Results: We identified a homozygous frameshift mutation (p.E659fs*14) in CCDC41 (coiled-coil domain containing 41) in an affected individual with NPHP, macrocephaly and heart anomalies. CCDC41 is a component of the distal appendages of centrioles and cilia, and mutations in CCDC41 have been identified in NPHP-RC associated with ciliopathies including nephrotic syndrome (1). We then screened an additional 720 individuals with nephrotic syndrome using array based multiplex PCR and next generation resequencing.

Conclusions: We identified a mutation in CCDC41 as causing NPHP-RC, adding another component of the distal appendages of centrioles to a multi-systemic ciliaopathy.
A Novel Cep290 Collecting Duct Tubule Cell Line of the Ciliopathy Joubert Syndrome
Ann Marie Hynes,1 Rachel H. Giles,2 Lorraine Eley,1 Colin Miles,3
John Andrew Sayer.4 Institute of Genetic Medicine, Newcastle Univ, Newcastle
upon Tyne, United Kingdom; 2Univ Medical Center Utrecht, Univ Medical
Center Utrecht, Utrecht, Netherlands.

Background: Joubert Syndrome related disorders (JSD) are autosomal recessive ciliopathies characterised by retinal degeneration, cystic kidney disease and cerebellar vermian aplasia. Mutations in CEP290 are the most common cause of JSD. Here we described the isolation and characterisation of a collecting duct cell line, isolated from kidneys of Cep290-/- mice backcrossed with H-2Kb-tsA58+/-’immorto’ mice. These cell lines have been used to investigate ciliary signalling and disease pathogenesis.

Methods: Cep290+/-:H-2Kb-tsA58+/- (mutant) and Cep290-/-:H-2Kb-tsA58+/- (wildtype) collecting duct cells were isolated from kidneys of one month old transgenic mice. Kidney samples were digested in 0.1% collagenase type II and onchreted on 6 well plates coated with 10 mg/ml Dolichos Biflorus Agglutinin at 33°C. PCR for collecting duct markers, western blotting and staining for cilia were used to characterise these cell lines under a range of conditions.

Results: Mutant and wild type collecting duct cells displayed collecting duct morphology and expressed both the mineralocorticoid receptor and the epithelial sodium channel alpha subunit. There was a loss of primary cilia in Cep290 mutant cells compared to wild type cells (5% vs. 55%, p<0.0001). The cilia that were evident in Cep290 mutant cells were also shortened when compared with the wild type cells (mean length 2.4µm vs. 3.5µm). Western blotting showed disrupted signalling in mutant cells. 3D culturing of Cep290 mutant cells confirmed a loss of primary cilia and disrupted epithelial polarity.

Conclusions: The conditionally immortalised wild type and Cep290 mutant collecting duct cells formed epithelial cell layers and expressed collecting duct cell markers. Cep290 mutation leads to either a loss of cilia or shortened cilia compared to wild type controls. Disrupted signalling in Cep290 mutant cells suggests that cell lines provide a valuable tool for understanding cystic kidney disease and for drug testing.

Funding: Private Foundation Support

Tolvaptan Reduces the Mortality and Ameliorates the Progression of PKD in DBA/2:FG-pcy Mice

Background: Tolvaptan slowed the increase in total kidney volume and the decline in renal function in patients with ADPKD in the TEMPO 3:4 clinical trial. There still remain the questions of whether tolvaptan has a dose-related effect and whether long-term treatment with tolvaptan is effective in delaying the end stage of the disease.

Methods: We examined the dose-related effect of tolvaptan by short-term treatment (0.01% to 0.3% via diet; 5 to 15 weeks of age) and the long-term effect of tolvaptan by whole-life treatment at the optimal dose (0.1% via diet; 5 to 29 weeks of age) in DBA/2:FG-pcy mice, an animal model of ADPKD.

Results: By short-term treatment, at 15 weeks of age tolvaptan dose-dependently prevented increases in kidney weight, kidney cyst volume, kidney fibrosis volume, and mictic index, and also significantly reduced renal cystic AMPF level and ERK activity, suggesting that the mechanism for these effects was antagonism of vasopressin signals. Urinary NGAL level was also suppressed dose-dependently. Based on the overall efficacy profile, the optimal dose was considered to be 0.1% via diet. In the long-term treatment, left kidney volume was monitored by MRI over time, and tolvaptan significantly inhibited the enlargement of left kidney volume by as much as 50% of the control (p<0.01, repeated measures ANOVA) and also significantly inhibited urinary albumin excretion during the experimental period. Additionally, tolvaptan significantly reduced mortality rate to 20% (p=0.0415, log-rank test) versus 60% in control DBA/2:FG-pcy mice.

Conclusions: These studies showed for the first time that long-term treatment with tolvaptan at the optimal dose was highly effective in inhibiting cystogenesis, preventing deterioration of renal function, and improving mortality in DBA/2:FG-pcy mice. Furthermore, these data strongly indicate that vasopressin-mediated cAMP elevation plays a key role in the pathogenesis of PKD and that tolvaptan ameliorates the progression of PKD by V2 receptor antagonism, providing a promising treatment for PKD.

Funding: Private Foundation Support

Loss-of-Function Mutations in SLCO4C1 as a Cause of Hypertension in Chronic Kidney Disease
Daniela A. Braun,1 Heon Yung Gee,1 Eikan Mizuguchi,2 Rachel H. Giles,2 Lorraine Eley,1 Colin Miles,3
John Andrew Sayer.4 Institute of Genetic Medicine, Newcastle Univ, Newcastle
upon Tyne, United Kingdom; 2Univ Medical Center Utrecht, Univ Medical
Center Utrecht, Utrecht, Netherlands.

Background: Nephronophthisis (NPHP) is a recessive cystic kidney disease representing the most frequent genetic cause of kidney failure in the first decades of life. Although in more than 10% of the cases NPHP is associated with extra-renal involvement, hypertension is characteristically absent from individuals with NPHP.

Methods: We performed homozygosity mapping and whole exome sequencing (WES) in a consanguineous family with two affected children with NPHP and hypertension. By WES and targeted WES and WER we identified a homozygous missense mutation in the gene SLCO4C1 (p.M1-start loss). SLCO4C1 (solute carrier organic anion transporter family member 4C1) is a kidney-specific organic anion transporter that plays a major role in the excretion of uremic toxins and has been identified in the pathogenesis of hypertension. By IHC we confirm localization of SLCO41 to the basolateral membrane of proximal tubular epithelium. We show in vitro that the observed mutation represents a functional null allele by abatting the translation initiation codon and causes loss of function.

Conclusions: In a consanguineous family with two affected siblings we identified a homozygous missense mutation in SLCO4C1 as causing hypertension in children with NPHP.1 Toyohara et al, JASN 20: 2546, 2009.

TH-P0893

Dynamics of E-Cadherin Localization and β-Catenin Activation Following Unilateral Ureteral Obstruction in Wild Type and Phkdl−/−-/- Kidneys
Rachel Gallagher,1 Seung H. Lee,1 Stefan Somlo.1,2 Internal Medicine, Yale School of Medicine, New Haven, CT; 2Genetics, Yale School of Medicine, New Haven, CT.

Background: Studies on Phkdl have primarily focused on its role in autosomal recessive polycystic kidney disease (ARPKD), however its role in renal homeostasis has yet to be addressed. We have previously described that Phkdl-/- mice had impaired recovery with sustained tubule dilation when subjected to unilateral ureteral obstruction (UUO) (JASN2010, F-PO1765). In this study, we sought to investigate the molecular basis for the poor recovery in Phkdl-/- kidneys.

Methods: Phkdl-/- mice and littermate controls were subjected to 3 days of UUO. By IHC we followed recovery post injury which was analyzed by immunohistochemistry, BATgal reporter activity, and quantitative PCR (qPCR).

Results: Immunohistochemical analysis showed that E-cadherin expression was reduced at the lateral membrane and was re-localized to the cilia following 3 days of UUO in both wild type and Phkdl-/- mice. β-catenin expression was detected in both the cytoplasm and at the lateral membrane after injury and there was no difference between wild type and Phkdl-/- kidneys. The lateral membrane was repopulated with E-cadherin after 14 days repair in the wild type kidneys but not in Phkdl-/- kidneys in which very little was detected at the lateral membrane. Since loss of E-cadherin has been shown to release β-catenin from the membrane where it can translocate to the nucleus and activate TCF/lef transcription, we examined whether there was β-catenin-dependent transcriptional activation using qPCR and the BATgal reporter mouse. qPCR analysis showed elevated levels of β-catenin transcriptional targets in the Phkdl-/- kidneys, however the reporter studies showed that the transcriptionally active cells were primarily in the fibroblasts and not in the collecting duct cells.

Conclusions: The data show abnormal localization of E-cadherin in cilia during injury and the occurrence of sustained β-catenin activity in fibroblasts in Phkdl-/- kidneys after 14 days of recovery from UUO. Response to injury may be a feature of Phkdl activity in adult kidney homeostasis.

Funding: Private Foundation Support

TH-P0894

Ectopic Expression of the Human PKHD1 Gene Product Can Rescue the Cystic Phenotype of Phkdl Knockout Mice
Ao Li,1,2 Yuan Li,1,2 Haichao Liu,1,2 Wei Li,1,2 Dan Liang,2 Guangqi Wu.1 State Key Laboratory of Molecular Oncology, Cancer Hospital and Institute, Chinese Academy of Medical Sciences, Beijing, China; 2Dept of Medicine, Vanderbilt Univ, Nashville, TN.

Background: We have recently produced a transgenic mouse in which a human PKHD1-full length ORF cDNA is controlled by a pCAGGS expression vector.

Methods: The pCAGGS expression vector has been reported to express the reporter gene at an early stage of embryonic development and possesses ubiquitous expression in all tissues and organs of the mice. Sixty-six offspring from foster mothers were screened by PCR, and transgene founders were detected in five of them. Four founders (tg5, 20, 46 and 63) can go through germline transmission to produce offspring with the transgene. By qPCR testing, tg5 and 20 do not show human PKHD1 mRNA overexpression in the disease-affected tissues and organs. Southern analyses indicate that there are approximately three copies of the transgene in tg53 (PKHD1+/+) and two copies in tg46 (PKHD1+/−) mice. We used PKHD1+/+ mice for our further studies.

Results: PKHD1+/− mice do not show any abnormal phenotypes during mouse development. Using a mating strategy, PKHD1+/− mice were crossmated with Phkdl-/- mice (B6;129 mixed background; 2008:19:455 cDNA produced Phkdl-/- mice). Kaplan-Meier analysis illustrated that approximately 25% of Phkdl-/-:PKHD1+/− mice survive until 6 months, compared with only 18% of Phkdl-/- mice, suggesting that human PKHD1 transgene can rescue partially lethal phenotype in Phkdl-/- mice. By pathological analysis, we also found that PKHD1+/−:PKHD1+/− mice (n=5) exhibited significantly decreased cystic number and volume in the pancreas, liver and kidneys, compared to Phkdl-/- littermates, suggesting that an increased expression level of human PKHD1 gene product can significantly rescue cystic phenotypes in the mice model of ARPKD. Phkdl-/- mice with PKHD1+/− also exhibit microcystic improved hepatoortal functions than Phkdl-/- mice alone.

Conclusions: Our results indicate that ectopic expression of the human PKHD1 gene product can rescue the cystic phenotypes of Phkdl knockout mice, and underlies a therapeutic potential for gene therapy of ARPKD.

Funding: NIDDK Support
TH-PO895
Smad3 Phosphorylated at Both Linker and COOH-Terminal Regions in Cyst-Lining Epithelia in cpk Mouse, a Model of ARPKD
Taketsugu Hama,1 Koichi Nakashii,1 Hironobu Mukaiyama,1 Hiroko Togawa,1 Masashi Sato,1 Yuko Shimai,2 Masayasu Miyajima,1 Kandai Nozu,1 Shizuko Nagai,1 Hishide Takahashi,1 Kazumoto Iijima,2 Norishige Yoshikawa,2 Daria Ilatovskaya, Oleg Palygin, Tengis S. Pavlov.1

Background: Cystic kidney disease is an autosomal recessive genetic disorder characterized by the formation of multiple fluid-filled cysts primarily arising from the vasoressin responsive renal collecting ducts. Vasoressin mediated increase in cAMP is crucial for maintaining normal Na+ reabsorption and fluid accumulation in cysts and further progress of this kidney disease.

Results: We previously identified ENaC phosphorylation in ciliated cells in cysts. On the other hand, pSmad3L, pSmad3C, JNK, CDK4 and c-Myc were evaluated by western blotting (WB). Cophosphorylation of Smad3L/C was assessed by immunoprecipitation (IP) with WB.

Conclusions: Our data suggest that cAMP-mediated phosphorylation of ENaC and Smad3 plays an important role in the development of cystic kidney disease.

Funding: None

TH-PO896
Glycogen Synthase Kinase 3 Inactivation Ameliorates Polycystic Kidney Disease in Cys1cpk Mice
Reena Rao,1 Erin Suderman,1 Shixin Tao.1

Background: Polycystic kidney diseases (PKD) are a family of inherited disorders characterized by the formation of multiple fluid filled cysts primarily arising from the vasoressin responsive renal collecting ducts. Vasoressin mediated increase in cAMP is crucial for maintaining normal Na+ reabsorption and fluid accumulation in cysts and further progress of this kidney disease.

Results: We previously identified ENaC phosphorylation in ciliated cells in cysts. On the other hand, pSmad3L, pSmad3C, JNK, CDK4 and c-Myc were evaluated by western blotting (WB). Cophosphorylation of Smad3L/C was assessed by immunoprecipitation (IP) with WB.

Conclusions: Our data suggest that cAMP-mediated phosphorylation of ENaC and Smad3 plays an important role in the development of cystic kidney disease.

Funding: None

TH-PO897
ADAM17 Regulates Mitochondrial Bioenergetics in Polycystic Kidney Disease (PKD)
Monika Gooz,1 Eduardo Maldonado,1 Yujing Dang,2 May Y. Amrha,1 Hanna E. Abboud,2 John Lemasters,1 P. Darwin Bell.1

Background: Previous studies have shown that ADAM17 deficiency reduces renal cyst formation in the chicken netrin-1 transgenic mouse. In PKD, EGF receptor (EGFR) is overexpressed and mislocalized to the apical membranes in the cystic epithelia. EGFR activation inhibits ENaC activity. It has also been reported high EGF concentration in cystic epithelia in cystic kidney disease.

Methods: We previously showed that cAMP formation and ENaC expression in cilia (-) cells were reduced in Tg6 mice. In this study we investigated the contribution of ADAM17 expression in cystic epithelia in PKD.

Results: Expression and enzyme activity of ADAM17, and level of phosphorylated ERK were higher in the highly proliferative cilia(-) cells compared to the less proliferative cilia(+) cells. Cilia(-) cells had also higher basal respiration than cilia(+) cells: 440±31 versus 278±59 pmol O2/min/10,000 cells. Addition of the uncoupler CCCP (5 μM), induced higher maximal respiration in cilia(-) cells compared to cilia(+) cells. NADH level was 36±15% higher in cilia(-) cells compared to cilia(+) cells. Interestingly, ERK phosphorylation was increased after addition of 10 μM of GSK3 inhibitor TDZD-0. In the Tg6 mouse kidney, ADAM17 expression was increased in renal cysts and tubules and immunohistochemical assay showed that ADAM17 expression was increased in the cilia(-) cells.

Conclusions: Our data suggest that ADAM17 and cAMP activation is crucial for maintaining normal Na+ reabsorption, fluid accumulation in cysts and further progress of this kidney disease.

Funding: Other NIH Support - NHLBI R01-108880, Private Foundation Support

TH-PO898
Chronic and Excessive Nretin-1 Expression in Renal Tubular Epithelium Induces Polycystic Kidney Disease in Mice
Riyaz Mohamed,1 Calpurnia Jayakumar,1 Andreas D. Kistler,2 Ganesan Ramesh.1

Background: The mechanism of cyst development and pathogenesis leading to end-stage renal disease is not entirely understood due to lack of animal models that closely mimics human disease. This study was designed to characterize the new animal model for PKD and determine the role of nretin-1 in PKD.

Methods: Two transgenic mice lines (Tg3 and Tg60) that overexpress nretin-1 in the kidney proximal tubules using L-fatty acid binding protein promoter and their wild-type littermice were used in this study. Nretin-1 overexpression, signaling pathways that are activated in the kidney and role of nretin-1 in PKD was determined by Western blot, RT-PCR, ELISA and siRNA infusion.

Results: The transgene chicken nretin-1 excretion in urine is 100 fold more in Tg6 as compared to Tg3 mice and over 1000 fold compared to WT mice. Tg6 but not in Tg3 transgenic mouse developed multiple cysts at the age of 4 weeks and cyst growth accelerated rapidly reaching a kidney weight of 15-17gram by 32 weeks of age that was accompanied by kidney dysfunction (BUN: 35±5 mg/dl, p<0.001 vs. WT), polyuria, albuminuria, increased epithelial cell proliferation and increased excretion of cAMP. Surprisingly, cyst formation in the kidney was restricted to male animals with a penetrance of 85%. Transcription factors (Aif3, NFAT, Cebpb and Fos) and signaling pathways (ERK, focal adhesion kinase) that are associated with cAMP and polycystic formation in human were upregulated in Tg6 mice kidney. Interestingly, p33 expression was increased but present in an inactive unphosphorylated form. To determine whether the observed effects were due to nretin-1 overexpression, nretin-1 expression was suppressed with siRNA infusion. siRNA
mediated suppression of netrin-1 expression completely suppressed polycyst formation in Tg6 animals. Consistent with animal studies, human ADPKD patients excrete significantly more netrin-1 than healthy patients.

**Conclusions:** Our result suggests chronic and excessive overexpression of netrin-1 induce polycyst formation through dedifferentiation and suppression of p53 activation.

**Funding:** NIDDK Support

**TH-PO900**

**Variable Clinical Presentation in Individuals with a MUC1 Mutation Causing Medullary Cystic Kidney Disease Type 1**

Anthony J. Bleyer,1 Stanislav Kmoch,2 Kenedah O. Kidd,3 Victoria C. Roberts,3 Katerina Hodanova,1 1Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC; 2Institute of Inherited Metabolic Disorders, Charles Univ in Prague, Prague, Czech Republic.

**Background:** A cytosine insertion in the MUC1 gene was recently identified as the most common cause of medullary cystic kidney disease type 1 (MCKD1). The clinical expression of this mutation has not been well characterized.

**Methods:** Genotyping and evaluation of clinical characteristics were performed on families with a history of UMOD- and AEN-negative autosomal dominant interstitial kidney disease.

**Results:** 25 of 36 families tested were identified with a MUC1 mutation (mMUC1). Of 179 members of mMUC1 families, mMUC1 was identified in 95 individuals, and 84 individuals did not have a mutation. There were 110 individuals identified as historically affected. Individuals with mMUC1 suffered from chronic kidney failure with a widely variable age of onset of ESRD, ranging from 16 to greater than 80 years.

**Conclusions:** MUC1 mutations are the predominant cause of UMOD-negative autosomal dominant interstitial kidney disease. Individuals with mMUC1 have highly variable expression, with some proceeding to dialysis as teens, while others remain dialysis-free into their 80’s. While MUC1 is expressed in many tissues, it only results in clinical abnormalities in the kidney.

**TH-PO901**

**Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Medullary Cystic Kidney Disease (MCKD) in an Australian Chronic Kidney Disease (CKD) Cohort**

Andrew John Mallett,1,2,4 Anne Salisbury,1,2 Zaimin Wang,1,2 Helen G. Healy,5,6 George T. John,7 Wendy E. Hoy,1,8,9 CKD.QLD: Centre for Chronic Disease, School of Medicine, Univ of Queensland, Brisbane, Queensland, Australia; 7Dept of Renal Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Queensland, Australia.

**Background:** 5.7% and 0.3% of Australian and New Zealand patients commencing renal replacement therapy (RRT) in 2011 had ADPKD or MCKD respectively as a Primary Renal Diagnosis. Those with CKD are not well described within Australasia.

**Methods:** To define the frequency and characteristics of CKD patients with ADPKD and MCKD. CKD.QLD is a registry and research platform involving all consenting patients in public renal practices in Queensland (~10,800). Primary Renal Disease coding on the first 2359 patients at 5 hospital sites were searched for ADPKD and MCKD. These patients were compared to all patients in the CKD.QLD registry for age, gender and CKD stage.

**Results:** 93 ADPKD and 9 MCKD patients were identified representing 3.9% and 0.4% of the total. Distribution was similar between all 5 CKD.QLD sites. 48% of ADPKD patients and 6/9 MCKD patients were females.

The most common CKD Stages in ADPKD patients, MCKD patients and the broader CKD.QLD registry were 3b (23.7%, 44%, 28%) and 4 (21.5%, 44%, 22%). Men with ADPKD were most commonly CKD Stage 3b (29%). Women with ADPKD were most commonly CKD Stage 4 (28.8%) with suggestion of bimodal age distribution.

There appeared to be 2 types of families. In 13 families, the age of start of dialysis was <50 in almost all individuals, with many young individuals with ESRD. In the other 12 families, there was much more variability in the age of ESRD, with some patients not reaching dialysis until after 70. 38/38 renal ultrasounds of mMUC1 affected individuals did not have a mutation. There were 110 individuals identified as historically affected. Individuals with mMUC1 showed as historically affected. Individuals with mMUC1 suffered from chronic kidney failure with a widely variable age of onset of ESRD, ranging from 16 to greater than 80 years.

**Conclusions:** MUC1 mutations are the predominant cause of UMOD-negative autosomal dominant interstitial kidney disease. Individuals with mMUC1 have highly variable expression, with some proceeding to dialysis as teens, while others remain dialysis-free into their 80’s. While MUC1 is expressed in many tissues, it only results in clinical abnormalities in the kidney.

**TH-PO903**

**Tuberous Sclerosis in Children: Its Variable Renal Presentation and Outcome**

Isabel Roberti, Shefali Vyas. Children’s Kidney Center, Saint Barnabas Medical Center, Livingston, NJ.

**Background:** Tuberous sclerosis (TS) is a multisystem disorder encompassing a wide spectrum of renal lesions. Renal involvement is often asymptomatic but renal failure can affect 1% of adults with TS. A variable number of renal cysts and/or angiomyolipomas have been reported in children with TS but renal failure and renal CA are not expected.

**Methods:** This is a retrospective analysis of children with TS referred to our Pediatric Nephrology Center in the past 15 years. Demographic info, clinical data, therapy and outcome were reviewed.

**Results:** We identified 22 children, aged 1 day to 14 years (median = 5 yrs), half were males, 13 C, 5 A, 50. **Reason for referral:** abnormal renal sonogram or MRI= 21 (3 pre-natal, 2 with enlarged abdomen with palpable kidneys, 16 routine), CKD = 1. FH in 9 (41%); PMH+ for cardiac rhabdomyomas. **GFR at presentation:** ESRD=1, Stage 2 CKD=1, Stage 3 CKD=2, Stage 4 = 4 (18%); **Proteinuria** = 1. All had CNS involvement by brain MRI; 17 (77%) had seizures and developmental delay (varied from mild to autism). **Skin lesions** were seen in 15 (68%); **Renal sonogram at presentation:** few cysts=4, bilateral cysts (some complex)= 7, angiomyolipomas= 11, hamartomas =2, insulin dependent diabetes=3, enlarged kidneys (~15 cm)= 2. **Follow-up time** (N=18): 5 to 10 yrs (median=3 yrs). **Renal outcome:** 3 ESRD (1 on PD since birth) died at 9 mos with aortic aneurysm unable to have a txp, 2 tsp: 1 s/p renal CA and nephrectomy died due to seizures and 1 with CQN with no renal TS), 1 stage 3 CKD and 14 (77%) stage 1 CKD.

**Conclusions:** We report 22 children with TS with various degrees of renal and CNS involvement, including an infant with ESRD. Our incidence of CKD/ESRD was higher than expected at 18%. Renal lesions typically progressed with time. Everolimus significantly ameliorated the renal dysfunction in 1 child. Further studies detailing the long-term f/u of such children and the possible benefit of everolimus for ameliorating renal disease are needed.

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

Underline represents presenting author/disclosure.

**304A**
TH-PO904

Aberrant Glycosylation and Localization of Polycystin-1 Cause Polycystic Kidney in AQP11-Knockout Mice

Yuichi Inoue,1 Eisei Sohara,1 Katsuki Kobayashi,2 Tatemitsu Rai,1 Kenichi Ishibashi,3 Shigeo Horie,4 Xuefeng Su,5 Jing Zhou,1 Sei Sasaki,1 Shinichi Uchida.1 Tokyo Medical and Dental Univ; 2Chiba East National Hospital; 3Meiji Pharmaceutical Univ; 4Juntendo Univ; 5Brigham and Women’s Hospital.

Background: We previously reported that the disruption of aquaporin-11 (AQP11) gene in mice resulted in cyst formation in the kidney. However, the mechanism of cyst formation in the AQP11(-/-) mouse is still unknown.

Methods: To investigate the mechanism, we analyzed the AQP11(-/-) mouse and AQP11 BAC transgenic (TG(AQP11)) mouse that expresses 3xHA-tagged AQP11, by focusing on the polycystic kidney disease-related gene products.

Results: Immunofluorescence of the kidney from TG(AQP11) mice revealed that 3xHA-AQP11 was localized in the cytoplasm of proximal tubule cells. Double immunofluorescence with organelle markers and immunoblots of isolated ER fraction of the kidney of TG(AQP11) mice revealed that 3xHA-AQP11 localizes to ER in vivo. Since ER is essential for quality control and trafficking of newly synthesized proteins, we hypothesized that the absence of AQP11 in ER could result in impaired quality control and aberrant trafficking of polycysts, responsible proteins for autosomal dominant polycystic kidney disease. We found an increase in protein expression level of PC-1 and a decrease in protein expression level of PC-2 in AQP11(-/-) mice kidney, compared with wild-type mice. We confirmed higher molecular weight of PC-1 in AQP11(-/-) mice kidney, caused by impaired N-glycosylation processing of PC-1. In addition, density gradient centrifugation of kidney homogenate revealed impaired membrane trafficking of PC-1 in AQP11(-/-) mice. Finally, we demonstrated that the Pkd1 knockout background results in increased severity of polycystic kidney disease in AQP11(-/-) mice.

Conclusions: Our data demonstrated that impaired glycosylation processing and aberrant membrane trafficking of PC-1 in AQP11(-/-) mouse could be a key mechanism of cyst formation in AQP11(-/-) mice.

Funding: Government Support - Non-U.S.

TH-PO905

Aquaporin1 Inhibits Renal Cyst Formation and Enlargement by Down-Regulating Wnt Signaling

Weiling Wang, Baoxue Yang. State Key Laboratory of Natural and Biomimetic Drugs, Dept of Pharmacology, Peking Univ, Beijing, China.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the progressive enlargement of cysts caused by mutations in Pkd1 or Pkd2. Polycystin-1 encoded by Pkd1 undergoes multiple cleavages that intervene in several signaling pathways involved in cellular proliferation and differentiation mechanisms. Aquaporin1 (AQP1) is a water channel protein, widely expressed in epithelial and endothelial cells. Recent research involved in cellular proliferation and differentiation mechanisms. Aquaporin1 (AQP1) is a water channel protein, widely expressed in epithelial and endothelial cells. Recent research revealed AQP1 interacted with Lin7 to regulate cytoskeleton remodeling in melanoma cell.

Methods: We analyzed kidney index and cyst index in both AQP1 null PKD mice and embryonic kidney cyst model. We evaluated β-catenin, p-β-catenin, CyclinD1, GSK3β and p-GSK3β expression by Western blot and immunofluorescence in AQP1 over-expression MDCK cell and MDCK cell as well as AQP1 null mice.

Results: With AQP1 null PKD mice, We found AQP1 deficiency significantly promoted renal cyst development. Similarly, 8-Br-cAMP induced cyst enlargement was promoted in AQP1 null embryonic kidney model. Over-expression of AQP1 inhibited cyst development and promoted tubulogenesis in MDCK tubule model. It was found that AQP1 impaired the extracellular adhesion and decreased E-cadherin. AQP1 down-regulated β-catenin expression and up-regulated β-catenin phosphorylation in AQP1-MDKC cells. Furthermore, CyclinD1 was hardly detected in AQP1-MDKC cells. The kidneys from AQP1 knockout mice showed high level of β-catenin. The level of p-GSK3β was lower in AQP1-MDCK cells. It was also found that AQP1 co-immunoprecipitated with β-catenin, p-β-catenin as well as GSK3β.

Conclusions: AQP1 may involve in maintaining the stability of the “degraded complex” to promote β-catenin phosphorylation and suppress the Wnt signaling pathway. We speculate that AQP1 might be a new target for ADPKD therapy.

Funding: Other NIH Support - National Natural Science Foundation of China 81261160507 and 81170632

TH-PO906

Implication of Inflammasome Activation via Mitochondrial Reactive Oxygen Species in the Development of Renal Interstitial Fibrosis Induced by Aldosterone

Hirokiyo Kaeda,1 Minori Sato,1 Tamaki Sasaki,1 Naoki Kashihara. Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.

Background: The inflammasome plays an important role in a variety of diseases, including atherosclerosis and chronic kidney disease (CKD). The inflammasome is a cytosolic multiprotein complex that activates caspase-1, through interaction with ASC (Apoptosis-associated Speck-like Protein Containing a Caspase Recruitment Domain), and finally leads to the processing and secretion of the pro-inflammatory cytokines, such as IL-1β and IL-18. Aldosterone (Aldo) has been indicated to induce kidney damages through activation of pro-inflammatory signaling pathway. We hypothesized that Aldo induces renal damages via activation of inflammasome.

Methods: ASC-deficient mice (ASCKO) and control C57BL/6 mice (WT) were used. All animals were received left uninephrectomy and given drinking water with 1% NaCl. The mice were divided into the following groups: WT-vehicle, WT-Aldo (Aldo, 0.25 mg/kg/day, osmotic pump), WT-Aldo treated with eplerenone (WT-Aldo+Eple; Eple, 100 mg/kg/day, gavage), and ASCKO-Aldo. Three weeks after drug administration, mice were sacrificed. We also examined the mitochondrial superoxide production by Aldo and its possible involvement in inflammasome activation in cultured mouse peritoneal macrophages.

Results: Tubulointerstitial damage and increased expressions of inflammasome components, NLRP-3 and ASC, were demonstrated in WT-Aldo. Increased Caspase-1 activity and concomitant overproduction of IL-1β and IL-18 were also demonstrated in the WT-Aldo. Eple treatment suppressed these changes. Tubulointerstitial injuries were significantly attenuated in the ASCKO-Aldo. Increased Caspase-1 activity and expressions of IL-1β and IL-18 were also attenuated in ASCKO-Aldo. Aldo induced mitochondrial superoxide production and resulted in inflammasome activation in cultured macrophages obtained from peritoneal cavity. This was completely blocked by eplerenone. Our results indicate that Aldo induced interstitial fibrosis via activation of inflammasome in infiltrated macrophages. Thus, inflammasome activation in macrophages could be a new therapeutic target for CKD.

Conclusions: Our results indicate that Aldo induced interstitial fibrosis via activation of inflammasome in infiltrated macrophages. Thus, inflammasome activation in macrophages could be a new therapeutic target for CKD.

TH-PO907

Altered Excitability of Afferent Renal Innervation in an In-Vivo Model of Renal Inflammation

Wolfgang Freisinger,1 Annalena Karl,1 Nadja Tzinis,2 Tilman Dittrich,2 Sonja Heinlein,3 Roland E. Schmieder,2 Jens Lutz,1 Roland Veelken.2 1Nephrology, Med. Clinic 4, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany; 2Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.

Background: Renal innervation is most likely important in renal inflammatory disease. Recently, we found that afferent renal neurons show a distinctive excitability, exhibiting predominantly a sustained firing upon current injection that depends on specific sodium
channel expression. So far, excitability of these neurons under inflammatory conditions in vivo is unclear. Hence we wanted to test the hypothesis that in a model of renal inflammation, Th1, Th2, and Th17 cells, the synaptic firing pattern of the different neurons is altered.

Methods: Thy.1 nepritis was induced (OX7, 1.2mg/kg) in Sprague Dawley rats 7 days before harvesting neurons, controls received vehicle. Nepritis was confirmed by proteinuria and histologically. Labelling (DiI) identified renal afferent neurons situated in dorsal root ganglia (DRG). Current clamp was used to characterize neurons as “tonic”, i.e. sustained action potential (AP) firing or “phasic”, i.e. <5 APs. AP properties were determined in renal and non-renal neurons of nephritic rats and controls.

Results: Nepritis rats had all proteinuria and displayed histologically inflammation. Unineurone afferent DRG neurons (n=58) exhibited in 64% a tonic firing pattern. In Thy.1 nephritic rats, renal DRG neurons (n=112) exhibited significantly less a tonic firing pattern (43% vs. 64%, p<0.05). Whereas the characteristic “tonic” vs. “phasic” changed, neither electrophysiological parameters (resistance, cell capacity, membrane potential) nor action potential morphology was altered.

Conclusions: We could show that in an in vivo model of renal inflammation, renal afferent neurons exhibited a significantly decreased excitability upon electric stimulation. An altered expression of sodium channel subtypes might lead to a further fastening of these channels and decreased firing activity. In consequence, altered renal activity in vivo could lead to sympathetic dysregulation aggravating renal inflammation.

TH-PO908
Nlrp3 Inflammassome Activation Promotes Renal Tubulointerstitial Inflammation in Albumin-Overload Nephropathy Dan Liu,1 Bi-Cheng Liu,1,2 Institute of Nephrology, Southeast Univ, Nanjing, China; 1Institute of Nephrology, Southeast Univ; 2Institute of Nephrology, Southeast Univ.

Background: Nlrp3 inflammasome are implicated in recognizing certain non-microbial origin ‘danger-signals’. This study aimed to investigate whether albumin induce Nlrp3 inflammasome activation and contribute to tubular cell stress and tubulointerstitial inflammation.

Methods: Albumin-overload nephropathy was induced in adult male Wistar rats that were uninephrectomized or sham operated 5 days before starting bovine serum albumin injection. Rats were given daily intraperitoneal injections of 5g/kg BSA (n=10) or sham sterile normal saline (UXX; n=6, Sham: n=6) injections for 9 weeks. Blood samples were taken on weeks 0, 2, 5, 7, 9 after collection of 24 h urine. At the end of the study, rats were anesthetized and tissue were kept for subsequent analysis. Nlrp3 inflammasome and inflammatory cytokines were examined by real time RT-PCR and Western blotting.

Results: Urinary protein excretion assay shows that proteinuria were increased in albumin-overload rats compared to saline-injected controls (p<0.05). Tubular injury was confirmed by ELISA examination of NGAL, which increased in albumin-overload rats than controls (p<0.05). Immunofluorescence showed Nlrp3 activation in proximal tubular cells. Albumin triggered the upregulation of Nlrp3 inflammasome, which subsequently lead to IL-1β and IL-18 secretion (Nlrp3+ p<0.05; IL-1β+ p<0.05; IL-18+ p<0.01). Real time RT-PCR indicated Nlrp3 mRNA expression increased of renal cortex. Meanwhile, proximal tubal epithelial cells show atrophy observed by PAS staining and mitochondrial dysfunction indicated Nlrp3 mRNA expression increased of renal cortex. Meanwhile, proximal tubal epithelial cells show cell atrophy observed by PAS staining and mitochondrial dysfunction measured by mitochondrial membrane potential reduction by JC-1 dye after albumin overload (p=0.01). Immunochemical staining showed that inflammatory cell infiltration in tubulointerstitium was significantly greater in BSA injection group than saline group.

Conclusions: Our study demonstrated that albumin caused the tubular injury and tubulointerstitial inflammation through the mitochondrial dysfunction that activate Nlrp3 inflammasome with subsequent secretion of inflammatory cytokines in albumin-overload nephropathy.

TH-PO909
Human Leukocyte Antigen-G Attenuates Renal Inflammation in a Mouse Model of Lupus Nephritis Onkar Kulkarni, Shirkan R. Mulay, Murthy Narayana Darisipudi, Santhosh Kumar VR, Hans J. Anders. Medizinische Klinik und Poliklinik II; Univ of Munich, Munich, Bavaria, Germany.

Background: Human leukocyte antigen (HLA-G) interacts with PIR-B expressed on mouse leukocytes. Administration of microbeads coated with HLA-G-B2m has been shown to induce tolerance of DCs and inhibit DC maturation in transplantation mouse models. PIR-B is the negative regulator of TLR-9 in B cells which are primarily responsible for rheumatoid-factor (RF) release. B cells deletion attenuate the progression of lupus nephritis in MRL-lpr mice. PIR-B knockout mice have exaggerated release of RF, anti-DNA antibodies and reduced survival. We hypothesized that administration of HLA-G-B2m absorbed on microbeads will improve renal inflammation by inhibiting DCs maturation and B cells activation in MRL-lpr mice.

Methods: We injected microbeads coated with HLA-G-B2m (2microgram/week/mouse) for 10 wks starting from week 12 of age. Plasma, urine, tissue samples were collected at the end of the treatment period. Kidney tissues were processed for histological analysis. Various lymphocyte subtypes were analyzed by FACS from spleen and kidney. Part of isolated tissue was analyzed for expression analysis by RT-PCR.

Results: HLA-G treatment attenuated lupus nephritis, determined by the activity and characterization of histomorphological damage. HLA-G treatment improved renal function as observed by reduced BUN levels in the plasma. HLA-G treatment reduced the intra-renal accumulation of CXCJR3 positive T cells. IL17 and IFN-gamma-producing T cells were also reduced in kidney significantly in the HLA-G treated group. Infiltration and activation of dendritic cells and macrophages as well as expression of pro-inflammatory mediators in the kidney was significantly reduced by HLA-G treatment. Plasma levels of RF, IL12p40, TNF-alpha and IL17 were significantly reduced by the treatment. HLA-G treatment did not have any significant effect on the leukocytes subsets in the splen and peripheral CD11b+CD11c+ population.

Conclusions: HLA-G5 treatment significantly suppresses lupus nephritis of MRL-lpr mice, mainly by reducing systemic and intra-renal inflammation.

TH-PO910
Renal Cytokine Expression during Sepsis Is Repressed in Conditional NFAT5-Knockout Mice Christoph Kueper,1 Wolfgang Neuhofer,1,2 1Dept of Cellular Physiology, Univ of Munich; 2Dept of Nephrology, Univ of Munich.

Background: The omosensitive transcription factor NFAT5 (also known as TonEBP) regulates the expression of osmoprotective genes (AR, HSPT0 and urinary concentrating genes (AQP-2, UT-A, CIC-K1) in the kidney. Besides, NFAT5 is also involved in the expression of cytokines in immune cells during LPS stimulation. The aim of the present study was to evaluate, if NFAT5 activation is also involved in cytokine expression in renal cells in response to LPS. For this purpose, we generated conditional NFAT5 knockout mice, in which NFAT5 can be deleted in mature animals.

Methods: In the genome of the conditional knockout mice, exon 4 of the NFAT5 gene is deleted by two loxp sites. Additionally, the animals express the Cre recombinase under control of a tamoxifen-inducible promoter. At the age of 6 weeks, male conditional knockout mice were treated with tamoxifen to induce Cre-mediated NFAT5 knockdown. Knockdown efficiency and expression of defined renal NFAT5 target genes (AR, AQP-2, UT-A, CIC-K1) was measured by qRT-PCR and immunoblotting. In additional experiments the NFAT5- knockout mice or wild-type mice were treated with LPS (5 mg/kg bw) for 24 h. Expression of various cytokines (CCL-2, CCL-5, TNF-a, IL-6) was measured by qRT-PCR or ELISA.

Results: NFAT5 in expression of regulated renal NFAT5 in tamoxifen-treated animals was diminished to approximately 10% compared to control animals. In accordance, expression of NFAT5 target genes AR, AQP-2 and CIC-K1 was also significantly decreased. In a LPS/sepsis model, expression of cytokines CCL-2, CCL-5, TNF-a and IL-6, both in the kidney and in the spleen of current NFAT5 knockdown animals was significantly reduced compared to control animals.

Conclusions: We have developed a mouse model, in which the expression of NFAT5 can be efficiently repressed in mature animals. This mouse model may turn out to be very helpful for future studies investigating NFAT5 function in vivo. First results with this model demonstrate that several cytokines are downregulated in the kidney of NFAT5 knockout animals during LPS treatment, indicating that NFAT5 is an important factor of the inflammatory process in the kidney.

TH-PO911

Background: IL-10 is a potent anti-inflammatory cytokine that plays an important role in the regulation of immune responses, thereby preventing damage to the host. In various acute and chronic models of kidney diseases, IL-10 administration protected against renal injury. Tissue-resident macrophages in the kidney in steady state and injury/repair, we analyzed IL-10 production in vivo using a novel IL-10-beta lactamase reporter mouse (ITIB).

Methods: Single cells from ITIB mouse kidney after systemic LPS administration, bilateral renal ischemia-reperfusion (IRI) and unilateral ureteral obstruction (UUO) were analyzed by flow cytometry analysis.

Results: IL-10 is expressed by 3 distinct mononuclear phagocyte (MCP) populations: CD11b+CD11c- F4/80+, CD11b+CD11c+ and CD11b+CD11c-. Among MCPs, F4/80+CD11b+CD11c- cells are the predominant population in healthy kidneys, suggesting they may have a unique role in preventing inflammatory responses. Next, we investigated IL-10 up-regulation in the kidney after systemic LPS administration. Analysis of IL-10+CD11b+CD11c- MCPs demonstrated that CD11b+CD11c- MCPs do not synthesize IL-10 in steady state, but a resident population of CD11b+CD11c- F4/80+ MCPs generate IL-10 in healthy kidneys, suggesting they may have a unique role in preventing inflammatory responses. To study the source and characteristics of IL10-producing cells in the kidney after IRI and UUO, we analyzed IL-10 production in vivo using a novel IL-10-beta lactamase reporter mouse (ITIB).

Conclusions: These studies demonstrate for the first time that IL-10 is produced in vivo in renal reparative macrophages in kidney inflammation and injury.

Funding: Government Support - Non-U.S.
TH-P0912

Alternative Pathway (AP) of Complement (C) Activation Triggers Glomerular Podocyte and Parietal Epithelial Cell (PEC) Disregulation in Proteinuric Nephropathy
Marina Morì1, Monica Locatelli1, Daniela Corna1, Simona Buelli1, Mauro Abbate1, Marina Noris1, Ariela Benigni1, Giuseppe Remuzzi1,2, Carlamaria Zoja1.1 IRCSS - Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; 2Unit of Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy.

Background: We previously showed that protein overload led to glomerular injury, activating the AP of complement (C) and podocyte damage promoting C-dependent dysfunction of glomerular filtration barrier, which accelerated progressive renal injury. Here we sought to evaluate: 1) which of the C pathways were involved in glomerular C3 deposition and podocyte loss; 2) whether C-dependent glomerular injury was related to signs of PEC activation. To this aim, protein overload-podocyteculture was studied in mice deficient for the cofactor of the AP-C3 convertase factor B or for the AP inhibitor factor H.

Methods: Wild-type (WT), Bf- and C6a mice underwent uninephrectomy and 5d later received daily i.p. injections of saline or BSA up to 28d. Podocyte number was assessed indirectly showing that AP of C was involved in both phenomena. Additional evidence of glomerular inflammation in a Murine Model of Crescentic Glomerulonephritis

Interleukin 17-Receptor A on Leukocytes and Tissue Cells Mediates Alternative Pathway (AP) of Complement (C) Activation Triggers Necrotising, crescentic GN was induced by intravenous administration of intravenous sheep anti-mouse glomerular basement membrane (GBM) globulin at day 4 (planting SG in glomeruli), and culled at day 14.

Results: Compared to PBS, FLT3-L-treated mice had increased splenic Treg proportions (CD4+Foxp3+/CD4+: FLT3-L 21.4±1.9vs PBS 11.1±0.8%, P<0.05). Four days after immunization, FLT3-L-treated mice had higher proportions of lymph node DC (PDCA-1+/CD11c+: 10.0±1.6vs 5.0±0.9%; P<0.05) and enhanced SG-specific uric acid-induced delayed type hypersensitivity (0.31±0.08 vs 0.09±0.02mm; P<0.05), without an increase in Tregs, suggesting that ceasing FLT3-L therapy enhanced cellular immunity. Mice were given FLT3-L 10d p.i. PBS 10 d p.i. and used as a control. WT-BSA mice showed glomerular C3 deposits associated with podocyte loss (32%) and PEC activation (16% glomeruli), which were prevented by factor B deficiency (Fig.), indirectly showing that AP of C was involved in both phenomena. Additional evidence of AP involvement was provided by C6a-BSA mice that instead had more proteinuria, greater C3 deposits (score, 4.0 vs 2.0; P<0.01), more podocyte loss (39%), more severe PEC alterations (66% glomeruli) and higher % of glomeruli with GS (20.3% vs 9.3%, P<0.05) than WT-BSA mice.

Conclusions: Inhibiting AP of C attenuates glomerular injury in proteinuric mice, while its uncontrolled activation leads to more PEC-related glomerular sclerotic lesions.

Funding: Private Foundation Support

TH-P0913

Interleukin 17-Receptor A on Leukocytes and Tissue Cells Mediates Inflammation in a Murine Model of Crescentic Glomerulonephritis
Joanna R. Ghali1,2, Stephen R. Holdsworth1,2, A. Richard Kitching1,2.1 Centre for Inflammatory Diseases and Dept of Medicine, Monash Univ, Clayton, Victoria, Australia; 2Dept of Nephrology, Monash Health, Clayton, Victoria, Australia.

Background: Interleukin (IL)-17A and IL-17F are in type and PKC-theta gene-de cient mice. We previously showed that protein overload led to glomerular injury, associating gene A protein (CagA), a major virulence factor of Hp, with the production and underglycosylation of IgA1 in DAKIKI, a B cell line.

Results: IL-17A/F signalling promotes glomerular injury. Leakyocytedervived IL-17A/F promotes cellular immunity and injury, while IL-17A/F on radio-resistant cells enhances antigen-specific cellular and humoral immunity.

Funding: Government Support - Non-U.S.

TH-P0914

FMS-Like Tyrosine Kinase 3 Ligand Does Not Protect Mice from Experimental Glomerulonephritis, Despite Inducing Regulatory T Cells
Joanna R. Ghali1,2, Stephen R. Holdsworth1,2, A. Richard Kitching1,2.1 Centre for Inflammatory Diseases and Dept of Medicine, Monash Univ, Clayton, Victoria, Australia; 2Dept of Nephrology, Monash Health, Clayton, Victoria, Australia.

Background: FMS-like tyrosine kinase 3 ligand (FLT3-L) is a growth factor that can expand regulatory T cells (Tregs) and plasmacytoid dendritic cells (pDC). We hypothesised that FLT3-L-induced Tregs would protect mice from experimental glomerulonephritis (GN).

Methods: Naïve C57BL/6 mice were injected with FLT3-L 10mg or PBS intraperitoneally daily for 10 days. To determine whether FLT3-L altered immune responses to foreign antigen, FLT3-L/PBS was injected for 10 days then mice were primed with sheep globulin (SG) and culled 4 days later. To induce GN, mice were primed with SG, given intravenous sheep anti-mouse glomerular basement membrane (GBM) globulin at day 4 (planting SG in glomeruli), and culled at day 14.

Results: Compared to PBS, FLT3-L-treated mice had increased splenic Treg proportions (CD4+Foxp3+/CD4+: FLT3-L 21.4±1.9 vs PBS 11.1±0.8%, P<0.05). Four days after immunization, FLT3-L-treated mice had higher proportions of lymph node DC (PDCA-1+/CD11c+: 10.0±1.6 vs 5.0±0.9%; P<0.05) and enhanced SG-specific uric acid-induced delayed type hypersensitivity (0.31±0.08 vs 0.09±0.02mm; P<0.05), without an increase in Tregs, suggesting that ceasing FLT3-L therapy enhanced cellular immunity. Mice were given FLT3-L 10d p.i. PBS 10 d p.i. and used as a control. WT-BSA mice showed glomerular C3 deposits associated with podocyte loss (32%) and PEC activation (16% glomeruli), which were prevented by factor B deficiency (Fig.), indirectly showing that AP of C was involved in both phenomena. Additional evidence of AP involvement was provided by C6a-BSA mice that instead had more proteinuria, greater C3 deposits (score, 4.0 vs 2.0; P<0.01), more podocyte loss (39%), more severe PEC alterations (66% glomeruli) and higher % of glomeruli with GS (20.3% vs 9.3%, P<0.05) than WT-BSA mice.

Conclusions: Inhibiting AP of C attenuates glomerular injury in proteinuric mice, while its uncontrolled activation leads to more PEC-related glomerular sclerotic lesions.

Funding: Fundig Support - Non-US.

TH-P0915

PKC-Theta Modulates Activation of Murine Primary Macrophages via Regulation of Proinflammatory Cytokine Expression
Anna Bertram, Torsten Kirsch, Hermann G. Haller, Nelli Shushakova. Dept of Nephrology, Hannover Medical School, Hannover, Germany.

Background: Systemic inflammation is a hallmark of sepsis, which is afflicted with a high mortality. A better understanding of underlying mechanisms might lead to new therapeutic targets in inflammatory diseases. Macrophage activation and subsequent release of proinflammatory mediators are critical steps in inflammation. We investigated the role of PKC-theta in the activation of murine primary macrophages.

Methods: Peritoneal macrophages were obtained by peritoneal lavage of SV129 wild type and PKC-theta gene-deficient mice and stimulated with LPS. Expression of PKC-theta and cytokines was quantified using RT-PCR, and release of cytokines was measured with ELISA. Confocal microscopy was used to visualize nuclear translocation of NFkB. Peritoneal macrophages were obtained by intraperitoneal injection of 3% thioglycollate in wild type and PKC-theta gene-deficient mice.

Results: PKC-theta is expressed in peritoneal macrophages of SV129 wild type mice. Stimulation of isolated PKC-theta gene-deficient peritoneal macrophages with 100ng of LPS lead to a significantly increased secretion of TNF-alfa and MIP-2 after 2, 3 or 4 h in comparison to wild type peritoneal macrophages (44% for TNF-alfa, 34.2% for MIP-2 after 2 h). Consistently, mRNA levels of TNF-alfa and MIP-2, which show a peak 1 h after LPS stimulation, were markedly decreased in PKC-theta gene-deficient macrophages (55.2% for TNF-alfa, 49.8% for MIP-2). However, nuclear translocation of NFkB was not defective, but rather accelerated in PKC-theta gene-deficient macrophages, suggesting a downstream target of PKC-theta. These in vitro findings correlated with decreased neutrophil accumulation in a model of experimental peritonitis in PKC-theta gene-deficient vs. wild type mice (41.4%).

Conclusions: We conclude that PKC-theta modulates the activation of murine primary macrophages by regulating the expression of proinflammatory cytokines. Further experiments are required to pinpoint the molecular site of action of PKC-theta. Inhibition of PKC-theta may be a novel therapeutic target to modulate the inflammatory response in sepsis and other inflammatory disorders.

TH-P0916

Effection of CagA Protein on the Production and Underglycosylation of IgA1 in DAKIKI Cells
Joanna R. Ghali1,2, Fugang Li2, Li Liu3, Man Yang2, Zi Li1, Wei Qin1.1 Dept of Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China; 2Div of Nephrology, Dept of Internal Chinese Medicine, Luzhou Medical College, Luzhou, Sichuan, China.

Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis in the world. The infection rate of Helicobacter pylori (Hp) is very high in China and the Asia Pacific region.Hp infection is associated with IgAN, but the underlying molecular mechanism remains unclear. This study was to investigate the effects of cytotoxic associated gene A protein (CagA), a major virulence factor of Hp, on the production and underglycosylation of IgA1 in DAKIKI, a B cell line.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR-Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
TH-PO917
Transfer and Substrate Specificity of Neutrophil Serine Proteases towards Endothelial Cells
Uwe Jerke,1 Daniel Perez Hernandez,2 Brice Korkmaz,2 Gunnar Dittmar,2 Ralph Kettritz,1,4 Experimental and Clinical Research Center, a Joint Cooperation between the Charité and the Max-Delbrück Center for Molecular Medicine (MDC); MDC, 1 SINSERM U-1100/E4-6305 Univ Francois Rabelais; 2 Nephrology and Intensive Care Medicine, Campus Virchow.

Background: Active neutrophil serine proteases (NSPs) are released from neutrophils during inflammation and participate in vascular diseases, including ANCA vasculitis. Here, the proteolytic activity of NSPs was characterized using TAILS, active NSPs, and endothelial cell lines. Employing TAILS, active NSPs, and endothelial cell lines we identified native substrates: 93 for PR3, 48 for HNE and 65 for CG. We hypothesized that enzymatically active NSPs are acquired by endothelial cells (EC) and exert common, but also distinct cleavage patterns towards EC substrates.

Methods: We used western blotting, flow cytometry, confocal microscopy and Boc-Ala-Pro-Val substrate assay to monitor NSP transfer from neutrophils to EC and terminal-amino-isotopic labeling of substrates (TAILS) for substrate characterization.

Results: Activated neutrophils released enzymatically active NSPs into the supernatant and this activity was transferred to EC. EC acquired Alexa488-labeled purified NSPs in a time- and concentration-dependent manner by flow cytometry and confocal microscopy. Importantly, PR3 showed diffuse cytoplasmatic staining whereas HNE and CG localized to granular compartments. Approximately 3,000 potential substrates for NSPs were suggested using peptide model libraries. Employing TAILS, active NSPs, and endothelial cell lines we identified native substrates: 93 for PR3, 48 for HNE and 65 for CG. Clustering the substrate sequences showed characteristic extended recognition patterns. PR3 cleaved after valine and isoleucine with an unpolar amino acid (aa) cluster upstream and an acidic aa cluster downstream of the cleavage site. HNE cleaved after isoleucine or valine with acidic aa upstream and hydrophobic aa downstream, and CG showed a leucine or phenylalanine residue at the cleavage site with downstream aliphatic amino acids.

Conclusions: Thus, our data indicate distinct specificities and cellular localization of the three NSPs suggesting distinct biological effects towards EC. The findings could be of therapeutic relevance in inflammatory vascular diseases.

Funding: Government Support - Non-U.S.

TH-PO918
Different Functions of Soluble and Membrane-Bound TNF in Nephrotic Serum Nephritis

Background: TNF is a proinflammatory cytokine mediating inflammatory diseases such as immune complex glomerulonephritis. The two receptors TNFR1 and TNFR2 play distinct roles in this process, with TNFR2 strongly required for induction of disease. TNFR2 is predominantly activated by membrane-bound TNF (memTNF), but not by soluble TNF (sTNF). Thus, we examined the functional role specifically of memTNF in heterologous nephrotic serum nephritis (NTN).

Methods: NTN was induced by i.v. injection of anti-GBM sheep serum into C57BL/6 wild-type and memTNF-knock-in mice with two unique A1-K11-K11 TNF alleles, which express memTNF, but no sTNF (memTNF mice). At day 5 functional renal parameters, renal histology, leukocyte infiltrates and cytokine production were analysed in the two groups. In addition, we performed stimulation experiments in vitro with glomeruli isolated from wild-type and memTNF mice.

Results: NTN induced in memTNF mice was exacerbated compared to wild-type, indicated by increased albuminuria, higher serum levels of urea and more severe glomerulosclerosis and tubular cell injury. Surprisingly, this was accompanied by significantly lower renal leukocyte infiltrates in memTNF mice and correlated with reduced renal mRNA expression of inflammatory chemokines and cytokines. Decreased cytokine production was also present in isolated mTNF glomeruli stimulated with LPS or IL-1β, demonstrating that absent sTNF in the presence of intact mTNF decreases production of proinflammatory mediators in intrinsic glomerular cells.

Funding: Government Support - Non-U.S.

TH-PO919
Kinin B1 Receptor Deficiency Abrogates Induction of Anti-Myeloperoxidase Induced Crescentic Glomerulonephritis in Mice
Peiqi Hu, Hong Xiao, Masao Kakoki, Ronald J. Falk, J. Charles Jennette. Pathology and Laboratory Medicine, Univ of North Carolina, Chapel Hill, NC.

Background: Anti-myeloperoxidase (anti-MPO) IgG causes crescentic glomerulonephritis (CGN) in mice that is a model for human CGN caused by ANCA (anti-neutrophil cytoplasmatic autoantibodies). Neutrophils play a critical role in CGN induction in this model. The B1 and B2 receptors, two G-protein-coupled kinin receptors, are expressed on neutrophils and involved in modulation of all functions including neutrophil migration, activation and apoptosis. In this study, we investigated the role of these kinin receptors in anti-MPO induced CGN.

Methods: Anti-MPO IgG was purified from the sera of MPO−/− mice that had been immunized with murine MPO. Mice with knock out B1 receptor (B1 KO) and knock out of both B1 and B2 receptors (B1/B2 KO), and normal wild-type C57BL/6j mice (WT B6) were injected i.v. with 50ug/g body weight anti-MPO IgG. Circulating anti-MPO IgG was measured by ELISA. Proteinuria, hematuria and leukocyturia were monitored, and mice were sacrificed at day 6 and kidney tissue obtained for proteinic examination.

Results: At day 6, all 3 groups of mice that received anti-MPO IgG showed similar levels of circulating anti-MPO. All WT B6 mice developed hematuria and CGN (mean 12% glomeruli with crescents). In contrast, B1 KO mice and B1/B2 KO mice had normal urine and less CGN with mean 1% crescents in B1 KO mice (p<0.01 compared to WT) and 2% crescents in B1/B2 KO mice (p<0.01 compared to WT).

Conclusions: Absence of the B1 receptor ameliorates anti-MPO induced CGN. Slightly more severe CGN induction in B1/B2 KO mice than B1 KO mice suggests that B2 receptor modulate the B1 effect, but additional studies are needed to clarify this. Kinin B1 receptors may play an important role in the pathogenesis of CGN induced by anti-MPO antibodies, probably by recruitment and activation of neutrophils. Antagonists of kinin B1 receptors may have a therapeutic role in ANCA disease.

Funding: NIDDK Support

TH-PO920
19F-MRI for Noninvasive Visualization of Renal Inflammation in a Murine ANCA-Induced Glomerulonephritis Model
Aditi Acharya,1,2 Ralph Kettritz,1 Min-Chi Ku,3 Helmar Waiczies,2 Sonia Waiczies,2 Thoralf Niendorf,2 Andreas Pohlmann,3 Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine, Berlin, Germany; 2 Clinic for Nephrology and ICU, Medical Faculty of the Charité, Berlin, Germany; 3 Berlin Urological Field Facility (BUFF), Max Delbrück Center for Molecular Medicine, Berlin, Germany.

Background: ANCA-activated neutrophils and monocyte cause necrotizing crescentic glomerulonephritis (NCGN). Renal inflammation is assessed in patients biopsies or in murine kidneys after animals were sacrificed. Non-invasive methods with potential for serial studies are needed. We tested the hypothesis that 19F-MRI visualizes renal inflammation in a murine ANCA-induced NCGN model.

Methods: 19F MRI:
First study we used a naive cohort of mice to assess technical feasibility. Mice were injected with 100 μL 19F-DiL-lysine (50mM, 153nm). Phagocytosis of 19F-DiL-lysine was monitored by ELISA. Proteinuria, hematuria and leukocyturia were monitored, and mice were sacrificed at day 6 and kidney tissue obtained for proteinic examination.

Results: We used T1-mapping to analyze 19F-nanoparticle uptake by human myeloid cells. Phagocytosis of 19F-DiL-lysine was analyzed up to 48 h. Approximately 3,000 potential substrates for NSPs were suggested using peptide model libraries. Employing TAILS, active NSPs, and endothelial cell lines we identified native substrates: 93 for PR3, 48 for HNE and 65 for CG. Clustering the substrate sequences showed characteristic extended recognition patterns. PR3 cleaved after valine and isoleucine with an unpolar aa cluster upstream and an acidic aa cluster downstream of the cleavage site. HNE cleaved after isoleucine or valine with acidic aa upstream and hydrophobic aa downstream, and CG showed a leucine or phenylalanine residue at the cleavage site with downstream aliphatic amino acids.

Conclusions: Thus, our data indicate distinct specificities and cellular localization of the three NSPs suggesting distinct biological effects towards EC. The findings could be of therapeutic relevance in inflammatory vascular diseases.

Funding: Government Support - Non-U.S.
TH-PO921
Tissue-Type Plasminogen Activator Promotes Macrophage Mobility through a Novel Signaling Cascade
Ling Lin, Kebin Hu. Dept of Medicine, Penn State Univ College of Medicine, Hershey, PA.

Background: Macrophage accumulation in the renal interstitium is one of the hallmarks of progressive kidney disease. Our recent work discovered that tissue-type plasminogen activator (tPA) promotes macrophage infiltration and renal inflammation in a model of chronic kidney injury. However, the underlying mechanism remains largely unknown.

Methods: We investigated the role of tPA in macrophage mobility and elucidated the underlying signaling mechanism using both in vitro and in vivo approaches.

Results: It was found that tPA promotes macrophage migration through its protease-independent function. tPA activated focal adhesion kinase (FAK) and Rac-1 signaling in macrophages in a temporal order. Both FAK and Rac-1 were indispensable to tPA-induced macrophage migration as either infection of macrophages with FAK dominant-negative inhibitor adenovirus or pretreatment of macrophages with Rac-1-specific inhibitor abolished the effect of tPA. We also investigated the role of tPA in macrophage mobility in vivo. Macrophages derived from bone marrow were labeled by fluorescence and adoptively transferred into tPA knockout and wild-type mice, followed by unilateral ureteral obstruction for 7 days. It was found that the number of infiltrated fluorescence-labeled macrophages in the obstructed kidneys from tPA deficient mice was significantly less than that from the wild-type mice. In addition, tPA knockout mice displayed reduced Rac-1 activity in comparison with their wild-type counterparts.

Conclusions: Therefore, it is clear that tPA promotes macrophage migration through a novel signaling cascade involving FAK and Rac-1 pathway.

Funding: Private Foundation Support

TH-PO922
Uric Acid-Induced NLRP3 Inflammasome Contribute to Diabetic Kidney Injury
Yu-Mi Kim, Kyung Hwan Jeong, Sang Ho Lee, Chun-Gyoo Ihm, Ju Young Kim. Div of Nephrology, Dept of Internal Medicine, Kyung Hee Univ College of Medicine, Seoul, Korea.

Background: Despite the fact that hyperuricemia is frequently found in a diabetic nephropathy, the definite cause and effect between hyperuricemia and kidney injury have not well investigated yet. Recently, reports showed IL-1β-secreted NLRP3 inflammasome in cytoplasm plays a role as a sensor of the innate immune injury in metabolic disease. Therefore, we investigated the cause and effects of hyperuricemia and kidney injury in diabetic nephropathy to demonstrate the role of NLRP3 inflammasome in uric acid-induced kidney injury in diabetes.

Methods: We designed four animal groups as following: 1) LETO (Long Evans Tokushima Osaka); 2) OLETF (Osaka Long Evans Tokushima Fatty); 3) OLETF + HFD (high fructose diet) for 16 weeks; 4) OLETF + HFD + allopurinol (10mg/dL in drinking water). HK-2 (Human renal proximal tubule cells) and THP1 (Human acute monocytic leukemia) cells were treated with uric acid.

Results: OLETF + HFD group showed a higher serum uric acid (1.4 ± 0.1 vs 2.2 ± 0.4 mg/dL) and urinary albumin creatinine ratio (350 ± 72 vs 594 ± 102 μg/mg) than OLETF group. In the OLETF + HFD group, the increase trend of NLRP3 and IL-1β expression in kidney was observed. Immunohistochemical staining of CD68 cells showed significant increase in HDF group compared to OLETF group. Allopurinol attenuated hyperuricemia and NLRP3 activation-related renal inflammation. Uric acid-induced NLRP3 activation and IL-1β secretion in THP1 cells were also observed. During the THP1 and HK-2 co-culture it is confirmed that IL-1β-secreted in THP1, plays a pivotal role in activating IL-1β/R1, NLRP3 and ASC signaling in HK-2 cells. This up-regulated IL-1β/R1 signaling was reduced in NF-κB activation in HK-2 cells.

Conclusions: According to these results we can conclude that hyperuricemia activates NLRP3 inflammasome of macrophage and contribute in renal injury by secretion of IL-1β.

TH-PO923
Phenotype Transition of Endothelial Cells with an Activation of NLRP3 Inflammasome by Globotriaosylceramide (Gb3) in Fabry Mice Kidney
Ye-Jin Choi, Hyun-Soo Shin, Kyu Bok Choi, Duk-Hee Kang. Inflammasome Research Center, Department of Laboratory Medicine, College of Medicine, Yonsei University, Seoul, Republic of Korea.

Background: The lysosomal storage disorder Fabry disease is characterized by Gb3 accumulation in kidney. Defective lysosomal alpha-galactosidase A is responsible for Gb3 accumulation, and vascular endothelium is one of the sensitive cells to the effects of Gb3 accumulation. Recently, NLRP3 inflammasome activated by cellular signals is known to play a role in endothelial dysfunction and renal fibrosis. We aimed to investigate whether Gb3 induced phenotype transition of endothelial cells and activated NLRP3 inflammasome in endothelial cells and Fabry mice.

Methods: Endo-MT was evaluated by the changes in morphology and a comparison of the expression of the endothelial markers, VE-cadherin or CD31 and the mesenchymal marker, α-SMA by real time PCR, WB and ICC in HUVEC exposed to Gb3. Activation of inflammasome was evaluated by real time PCR of NLRP3 and ASC. Effects of recombinant Gla (rGla), anti-oxidant and NO donor on Gb3-induced Endo-MT were investigated. Endo-MT in the kidney of Fabry mouse was examined by double IHC of CD31 and α-SMA.

Results: HUVEC with Gb3 (0-40 μM) dose-regulated the expression of CD31 and VE-cadherin. Gb3 induced NLRP3 activation in an dose-dependent manner. Gb3 induced a differential phosphorylation of Ser1177eNOS and Thr495eNOS in HUVEC with a decrease in NO production. Gb3 also activated NLRP3 and ASC expressions. rGla or N-acetyl cysteine ameliorated Gb3-induced endo-MT and NLRP3 inflammasome. Although NO donor inhibited Gb3-induced endo-MT, the expression of NLRP3 and ASC was not altered by NO donor. In Fabry mouse, Gb3 accumulation was observed in glomerular podocyte, tubular cell and peri-tubular capillaries (PTC) with vascular generation in renal tubules. Immunostaining with CD31 and α-SMA revealed capillary rarefaction both in glomerular and PTC with de-novo expression of α-SMA in PTC, suggesting endo-MT in the kidney of Fabry mouse.

Conclusions: These findings suggested that Gb3 induced a phenotypic transition of endothelial cells and the activation of NLRP1 inflammasome, which could be the mechanisms of Gb3-induced endothelial dysfunction and nephropathy in Fabry disease.

TH-PO924
Lactoferrin Is a Suppressor of Neutrophil Extracellular Traps in Inflammation
Kosho Okada, 1 Masao Nangaku, 1 Yoshio Fujita, 1 Junichi Hirahashi. 1 1Graduate School of Medicine, The Univ of Tokyo, Bunkyo, Tokyo, Japan; 2 Div of Clinical Epigenetics Research Center for Advanced Science and Technology, The Univ of Tokyo, Meguro, Tokyo, Japan.

Background: Neutrophils are endowed with microbialidal functions including phagocytosis, degranulation and neutrophil extracellular traps (NETs), recently identified web-like structures composed of chromatin fibers and serine proteases that protect against invading pathogens. On the other hand, NETs are associated with the development of autoimmune and/or inflammatory diseases and thrombosis. We found that lactoferrin(Lf), one of the components of NETs, is a suppressor of NET formation.

Methods: We isolated neutrophils from healthy donors for assay of NET formation. To silence the expression of Lf, we treated Human Leukemia-60 cells with Lf small interference RNA. We observed NET formation under a confocal microscopy with time lapse analysis. We utilized two fluorescence probes, HFP and HYSOx, to hydrorxy radical and hypochlorous acid, respectively, to examine the effects of Lf on reactive oxygen species (ROS) generation during NETs. Spontaneous and low dose LPS-induced reactive oxygen species (ROS), localized Shwartzman reaction (LSR), and the model of immune complex (IC)-induced NET formation in the crenemus muscle were used.

Results: Lf translocated from the cytoplasm to the inner plasma membrane of neutrophils and suppressed NET formation without effects on ROS upon stimulation. Furthermore exogenous Lf shrunk the chromatin fibers in the released NETs and bound to NETs through charge-charge interaction. In SCG/kj mice plasma DNA release and ANCA titer were decreased and the survival rate improved in Lf-treated mice. Subcutaneous injection of Lf in the kidney of OLETF mice also suppressed NET formation. Further, we found that Lf suppressed the IC-induced NET formation. These observations suggest that Lf serves as an innate inhibitor of NETs and prevents DNA release into the circulation.

Conclusions: We found that Lf suppresses NET formation and DNA release into the circulation. Our data indicated that Lf may represent a therapeutic lead for controlling NET release in autoimmune and/or inflammatory diseases.

TH-PO925
Potential Immunological Role of Renal Intercelated Cells via the P2Y14 Receptor
Anie Azroyan, Virna F. Cortez-Retamozo, Ye Chun Ruan, Mikael Pittet, Dennis Brown, Sylvie Breton. Program in Membrane Biology, Center for Systems Biology, Nephrology Div, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Background: Endothelial cell injury leads to inflammation in the kidney. UDP-glucose is a damage-associated molecular pattern (DAMP) molecule that is released from injured cells. We hypothesized that DAMP release into the circulation may initiate the release of pro-inflammatory chemokines (PIC).

Methods: Immunofluorescence (FI) labeling was used to examine the expression of P2Y14 in mouse kidney sections. Downstream effectors of P2Y14 were analyzed by RT-qPCR and in the MDCK-C11 cell line and intercelated cells (ICs) isolated by FACS from B1-EGFPE mice. Infiltration of immune cells in the kidney was assessed by flow cytometry.

Results: We found high expression of P2Y14 specifically in intercelated cells (ICs), identifying their positive labeling for the V-ATPase B1 subunit. RT-qPCR showed P2Y14 mRNA expression in FACS-isolated EGFP-positive ICs, but not in EGFP-negative cells. In vitro stimulation with UDP-glucose increased ERK phosphorylation (p-ERK) and up-regulated PIC mRNA transcripts in isolated EGFP-positive ICs (CXCL1, CXCL2, CCL2 and CCL3) and in MDCK-C11 cells (IL8, CCL2). Inhibition of p-ERK with a MEK1 inhibitor prevented the UDP-glucose-dependent PIC mRNA increase in MDCK-C11 cells. Tail vein injection of mice with UDP-glucose increased ERK phosphorylation and PIC mRNAs in ICs isolated by FACS after 4 hours, and induced an increased infiltration of neutrophils into the renal medullary region containing collecting ducts after 48 hours.

Conclusions: In summary, our data provide evidence for the participation of ICs as DAMP sensors via P2Y14, and indicate the role of ICs as novel mediators of inflammation in the kidney.

Funding: NIDDK Support
Extradiol Reduces Ischemic Renal Atrophy in the 2K1C Model in Female ApoE KO Mice
Carolyn M. Ecelbarger, Chelsea Holloway, Nikhil Sharma, Hong Ji, Kathryn Sandberg, Lijun Li.
Department of Medicine, Georgetown University, Washington.

Background: The incidence of atherosclerosis increases in post-menopausal women likely as a result of the fall in circulating estradiol (E2) levels, although the mechanisms remain obscure. The two-kidney, one clip model (2K1C) of renal ischemia has been demonstrated to lead to marked systemic inflammation in the ApoE knockout (KO) mouse, a mouse model of atherosclerosis. We aimed to elucidate the protective effects of E2 on kidneys in the 2K1C Apo E KO mouse.

Methods: Left renal artery incomplete ligation (LRLA) was performed on 12-week-old C57BL/6j:KO mice. In the same surgery, mice were ovariectomized (OVX) and physiologically replaced with 17 estradiol (E2, 2g/day, slow-release placebo) or placebo pellet (P, n = 6/group). Urine volume (24-hour) was collected in mice metabolic cages. Kidneys, blood, liver, and vasculature were obtained at euthanasia after 60 days. Histology was done on fixed tissue sections and blinded sections scored for analysis.

Results: E2 replacement did not lead to differences in final body weight (BW, g): 24.5 ± 0.5 (OVX + P) versus 23.7 ± 0.5 (OVX + E2), p = 0.22. However, left kidney (LK) atrophy was markedly attenuated by E2 (LKW, g): 0.058 ± 0.016 (OVX + P) versus 0.125 ± 0.017 (OVX + E2), p = 0.018. In contrast, the contralateral right kidney was similarly sized in both groups (RKW, g): 0.185 ± 0.008 (OVX + P) versus 0.185 ± 0.018 (OVX + E2), p = 0.97. Urine volume (24-hour) was also significantly higher (−30%) in the E2-treated mice, p = 0.007. Semi-fasting (4-hour fast) glucose levels were: 150 ± 6 and 121 ± 13 in the OVX + P and OVX + E2 groups, respectively, not significantly different, p = 0.07. In addition, E2 reduced qualitative indices of renal damage including glomerular injury, tubular atrophy, interstitial fibrosis, and inflammation, with lymphocyte and macrophage infiltration in the LK, as compared to placebo-treated mice.

Conclusions: E2 replacement to OVX female ApoE KO in 2K1C mice significantly attenuated atrophy and renal injury due to ischemia. We suggest these differences might result from alterations in inflammatory cascades and/or differential blood pressure control.

Funding: Private Foundation Support

Extracellular Histones Drive the Progression of Inflammation and Crescent Formation in Necrotizing Glomerulonephritis
Santhosh Kumar VR, Onkar Kulkarni, Shrikant R. Mulay, Dana Thomasova, Murthy Narayana Darisipudi, Hans J. Anders.
Klinische Biochemie, Universität München, Munich, Bavaria, Germany.

Background: Crescentic glomerulonephritis is characterized by extensive glomerular necrosis. Dying cells release intracellular proteins that act as DAMPs to activate innate immunity. Early we demonstrated that dying tubular cells release histones which drive tubulointerstitial inflammation in septic or post-ischemic AKI by activating TLR2/4. Here we speculate that extracellular histones also elicit similar pathogenic effects in necrotizing glomerulonephritis.

Methods: Necrotic glomerulonephritis was induced in mice by single i.v. injection of 100g of anti-GMB serum. Effect of histone neutralisation was evaluated on day 7.

Results: Anti-GMB treated mice showed increased proteinuria, plasma creatinine and BUN levels. This was associated with reduced number of podocytes, increased crescentic glomerulitis and infiltration of neutrophils/macrophages in kidney. Neutralization of extracellular histones significantly reduced proteinuria with significant less damage to podocytes. This was associated with improved renal function defined by lower plasma creatinine and BUN levels. Also improved renal inflammation marked with less infiltration and activated neutrophils/macrophages in kidney. Histone blockade also significantly reduced renal mRNA expression of TNFα and reduced fibrogenesis in glomerular capillaries, which was associated with less glomerulosclerosis, crescents and tubular atrophy. In contrast, the autologous variant of the Anti-GMB model that lack necrotizing glomerular lesions did not benefit from anti-histone antibody treatment. In-vitro studies demonstrated that, stimulation of BMDMCs with histones significantly increased the TNFα and IL6 levels. Histones show dose dependent cytotoxic effect on GEnC and increased podocyte detachment. Neutralization of histones reverses these cytotoxic effects.

Conclusions: We conclude that the release of histones from dying glomerular cells contribute to renal immunopathology and dysfunction during crescentic glomerulonephritis. This may either relate to their direct toxic effects on endothelial and epithelial cells or potential to activate innate immunity via TLR2/4.

Extracellular Dopamine Induces Delayed Preconditioning Is Mediated by Hsp90 and Involves LPS-induced Heat Shock Protein Induction and Endotoxin Tolerance
Imperial College London.

Background: The WKY rat strain is susceptible to experimental glomerulonephrites, including nephrotoxic nephritis (NTN) and experimental autoimmune glomerulonephritis (EAG), whereas the LEW strain is resistant. In previous studies by our group, genome-wide screening identified a QTL on Chr13 (crgn1) linked to disease severity in both models. A QTL on Chr13 (crgn2) was additionally linked to disease severity in NTN. We have previously shown that introduction of LEW.crgn1 onto a WKY background conferred partial protection from disease in EAG. We sought to (1) examine the additional effect of introducing LEW.crgn2 onto a LEW background in this model, and (2) establish if susceptibility to EAG could be conferred to LEW rats by co-introgession of WKY.crgn1 and WKY.crgn2 to a LEW background.

Methods: Reciprocal double-congenic (DC) rats were generated - LEW.WKY.crgn2 (WKY.WKY.crgn2), and WKY.DC (WKY.WKycrgn1) - and immunized with recombinant rat ovalbumin (rOVA) for 310 days.

Results: Summarised in the table, below at 28 days after disease induction. Expressed as mean/group. Statistical analysis was by one-way ANOVA with Newman Keuls Comparison test.

Conclusions: Additional introgression of LEW.crgn2 onto a WKY background confers greater protection from EAG than seen with LEW.WKY.crgn1 alone (Reynolds et al, Am J Pathol 2012) and confirms our previous observations in NTN, and highlights the importance of macrophage activation regulated by crgn2 in these models, and as a potential therapeutic target. Despite making similar levels of anti-GM antibodies at WKY rats, LEW.DC did not develop disease, suggesting that additional genetic factors contribute to disease susceptibility in the parental WKY rat in this model.

Potential Role of Lysosphatidic Acid in HIV-Induced Tubular Cell Microcyst Formation
Medicine, Hofstra North Shore LIJ Medical School, New York, NY.

Background: HIV-associated nephropathy is characterized by microcyst formation and collapsing glomerulopathy. Lysosphosphatidic acid (LPA) and its receptors (LPA1-4) have been implicated in the tubular cell fibrosis (TIF) and cyst formation in autosomal dominant polycystic kidney disease (ADPKD). We hypothesized that LPA might be contributing to tubulointerstitial lesions in HIV infection.

Methods: Primary human proximal tubular cells (HRPTCs) were transduced with either empty vector or HIV (NL4-3). C/HRPTCs, EV/HRPTCs, and HIV/HRPTCs were incubated in media containing either buffer, KI 16425 (LPA inhibitor), AAOCCF3 (LPA synthesis blocker) or D.AG kinase inhibitor for 24 hours (n=3). Subsequently, protein blots were probed for TGF-β, α-SMA, fibronectin, collagen I, III, IV, and α-smooth muscle actin. The same blots were re-probed for actin. Intact cAMP Incubation of cells (ILK-1), focal adhesion kinase (FAK), and G-protein coupled receptor (GPCR) serve as molecules involved in intermediate signaling. We have previously evaluated expression of these molecules on tubular cell injury in HIV/LHA milieu.

Results: Both LPA and HIV milieu altered tubular cell expression of cTGF, α-SMA, collagen I, III, IV and fibronectin. HIV/HRPTCs also displayed enhanced expression of p-ILK-1, p-FAK, pT3k, p-Akt, and p-JNK MAPK. Moreover, HIV enhanced transcriptional binding activity of NF-κB in HIV/HRPTCs, however, LPA inhibitors attenuated these effects of HIV.

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

Pathobiology: Basic/Experimental Inflammation
Poster/Thursday

Funding: Government Support - Non-U.S.

TH-PO926

TH-PO927

TH-PO929

Potential Role of Lysosphatidic Acid in HIV-Induced Tubular Cell Microcyst Formation
Medicine, Hofstra North Shore LIJ Medical School, New York, NY.

Background: HIV-associated nephropathy is characterized by microcyst formation and collapsing glomerulopathy. Lysosphosphatidic acid (LPA) and its receptors (LPA1-4) have been implicated in the tubular cell fibrosis (TIF) and cyst formation in autosomal dominant polycystic kidney disease (ADPKD). We hypothesized that LPA might be contributing to tubulointerstitial lesions in HIV infection.

Methods: Primary human proximal tubular cells (HRPTCs) were transduced with either empty vector or HIV (NL4-3). C/HRPTCs, EV/HRPTCs, and HIV/HRPTCs were incubated in media containing either buffer, KI 16425 (LPA inhibitor), AAOCCF3 (LPA synthesis blocker) or D.AG kinase inhibitor for 24 hours (n=3). Subsequently, protein blots were probed for TGF-β, α-SMA, fibronectin, collagen I, III, IV, and α-smooth muscle actin. The same blots were re-probed for actin. Intact cAMP Incubation of cells (ILK-1), focal adhesion kinase (FAK), and G-protein coupled receptor (GPCR) serve as molecules involved in intermediate signaling. We have previously evaluated expression of these molecules on tubular cell injury in HIV/LHA milieu.

Results: Both LPA and HIV milieu altered tubular cell expression of cTGF, α-SMA, collagen I, III, IV and fibronectin. HIV/HRPTCs also displayed enhanced expression of p-ILK-1, p-FAK, pT3k, p-Akt, and p-JNK MAPK. Moreover, HIV enhanced transcriptional binding activity of NF-κB in HIV/HRPTCs, however, LPA inhibitors attenuated these effects of HIV.

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

TH-PO930
Conclusions: Lyosphosphatidic acid may be contributing to HI-induced tubular cell injury. 
Funding: NIDDK Support

TH-P0931
Protective Effect of Valproic Acid on Adriamycin-Induced Nephropathy by Regulation of Histone Acetylation
Qin Dai, Jian Liu, Fang Zhong, Lili Xu, Weiming Wang, Nan Chen. Dept of Nephrology, Ruijin Hospital, Shanghai Jiao Tong Univ, Shanghai, China.

Background: Nephropathy and podocyte injury are involved in glomerulosclerosis. Histone acetylation takes a part in the renal disease. In the study, we explored whether HDAC inhibitor valproic acid (VPA) has a protective role in the Adriamycin-induced nephropathy (ADN) and podocyte injury. 

Methods: VPA were administered for 6 weeks after ADN modelling. Serum creatinine, urine creatinine, urinary protein, the total acetylation level of histone H3/H4 and mRNA of CTGF, PAI-1, COL-1, COL-III in the renal tissue were measured. Histone acetylation levels were detected by ELISA. HDAC2 and EP300 mRNA expression were detected by real-time-PCR methods. Renal inflammation were assessed by evaluating MCP-1, STAT3, suppressor of cytokine signaling-1 (SOCS-1) and SOCS-3 changes in the renal cortex by real-time-PCR. ChIP-qPCR was used to detect H3 and H4 acetylation levels in the promoter of MCP-1 and STAT3. 

Results: Compared with ADN group, urinary albumin/creatinine was decreased significantly in VPA group (P<0.05); serum creatinine, urinary albumin/creatinine, the total level of histone H3, H4 acetylation, the expression of mRNA of CTGF, PAI-1, COL-1, COL-III were decreased significantly (P<0.05) in renal tissue in VPA group. VPA intervention could reduce glomerulosclerosis, change histone acetylation levels and the expression of HDAC, HAT and inflammatory cytokines. VPA could change the MCP-1 expression by regulating the SOCS-1 and SOCS-3 expression. VPA intervention could reduce podocyte death induced by ADN, increased podocyte proliferation, reduce podocyte motility and improve the structural changes of podocytes.

Conclusions: Histone acetylation modification participates in the process of glomerular sclerosis, and regulation of histone acetylation may be a promising mean of intervention in progression of kidney disease.

TH-P0934
SCAP Is a Dual Regulator for Both Cholesterol Homeostasis and Inflammatory Stress in Macrophages and Renal Proximal Tubule Cells
Lung-Chih Li,1,2 Xiong Z. Ruan. 1Centre for Nephrology, John Moorhead Research Laboratory, Centre for Nephrology, University College London (UCL), London, United Kingdom; 2Nephrology Dept, Chang-Gung Memorial Hospital-Kaohsiung Medical Centre, Kaohsiung, Taiwan.

Background: Both macrophages and renal proximal tubular cells play important roles in the progression of chronic kidney disease (CKD). Sterol regulatory element binding protein (SREBP) cleavage-activating protein (SCAP) is a cholesterol sensor that regulates LDL receptor (LDLR) and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCOR) transcription and maintains the intracellular cholesterol homeostasis. The aim of this study is to investigate if SCAP regulates inflammatory response.

Methods: SCAP in PMA-activated THP-1 and HK2 cells was knocked down using siRNA or over-expressed by gene transfection. Intracellular cholesterol content was assessed by Oil Red O (ORO) staining and quantitative assay. The mRNA and protein expression of SCAP, pro-inflammatory cytokines, LDLR and HMGCOR were examined by real-time quantitative RT-PCR and Western blotting. Nuclear p65, phosphorylated IκB and JNK were investigated.

Results: Over-expression of SCAP increased, while knockdown of SCAP decreased LDLR and HMGCOR expression in both cells. Intracellular cholesterol content was significantly increased after over-expression of SCAP and remarkably reduced after knocking down SCAP. Interestingly, over-expression of SCAP also increased the pro-inflammatory cytokines IL-6 and TNF-α. LPS increased IL-6 and TNF-α expression as expected. However, knocking-down SCAP abolished the up-regulatory effects by LPS on IL-6 and TNF-α, accompanying with reduction of phosphorylation of IκB (rather than JNK phosphorylation) and nuclear p65 levels, indicating that SCAP mediates inflammatory response in THP-1 and HK2 cells via IκB phosphorylation.

Conclusions: SCAP is not only a cholesterol sensor but also a key regulator for inflammatory response in THP-1 and HK2 cells. SCAP may serve as a novel target for both lipid-lowering and anti-inflammatory therapies in renal diseases.

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

TH-P0935
Overexpression of Leukocyte Kvl.13-Channels Promotes Renal Fibrosis in Rats with Advanced Chronic Renal Failure
Itsuru Kazama, Physiology I, Tokohu Univ Graduate School of Medicine, Sendai, Miyagi, Japan.

Background: Leukocytes, such as lymphocytes and macrophages, predominantly express the rectifier K+ channels (Kvl.3), and the channels play crucial roles in the activation and proliferation of the cells. Since lymphocytes are activated in patients with end-stage renal disease (ESRD), the channels expressed in those cells would contribute to the progression of renal fibrosis in advanced stage chronic renal failure (CRF).

Methods: Male Sprague-Dawley rats that underwent 5/6 nephrectomy followed by a 14-week recovery period were used as the model of advanced CRF. Age-matched sham-operated rats were used as controls. Cellular proliferation of leukocytes and the expression
of Kv1.3-channels in the kidneys were examined. Histopathological features of the kidneys and the expression of cell cycle markers were also examined before and after treatment with margatoxin, a selective Kv1.3-channel inhibitor.

**Results:** In the cortical interstitium of advanced CRF rat kidneys, leucocytes proliferated in situ and overexpressed Kv1.3-channel protein in their cytoplasm. Treatment with margatoxin significantly suppressed the number of leucocytes and slowed the progression of renal fibrosis with a significant decrease in the cortical cell marker expression.

**Conclusions:** This study demonstrated for the first time that the number of leucocytes was dramatically increased in rat kidneys with advanced CRF. The overexpression of Kv1.3-channels in the leucocytes was thought to contribute to the progression of renal fibrosis by stimulating cell cycling and promoting cellular proliferation.

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

---

**TH-PO936**

**Modulation of Endothelial Function Attenuates Kidney Fibrosis by Regulation of Soluble Epoxide Hydrase**

Jae-Yoon Park, Jung Pyo Lee, Seung Hee Yang, Chun Soo Lim, Yun Su Kim, Yun Kyu Oh.

**Department of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, Korea; Seoul National Univ Kidney Research Institute, Seoul, Korea; Dept of Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea.**

**Background:** Soluble epoxide hydrase (sEH) in endothelial cells catalyses the degradation of eicosyenoic acids (EETs), which may act as vasodilatory agents to control vascular tone. Kidney fibrosis is the final common pathway for most progressive kidney diseases. Here we show that kidney fibrosis was reduced by regulation of sEH activity.

**Methods:** Unilateral ureteral obstruction (UO) was used as a model of kidney fibrosis in CD-1 mice. sEH activity was controlled by continuous use of the sEH inhibitor 12-(3-adamantan-1-ylreido)-dodecanic acid (AUDA) (8mg/kg/day) for 1 or 2 wks.

**Results:** AUDA treatment restored significantly improved tubulointerstitial fibrosis. Fibroblast marker FSP-1 and TGF expressions were significantly decreased. sEH inhibition increased uptake of the endothelial markers vWF, VE-cadherin, and CD31. On flow cytometric analysis, UUO increased FSP-1 positive cell population and AUDA treatment reduced CD 31 proportion in FSP-1 positive cell. Similarly, sEH inhibition reduced vWF/ FSP-1 double positive cell.

In an endothelial-to-mesenchymal transition (EndMT) in-vitro co-culture system using the Transwell™ system, AUDA treatment significantly decreased the expression of sEH activity. EndMT was arrested and high fat diet fed mice. In an endothelial-to-mesenchymal transition (EndMT) in-vitro co-culture system using the Transwell™ system, AUDA treatment significantly decreased the expression of sEH activity.

**Conclusions:** The results of this study suggest that direct inhibition of EndMT and indirect inhibition of EMT by treatment with sEH inhibitors may be an effective therapy for delaying the progression of renal fibrosis associated with CKD.

**TH-PO937**

**Low Dose Lipopolysaccharide (LPS) Sensitizes Macrophages (MO) and Aggravates Inflammation: An Effect Blocked by Polymyxin (PM) and Curcumin (CU)**

Siddhartha S. Ghosh, Sam Righi, Todd W. Gehr. Nephrology, VCU, Richmond, VA.

**Background:** LPS has been seen in the circulation following high fat diet (HFD) in men and mice. Our studies have shown increased levels of plasma LPS in uremic mice and high fat diet fed mice. Although, the amount of LPS in circulation following HFD or uremia is too low to cause significant inflammation, studies demonstrate that both HFD and uremia are in close relationship with renal inflammation, studies demonstrate that both HFD and uremia are in close relationship with renal inflammation, and overexpress LPS in circulation following HFD or renal illness.

**Methods:** Adult male Munich-Wistar rats (n=42) received no treatment (C), or ADE, 0.5% in chow for 1 week, after which Crs/mrn, serum creatinine (Sx, mg/dL), tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/day), % glomerulosclerosis (%GS), INT macrophages (MO; cells/mm²), and % INT collagen-1 (%COLL) were assessed. Measurements were repeated 4 and 24 wks later.

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>Week 1</th>
<th>Week 4</th>
<th>Week 8</th>
<th>12 wk</th>
<th>24 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MO</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
</tr>
<tr>
<td>ABC</td>
<td>1.1±0.1</td>
<td>0.9±0.1</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
</tr>
<tr>
<td>ALB</td>
<td>50±0.1</td>
<td>50±0.1</td>
<td>50±0.1</td>
<td>50±0.1</td>
<td>50±0.1</td>
</tr>
<tr>
<td>%COLL</td>
<td>51±1%</td>
<td>51±1%</td>
<td>51±1%</td>
<td>51±1%</td>
<td>51±1%</td>
</tr>
<tr>
<td>%GS</td>
<td>10±0%</td>
<td>10±0%</td>
<td>10±0%</td>
<td>10±0%</td>
<td>10±0%</td>
</tr>
</tbody>
</table>

**Mean±SE; ***, p<0.05 vs C; 1wk and 4 wk, respectively. At 1 wk, Group ADE exhibited, despite very few Crs, Sx elevation, hypertension, and INT MO infiltration, without excess COL or GS. Four wk after ADE withdrawal, MO regressed, while TCP and Sx were normalized. However, ALB, TCP, %GS and %COLL had risen 24 wk after ADE withdrawal, while MO remained elevated.

**Conclusions:** Despite regression of acute renal inflammation/function loss shortly after ADE was ceased, INT fibrosis and GS occurred in the long run, indicating that even light ADE excess can cause changes that lead to self-perpetuating CKD.

**FAPES/CPNPq.**

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

---

**TH-PO938**

**Effect of Curcumin (CU) and Polymin (PM) on Renal Failure and Glucose Intolerance in LDLR-/- ¾ Nephrectomy Mice**

Siddhartha S. Ghosh, Shobha Ghosh, Todd W. Gehr. Nephrology, VCU, Richmond, VA.

**Background:** Uremia and high fat diet (HFD) alters gut microbiota and intestinal permeability resulting in the absorption of lipopolysaccharide (LPS). LPS aggravates inflammation which worsens renal function and promotes glucose intolerance. Our previous studies have shown CU ameliorates renal failure. Since CU is poorly absorbed we speculated that it can mediate its effect by altering the gut absorption of LPS. To examine this hypothesis we compared CU to a nonabsorbable antibiotic, PM, a known inhibitor of LPS.

**Methods:** LDLR-/- mice fed either normal chow or HFD underwent ¾ nephrectomy (Nx) (control,n=6; Control+Nx,n=6; HFD+Nx,n=6). All groups received either CU (75 mg/kg,n=5) or PM (15 mg/L in drinking water,n=4).

**Results:** Creatinine (Cr), BUN and urinary albumin excretion (ACR) was significantly elevated in Nx and Nx+HFD (p<0.01). The parameters shown in table were measured. CU and PM significantly reduced BUN and ACR in Nx and Nx+HFD (p<0.05). CU in all the groups was significantly reduced by CU (p<0.05) but not by PM. CU and PM treatment significantly improved GTT, IL6 and TNFα in HFD, Nx and Nx+HFD groups (p<0.05). LPS was reduced by 45% by Cu (p<0.01) and 75% by PM (p<0.001).

**Conclusions:** In LDLR-/- mice CU and PM effectively blocked the inflammatory response to HFD and Nx and improved glucose tolerance test as measured by GTT. Renal function was also improved by both CU and PM, albeit CU was better than PM. Since PM is confined to the gut we contend that CU might have significant local effect on the gut and that its anti-inflammatory effect is partly mediated through alteration in gut permeability or inhibition of LPS absorption.

**Funding:** Private Foundation Support

---

**TH-PO939**

**Chronic Interstitial Nephritis after Brief Mild Adenine Excess Despite Scarce Crystal Deposition**


**Univ of Sao Paulo, Brazil.**

**Background:** We showed recently that, in rats on excess adenine (ADE) for 3 weeks, intratubular crystals (Crys) migrate to the interstitium (INT), causing INT nephritis. Here we studied whether renal damage caused by 1 wk ADE would regress/stabilize upon ADE withdrawal or would instead progress to chronic kidney disease (CKD).

**Methods:** Adult male Munich-Wistar rats (n=42) received no treatment (C), or ADE, 0.5% in chow for 1 week, after which Crys/mrn, serum creatinine (Sx, mg/dL), tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/day), % glomerulosclerosis (%GS), INT macrophages (MO; cells/mm²), and % INT collagen-1 (%COLL) were assessed. Measurements were repeated 4 and 24 wks later.

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>Ctrl</th>
<th>ADE 0.5%</th>
<th>ADE 1%</th>
<th>ADE 2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MO</td>
<td>0.2±0.1</td>
<td>0.6±0.1</td>
<td>1.1±0.1</td>
<td>5.1±1.0</td>
</tr>
<tr>
<td>ABC</td>
<td>5.6±0.1</td>
<td>31±1.0</td>
<td>54±1.0</td>
<td>91±1.0</td>
</tr>
<tr>
<td>ALB</td>
<td>43±1.0</td>
<td>91±1.0</td>
<td>50±1.0</td>
<td>50±1.0</td>
</tr>
<tr>
<td>%COLL</td>
<td>10±0%</td>
<td>10±0%</td>
<td>10±0%</td>
<td>10±0%</td>
</tr>
<tr>
<td>%GS</td>
<td>10±0%</td>
<td>10±0%</td>
<td>10±0%</td>
<td>10±0%</td>
</tr>
</tbody>
</table>

**Mean±SE; ***, p<0.05 from Ctrl; T P<0.05 from HFD; T P<0.05 from Nx.

**Conclusions:** In LDLR-/- mice CU and PM effectively blocked the inflammatory response to HFD and Nx and improved glucose tolerance test as measured by GTT. Renal function was also improved by both CU and PM, albeit CU was better than PM. Since PM is confined to the gut we contend that CU might have significant local effect on the gut and that its anti-inflammatory effect is partly mediated through alteration in gut permeability or inhibition of LPS absorption.

**Funding:** Private Foundation Support

---

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

Underline represents presenting author/disclosure.

3212
TH-P0940

dehydrated (75% relative humidity, 4°C). The bile duct ligated (BDL) mice served as the control group. The mice were divided into three groups: the control group (normal healthy), the DDL group (BDL for 2 weeks), and the DDL + TUDCA group (28 days of DDL treatment). The mice were fed a high-fat diet (HFD) for 12 weeks. The body weights, liver weights, and blood glucose levels were measured. The liver tissues were stained with hematoxylin and eosin (H&E) for histological analysis. Additionally, the expression of key proteins was evaluated using western blotting and immunohistochemistry.

Results: TUDCA treatment significantly reduced liver and fat tissue weights compared to the DDL group. The blood glucose levels were also lower in the DDL + TUDCA group compared to the DDL group. The liver tissues from the DDL + TUDCA group showed less inflammation and fibrosis compared to the DDL group. The expression of fibrosis-related markers such as collagen type I and III was significantly lower in the DDL + TUDCA group than in the DDL group.

Conclusions: TUDCA treatment significantly reversed liver and fat tissue fibrosis in the DDL model, which is a model for non-alcoholic fatty liver disease (NAFLD). These results suggest that TUDCA could be a potential therapeutic agent for the treatment of NAFLD.

Funding: This study was supported by grants from the Ministry of Science and ICT, Korea (NRF-2020R1A2C2005592, NRF-2020R1A2C2006298, and NRF-2021K1A3A80211213).

TH-P0941

Elevated Soluble Galectin-3 and Monocyte Galectin-3 Levels in Experimental Uraemia Are Reversed by Anti Advanced Glycemic End Products (AGE) Therapy


Background: Galectin-3 expressing monocytes and macrophages are implicated in the pathogenesis of chronic inflammatory and fibrotic diseases. Moreover, in human studies elevated soluble plasma Galectin-3 levels are associated with Advanced Glycemic End Product (AGE) and determine poor cardiovascular outcomes.

Methods: A murine model of progressive tubulointerstitial nephritis - The Adenine (AD) diet was used to define Galectin-3 levels in circulating immune cells and tissue resident macrophages (by FACS analysis and Real Time Quantitative PCR) subject to progressive uroarea. Plasma AGE was quantified by ELISA in AD compared to sham diet (SD) at 0 and 2 weeks. Mice were then given the anti-AGE compound Pyridoxamine in drinking water (400mg/kg) or standard drinking water for 2 weeks of 0.25% Adenine diet and Galectin-3 expression was re-evaluated.

Results: Plasma Galectin-3 is significantly raised at 7 days to 28 days in AD fed mice(+33% vs SD) at 2 weeks. Circulating monocytes and granulocytes in AD fed mice(+) demonstrate significantly higher Galectin-3 Median Fluorescence Intensity(MFI) on FACS analysis at 14-28 days vs SD(-3) (p=0.0317 AD vs SD at 28 days). At 28 days resting peritoneal macrophages and cardiac homogenate failed to show increased expression in Galectin-3 MFI and Galectin-3 mRNA levels respectively. Plasma AGE is significantly raised at 2 weeks 0.25% Adenine Diet and significantly reduced by supplementation with 400mg/kg of pyridoxamine in drinking water(-5%) vs standard drinking water(-5%) (p=0.0079).

Pyridoxamine supplementation also significantly reduced adenine diet induced Galectin-3 expression of circulating monocytes at 14 days.

Conclusions: Galectin-3 expression in circulating Galectin-3 monocyte levels are increased with accumulation of AGE's. Targeting elevated Galectin-3 levels by anti-AGE strategies may be important given Galectin-3's pathogenic role in inflammatory cardiovascular disease.

Funding: Clinical Revenue Support

TH-P0942

Oleic Acid Attenuates Renal Interstitial Fibrosis in Unilateral Ureteral Obstructive Nephropathy by Facilitating Nuclear Translocation of Nrf2

Shang Jun Kim, Hyun Soo Yoon, Seok Joon Shin, Cheol Whee Park, Sungjin Chun

Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea.

Background: Renal interstitial fibrosis is a common final pathological process in the progression of renal disease. This is primarily due to oxidative stress, which contributes to renal inflammation and fibrosis. Nuclear factor erythroid-2-related factor 2 (Nrf2) is known to coordinate induction of genes that encode antioxidant enzymes. We investigated the effects of oleic acid, a known Nrf2 activator, on oxidative stress-induced renal inflammation and fibrosis.

Methods: Oleic acid treatment was initiated one week before unilateral ureteral obstruction (UOU) in C57BL6/J mice, and was continued until 3, 7, and 14 days after UOU. Renal inflammation and fibrosis, markers of oxidative stress, and changes in Nrf2 expression were subsequently evaluated.

Results: Oleic acid significantly decreased tubulointerstitial fibrosis score that was increased in the kidneys of UOU mice. Furthermore, oleic acid attenuated UO-induced collagen deposition and macrophage infiltration on day 14. Additionally, significantly less apoptosis with a lower ratio of Bax to Bcl-2 expression, and fewer apoptotic cells on TUNEL staining were observed in the obstructed kidneys of oleic acid-treated mice. Oleic acid did not change the expression of HIF-1α and the levels of tissue hydrogen peroxide. There were no changes in the expression of total Nrf2 and Kelch-like ECH-associated protein 1 (Keap1), indicating that oleic acid enhanced nuclear translocation of Nrf2.

Conclusions: These results suggest that oleic acid may exert beneficial effects in renal fibrosis by increasing nuclear translocation of Nrf2 and subsequently reducing renal oxidative stress.

TH-P0943

Proteinase-Activated Receptor-2 Transactivation of EGFR- and TGFβ-Receptor Signalling Pathways Contributes to Renal Fibrosis

Hyunjae Chung, Morley Hollenberg, Daniel A. Muruve. Medicine, Univ of Calgary, Calgary, Canada.

Background: During renal injury, kidney-localized proteinases can signal by cleaving and activating proteinase-activated receptor-2 (PAR-2), a G-protein-coupled receptor involved in inflammation and fibrosis. It is abundantly expressed in renal tubular cells. We investigated the role of PAR-2 in the pathogenesis of renal fibrosis.

Methods: (i) We evaluated tubular injury and progression of fibrosis in a murine unilateral ureteral obstruction (UOU) model using both wildtype and PAR-2 null mice. Renal tissues were evaluated histopathologically for morphology (H&E), collage deposition (Masson’s Trichrome), collagen assay and biochemically (western blot) for α-smooth muscle actin (αSMA). (ii) We examined the mechanism of PAR-2 signaling that regulates fibrosis and the production of the profibrotic cytokine, connective tissue growth factor (CTGF) was measured using primary human proximal tubular epithelial cells (HPTC). Cells were activated with PAR-2 activating peptides (PAR2-AP) in presence or absence of signaling pathways inhibitors for TGFβRI (SB431542), ERG (AG1478) and MAPK inhibitor (U0126).

Results: Following UOU, PAR-2 null mice displayed reduced renal tubular injury, fibrosis, collagen synthesis and aSMA gene expression at 7 days, compared to wildtype controls. In HPTC in vitro, PAR2 activation with PAR-2-AP alone significantly upregulated the expression of CTGF and did so synergistically to augment TGFβ-induced CTGF. Consistent with these findings, stimulation of HPTC with PAR2-AP induced Smad2/3 phosphorylation in the canonical TGFβ signaling pathway. The Smad2 phosphorylation and the CTGF induction by PAR2 activation were downregulated by the use of inhibitors for TGFβRI and EGFR suggesting that PAR2 utilizes transactivation mechanisms of both receptors to initiate fibrogenic signaling.

Conclusions: Our data demonstrate that (i) PAR2 plays a role in the early stages of renal fibrosis in a murine UOU model and that (ii) PAR2 utilizes transactivation mechanisms of EGFR and TGFβRI to enhance fibrosis. Further studies to determine if PAR2 appears to be a contributor to renal injury and fibrosis in vivo and represents a potential therapeutic target for patients with CKD.

Funding: Government Support - Non-U.S.

TH-P0944

Oral Activated Charcoal Adsorbent, AST-120 Improves Intestinal Environment and Microbiota in CKD Rats

Ayumi Yoshitishi, Shu Wakiino, Junichiro Irie, Kozi Hosoya, Hiroshi Itoh. School of Medicine, Keio Univ, Tokyo, Japan.

Background: Although gut microbiota and colon barrier function were deteriorated in CKD, additional detailed mechanisms and clinical relevance has not been elucidated. Oral activated charcoal adsorbent (AST-120) has been reported to delay the progression of CKD by adsorbing uremic toxin from the intestine. However, the effects of AST on the gut environments in CKD have not been fully elucidated.

Methods: Six-week-old spontaneously hypertensive rats (SHR) were rendered CKD by 5/6th nephrectomy. Rats were divided into four groups (n=10 each); sham-operated SHR (SHR); SHR given AST-120 (SHR+AST); 5/6th nephrectomized SHR (Nx); Nx given AST-120 (Nx+AST). The analysis of the gut microbiota showed the decrease in the number of gut microbes and biofilm formation in Nx. This decrease was also reversed in Nx+AST.

Results: Serum level of indoxylsulfate, serum creatinine levels and urine protein excretion were increased in Nx. Glomerular sclerosis and tissue fibrosis were increased in Nx. These changes were attenuated in Nx+AST. The histological analysis of the colon tissue revealed that the number of goblet cells and the protein expression of mucin-2 were decreased in Nx. These decreases were restored by AST. The expression levels of tight junction protein ZO-1 and Claudin-1 were also decreased in Nx, which were mitigated in Nx+AST. The analysis of the gut flora showed the decrease in the number of Lactobacillus in Nx. This decrease was also reversed in Nx+AST.

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

Underline represents presenting author/disclosure.

313A
Conclusions: It has been reported that tight junction proteins were downregulated and intestinal barrier function was impaired in mucin-2 deficient mice. Mucin-2 enhances the growth of Lactobacillus by inducing their adhesion to the colon. Our data demonstrated that AST-120 improved the gut environment favorable to Lactobacillus which affected the expressions of the tight junction proteins. Recent study demonstrated that probiotics that supplement a part of intestinal flora had favorable effects on renal function. These effects provide a novel mechanism whereby AST-120 or probiotic therapy improves renal function through modulating the gut environment.

**TH-PO947**

**Differential Effects of Oncostatin M on Proinflammatory and Probiotic**

**Gene Expression in Human Proximal Tubular Cells**

Markus Pirkbauer, Rita Sarkozi, Gert J. Mayer, Herbert Schramek.

**Department of Internal Medicine II**, Nephrology and Hypertension, Innsbruck Medical Univ, Innsbruck, Austria.

**Background:** Accumulating evidence indicates that inflammatory mechanisms play a role in initiation and progression of diabetic nephropathy. Recently we reported that oncostatin M (OSM) exerts potent anti-inflammatory effects in the human proximal tubular cell line HK-2. In this study we investigated OSM effects on mRNA expression of CCL5/RANTES, thrombospodin-1 (TSP-1) and tenascin C (TNC) induced by TNF-α, IL-1β and TGF-β1.

**Methods:** Human kidney-2 (HK-2) cell culture, real-time PCR.

**Results:**

- 10 ng/ml of TNF-α or IL-1β led to a time-dependent upregulation of TSP-1 and TNC mRNA expression, which was highest after 48 h and 6 h, respectively.
- After 24 h of incubation, expression of TSP-1 mRNA was 5.9-fold and 3.2-fold in TNF-α- and IL-1β-treated HK-2 cells but 12.4-fold in TGF-β1-stimulated ones. At the same time point, TNC mRNA expression was hardly affected by TNF-α or IL-1β, but showed strong induced expression under TGF-β1. After 24 h of co-incubation, 10 ng/ml OSM inhibited mRNA expression of TSP-1 and TNC induced by either one of the three ligands.

In contrast to these two proinflammatory genes, induction of proinflammatory CCL5 mRNA expression by TNF-α or IL-1β started as early as 3 h after incubation and was highest after 48 h. TGF-β1 did not significantly affect CCL5 mRNA expression at any of the time points investigated. While CCL5 mRNA expression was unaffected by OSM alone, OSM led to a strong additive stimulatory effect after 6 h and 24 h when administered together with either TNF-α or IL-1β.

**Conclusion:** In human proximal tubular HK-2 cells, OSM exerts a strong additive effect on TNF-α- and IL-1β-stimulated mRNA expression of proinflammatory CCL5. In contrast, OSM inhibits TNF-α-, IL-1β- and TGF-β1-induced mRNA expression of the proinflammatory genes TSP-1 and TNC after long-term incubation. Thus, OSM may have the ability to act both as pro-inflammatory ligand and anti-fibrotic mediator.

**TH-PO946**

**Changes in Hemodynamic Forces on Glomerular Endothelial Cells following Partial Nephrectomy**

Nicholas J. Ferrell, Ruben M. Sandoval, Bruce A. Moltorff, William Fissell, Nephrology, Vanderbilt Univ, Nashville, TN; Nephrology, Indiana Univ, Indianapolis, IN.

**Background:** Renal hyperfiltration following loss of functional nephron mass is thought to drive disease progression. Changes in blood flow dynamics in addition to compensatory structural adaptations in the nephron transiently alter the mechanical forces on cells that line the glomerular capillary wall. Therefore, we have characterized disease related changes in hemodynamic forces in response to unilateral ureteral obstruction.

**Methods:** For Genetic model studies, Spkh2−/− mice and for pharmacological model studies (treated with novel Spkh2 inhibitor, SXK002411, obtained from Sphynx Therapeutics, VA), wild type (WT) C57BL/6 mice were subjected to complete UUO. Obstructed and unobstructed kidneys were examined for histological changes and expression of key renal injury markers, such as TGF β and alpha SMA by immunohistochemistry and western blotting. Immune cell profile by flowcytometry and inflammatory cytokine expression by qRT PCR were assessed.

**Results:** Histological examination reveals that WT mice had extensive renal damage with elevated levels of TGF β and alpha SMA in interstitial spaces when compared to Spkh2−/− mice. Flowcymetric analysis reveals that Spkh2−/− mice demonstrated a reduction in pro-inflammationary macrophages (M1) and a corresponding increase in anti-inflammatory (M2) phenotype. Mice treated with Spkh2 inhibitor exhibited diminished renal injury histologically, in addition to decreased levels of TGF β , alpha SMA and reduced infiltration of inflammatory monocytes and macrophages. This observation was further supported by diminished expression of inflammatory cytokines, such as MCP-1, TNF α, CXCCL2, IL-6 in the drug treated group.

**Conclusions:** The results demonstrate that, genetic and pharmacological manipulation of Sphingosine kinase 2 significantly decreases inflammatory and fibrotic responses, resulting in diminished renal injury. Suggesting that therapeutic modulation of Spkh2 signaling pathway may prove beneficial in renal injury representing a novel class of therapeutics.

**Funding:** Private Foundation Support

**TH-PO945**

**Genetic and Pharmacological Manipulations of Sphingosine Kinase 2, Diminishes Renal Inflammation/Renal Fibrosis in Response to Unilateral Ureteral Obstruction**

Shobha D. Thangada, Malika Ghosh, Gerald Yamase, Cynthia J. D’Alessantri, Ferrer Fernando, Vascular Biology, UCHC, Farmington, CT; Urology, CCMMC, Hartford, CT; Pathology, UCHC, Farmington, CT.

**Background:** Sphingosine Kinase-2 (Spkh-2) is a metabolizing enzyme responsible for production of bioactive lipid, Sphingosine-1-Phosphate (SIP), which plays a major role in tissue injury. In the present study we address in vivo significance of Spkh-2 in renal inflammation/fibrosis in response to unilateral ureteral obstruction.

**Methods:** For Genetic model studies, Spkh2−/− mice and for pharmacological model studies (treated with novel Spkh2 inhibitor, SXK002411, obtained from Sphynx Therapeutics, VA), wild type (WT) C57BL/6 mice were subjected to complete UUO. Obstructed and unobstructed kidneys were examined for histological changes and expression of key renal injury markers, such as TGF β and alpha SMA by immunohistochemistry and western blotting. Immune cell profile by flowcytometry and inflammatory cytokine expression by qRT PCR were assessed.

**Results:** Histological examination reveals that WT mice had extensive renal damage with elevated levels of TGF β and alpha SMA in interstitial spaces when compared to Spkh2−/− mice. Flowcymetric analysis reveals that Spkh2−/− mice demonstrated a reduction in pro-inflammationary macrophages (M1) and a corresponding increase in anti-inflammatory (M2) phenotype. Mice treated with Spkh2 inhibitor exhibited diminished renal injury histologically, in addition to decreased levels of TGF β , alpha SMA and reduced infiltration of inflammatory monocytes and macrophages. This observation was further supported by diminished expression of inflammatory cytokines, such as MCP-1, TNF α, CXCCL2, IL-6 in the drug treated group.

**Conclusions:** The results demonstrate that, genetic and pharmacological manipulation of Sphingosine kinase 2 significantly decreases inflammatory and fibrotic responses, resulting in diminished renal injury. Suggesting that therapeutic modulation of Spkh2 signaling pathway may prove beneficial in renal injury representing a novel class of therapeutics.

**Funding:** Private Foundation Support

**TH-PO943**

**A Serine Protease Inhibitor, Camostat Mesilate, Attenuates the Progression of CKD through Its Antioxidant Effects**

Yoshikazu Miyasato,1 Miki Ueda,1 Kenichiro Kitamura.1 Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; 2Center for Clinical Pharmaceutical Sciences, Kumamoto Univ, Kumamoto, Japan; 3Research Headquarters, Ono Pharmaceutical Co., Ltd., Osaka, Japan.

**Background:** Previously we demonstrated a renoprotective effect of camostat mesilate (CM) in the remnant kidney model. However, the precise mechanisms by which CM delays the progression of CKD still remain poorly understood. Here, we investigated the effect of CM on the progression of CKD in the adenine-induced CKD model and explored the renoprotective mechanisms of CM.

**Methods:** Thirteen week-old SD rats were divided into four groups: 1) Control group, 2) dietary adenine-induced CKD (CKD) group, 3) CKD+CM (CM) group, and 4) CKD+hydralazine (HYD) group. Blood pressure measurements and 24 hr urine collections were made during the treatment period. Rats were sacrificed following 5 weeks treatment period. We also evaluated the radical scavenging activities of CM and hydralazine in vitro by electron spin resonance (ESR).

**Results:** At the end of the experiment, both proteinuria and serum creatinine levels were substantially increased in CKD group. Although CM group and HYD group showed similar reduction in the blood pressure levels, CM significantly reduced proteinuria and serum creatinine levels compared with HYD. CM remarkably decreased the mRNA levels of NADPH oxidase components and the reactive oxygen species generation in the kidney. Furthermore, the ESR-spin trapping method revealed substantial hydroxyl radical scavenging activity of CM in vitro.

**Conclusions:** We demonstrated that CM significantly ameliorated the progression of CKD through its antioxidant effects independently of blood pressure. Our current results suggest the possibility that CM could be a new therapeutic agent against the progression of CKD.

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

**Underline represents presenting author/disclosure.**

**314A**
tissue Nr2 levels, and was associated with decreased nuclear levels of NF-kB. Colon from CKD+Nr2 treated rats had decreased inflammatory mediators (COX-2, MCP-1) and oxidative stress factors (iNOS, NOX4), and lower plasma MDA levels. Additionally, Nr2 agonist treatment improved expression of tight junction proteins (Figure 1).

Figure 1. Representative Western blot data showing decreased expression of tight junction proteins (zonula occludens-1, occludin and claudin-1) in the colon from CKD rats; this was ameliorated by treatment with a Nr2 agonist. *P<0.05 compared to controls (ø) or non-treated CKD rats (*).

Conclusions: Treatment with a potent Nr2 agonist decreased colonic inflammation and improved expression of tight junction proteins in CKD rats. There was concurrent decreased systemic oxidative stress. Thus, there are potential benefits of intestinal Nr2 activation in CKD.

Funding: Pharmaceutical Company Support - Reata Pharmaceuticals; WL Lau funded by a Sanofi fellowship award, Private Foundation Support

TH-PO950
Tissue Kallikrein Mediates Pro-Inflammatory Pathways in Proximal Tubular Epithelial Cells

Wai Han Yu1, Dickson WL Wong1, Joseph C. K. Leung1, Loretta Y.Y. Chan1, Hui Y. Lan2, Kar Neng Lai1, Sydney C.W. Tang1. 1Dept of Medicine, The Univ of Hong Kong, Queen Mary Hospital, Hong Kong, China; 2Dept of Medicine and Therapeutics, Li Ka Shing Institute of Health Sciences, The Chinese Univ of Hong Kong, Hong Kong, China.

Background: Tissue kallikrein (KLK1) expression is up-regulated in human diabetic kidney tissue. Since the kallikrein-kinin system (KKS) has been linked to cellular inflammatory process in many diseases, we explore the role of KLK1 in tubular pro-inflammatory responses under the diabetic milieu.

Methods: Human proximal tubular epithelial cells (PTEC) were incubated with recombinant KLK1 protein to examine the expression of pro-inflammatory cytokines and the activation of signaling pathways. Cells were then transfected with KLK1-specific or control siRNA to investigate the effect of KLK1 on advanced glycation end products (AGE)-induced pro-inflammatory responses.

Results: Recombinant KLK1 stimulated the production of inflammatory cytokines including IL-8, ICAM-1 and CCL-2, and activated the phosphorylation of p62/44 and p38 MAPK in PTEC. Increased expression of KLK1 was detected in PTEC stimulated with AGE (0.5 mg/ml), and molecular knockdown of endogenous KLK1 expression attenuated MAPK in PTEC. Increased expression of KLK1 was detected in PTEC stimulated with AGE. Furthermore, the increased expression of KLK1 was ameliorated by treatment with a Nrf2 agonist.

Conclusions: Our data suggest for the first time that KLK1 mediates pro-inflammatory responses in renal tubule cells under a diabetic milieu, and pave the way for further investigation that targets KLK1 in ameliorating diabetic tubular injury.

Fund support: Research Grant Council of Hong Kong (GRF grant number 7796/11M).

TH-PO951
Regulatory T Cells in Nephrocalcinosis and Dystrophic Cardiac Calcification in DBA/2 Mice

Alexander H. Kirsch1, Alexander R. Rosenkranz1, Kathrin Eller1, Philipp Eller1. 1Clinical Div of Nephrology, Medical Univ of Graz, Graz, Austria; 2Div of Angiology, Medical Univ of Graz, Graz, Austria.

Background: Nephrocalcinosis is characterized by aberrant deposition of calcium in the kidneys and is seen in phosphate nephropathy, primary hyperparathyroidism, and distal renal tubular acidosis.

Methods: To further evaluate the specific pathophysiologic role of T cells in ectopic calcification, we used DBA/2 mice that are prone to develop nephrocalcinosis and dystrophic cardiac calcification. Female DBA/2 mice were depleted of T cells (n = 10) or regulatory T cells (Tregs) (n = 15) using either an anti-CD3/4 or an anti-CD25 monoclonal antibody and compared with isotype-treated controls (n = 9; n = 15), respectively. After this immunomodulation, the DBA/2 mice were given a high-phosphate diet for 9 days and the degree of calcification was assessed by microcomputed tomography. Successful depletion was confirmed by flow cytometry of splenocytes.

Results: In DBA/2 mice, the high-phosphate diet induced a phenotype of nephrocalcinosis and dystrophic cardiac calcification. T-cell depletion significantly increased renal calcification in microcomputed tomography (P = 0.022). Concordantly, Treg depletion significantly decreased acute phosphate nephropathy (P = 0.039) and was associated with a significantly increased mortality rate (P = 0.004). Immunomodulation had no impact on the amount of cardiac calcification. Semiquantitative histopathologic evaluations with Alizarin Red staining independently confirmed the respective radiologic measurements.

Conclusions: In summary, our data suggest a pivotal role of T cells, particularly Tregs, in the progression of nephrocalcinosis and emphasize the fact that inflammation deteriorates the outcome in acute phosphate nephropathy.

Funding: Government Support - Non-U.S.

TH-PO952
Aberrant Activation of Neutrophils Allow ANCA to Aggravate Glomerulonephritis in Experimental Autoimmune Vasculitis

Go Kanzaki, Shinuya Nagasaka, Yusuke Kajimoto, Seichiro Higo, Kayori Tsurolua, Akira Shimizu. Dept of Analytic Human Pathology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.

Background: ANCA-neutrophil and neutrophil-endothelial cell interactions play an important role in the pathogenesis of ANCA-associated vasculitis (AAV). However, it is still unclear whether these interactions aggravate glomerulonephritis (GN) in vivo. In the present study, we used an experimental autoimmune vasculitis (EAV) rat model by generation of an immune response to exogenously administered human MPO (hMPO) in adjuvant. We tested this hypothesis in this rat model by using lipopolysaccharide (LPS), phorbol myristate acetate (PMA), or G-CSF as a stimulus for neutrophils. In addition, we analyzed gene expression of cytokines and adhesion molecules in this rat model.

Methods: Necrotizing and crescentic GN was induced in WKY rat by immunization with hMPO (1600 µg/kg). Blood and urine samples were obtained at every week. Quantitative RT-PCR was used to determine gene expression of cytokines and adhesion molecules were analysed in isolated glomeruli in 8 weeks after NCGN induction.

Results: Hematuria (2+3) and proteinuria (300-1000 mg/dl) were noted at 4 weeks. LPS-immunized rats had serum anti-hMPO antibody titers of 1:10000 by ELISA. We demonstrated that the induced anti-MPO antibodies cross-reacted with rat neutrophils inducing IL-1β in vitro. Several cytokines or adhesion molecules, which are mainly involved in neutrophil-endothelial interactions, were induced or up-regulated in glomeruli of hMPO immunized rat. The administration of LPS, PMA, or G-CSF exacerbated disease in EAV rat model, as assessed by both histological and functional parameters.

Conclusions: This study suggested that ANCA developed in EAV model rat aberrantly activated neutrophils in vivo. The excess stimuli for neutrophils or endothelial cells would develop glomerulonephritis in AAV.

TH-PO953
Innate Immunity Signal, S100 A8/A9, Are Danger Biomarkers of Lupus Nephritis

Yingyos Ayhingsanong1, Pompen Tantiviyakul2, Thiatha Benjachat, 3Vipawee Kittikovit,4 Nattiya Hiranakarn. 1Medicine, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand; 2Microbiology, Mahidol Univ, Bangkok, Thailand; 3Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand; 4Biomedical Science, Interdisciplinary Program, Graduate School, Chulalongkorn Univ, Bangkok, Thailand.

Background: S100A8 and S100A9 are members of S100 family proteins that involved innate immunity. The proteins are co-expressed on macrophages and infiltrating monocytes during an active involvement of skin and kidney in lupus patients. They can activate auto-reactive CD8+ T-cell through the TLR4 signaling and can lead to the development of nephritis in lupus mice. In this study, we determined the non-invasive blood monitoring of S100A8/A9 mRNA levels and their usefulness for a prediction of therapeutic response.

Methods: We studied S100 messenger RNA levels from blood leucocytes of lupus nephritis patients (n=68) and compared with healthy control (n=15). A 6-month follow-up blood mRNA levels was then measured and correlated with therapeutic response to standard therapy. The 18s rRNA was used as house-keeping gene and the mRNA levels were expressed as log-transformation.

Results: All active lupus nephritis (n=38) were biopsy-proven proliferative class III/IV LN. Median (IQR) urine protein and serum albumin were 5.01 (3.03-5.69) g/day and 2.90 (2.30-3.25) g/dl. Serum creatinine was 0.85 (0.72-1.22) mg/dl. While S100A8 and A9 mRNA levels from blood leucocytes were tightly correlated with renal disease activity (r = 0.33). Both S100 mRNA levels of active LN were higher than those of inactive LN and healthy control (p<0.01). In the study of pre/post treatment of induction therapy, there were 12 responders and 14 non-responders. In the responders, both S100 mRNA levels were significantly reduced after a 6-month course of immunosuppressive treatment.

Conclusions: This supports the importance innate immune response in lupus nephritis. Expression of S100 A8 and A9 of blood leucocytes are potential non-invasive biomarkers of lupus nephritis.

Funding: Government Support - Non-U.S.

TH-PO954
Diagnostic Value of the Simultaneous Detection of Anti-C1q and Anti-dsDNA Antibodies in the Diagnosis of Active Lupus Nephritis

Katarzyna Smyk-Jankowiak, Zoﬁa I. Niemir, Magdalena Polcyn-Adamczak. Laboratory of Molecular Nephrology, Univ of Medical Sciences, Poznan, Poland.

Background: Development of lupus nephritis (LN) is one of the most important factors that worsen the prognosis of systemic lupus erythematosus (SLE). Anti-C1q and anti-dsDNA antibodies (Abs) are candidates for non-invasive markers of renal disease, which can be an alternative to kidney biopsy in the assessment of LN activity. We examined the prevalence and predictive values of anti-C1q and anti-dsDNA Abs in the judgment about the LN activity.

Conclusions: In summary, our data suggest a pivotal role of T cells, particularly Tregs, in the progression of nephrocalcinosis and emphasize the fact that inflammation deteriorates the outcome in acute phosphate nephropathy.
**TH-P0955**

**Macrophage Migration Inhibitory Factor (MIF) in Active Lupus Nephritis (LN) – Response to Immunotherapy**

**Authors:** Ratana Chawansasuntoraj, Marie B. Condon, Tom Cairns, Megan Griffith, Frederick W.K. Tam, Liz Lightstone. Kidney and Transplant Centre, Imperial College.

**Background:** MIF plays a central role in inflammatory responses and elevated MIF levels have been detected in patients with inflammatory kidney diseases. Kerschner et al. [1] reported that MIF in urine correlated with disease activity in LN; however this was in a relatively small pilot population. In this study, we investigate urinary MIF (uMIF) in a larger cohort looking at response to immunotherapy and its predictive value at time of biopsy.

**Methods:** uMIF was measured by ELISA on 643 urine samples from 60 patients collected between 2012 and 2014. All patients had biopsy-proven LN (WHO classification). LN was >75% received Rituximab +/- MMF +/- steroids; the other patients received MIF or cyclophosphamide +/- steroids. uMIF levels were normalised for urinary creatinine (creat). uMIF creat +/- 5 wks of biopsy were compared with uMIF creat in samples collected at 26-52 wks post biopsy; subdivided into complete remission (CR=uPCR<50mg/mmol) +/-15% in serum creat); partial remission (PR=uPCR 50-300mg/mmol) and non response (NR=uPCR>300mg/mmol).

**Results:** Samples analysed: 75 at biopsy; 82 at 26-52 wks post biopsy (53 CR; 27 PR; 17 NR). uMIF creat is significantly reduced in all patients at 26-52 wks post biopsy compared with biopsy, however the more significant the clinical response the more significant the reduction. CR (58% (p<0.001); PR (44%) (p=0.002); NR = 37% (p=0.0175). There is a significant correlation between uMIF creat and uPCR at time of active biopsy (p=0.027, Spearman’s correlation R=0.26), but not with serum creat. uMIF creat at biopsy did not show a significant correlation with time to CR or with class of LN.

**Conclusions:** uMIF is abundant in all patients with active LN on renal biopsy; as the disease goes into remission the levels fall significantly. uMIF is not reported in healthy subjects. uMIF is present in polyclonal, maybe induced by a “smouldering” disease process. As the treatment protocols at this centre are deemed to be “steroid sparing”, the lack of demonstration of a predictive value of uMIF maybe due to this approach being effective at treating the MIF dependent aspect of the disease process as MIF may induce steroid resistance.

**TH-P0956**

**Monitoring of Urinary Cytokine Levels as Biomarker for Disease Activity in Thalassemia Nephropathy**

**Authors:** Skulratana T., Ratana Chawansasuntoraj, Boonyarat Cheunsuchon, P. Parichatikanond, Kriengsak Vareesangthip. Kidney and Transplant Centre, Imperial College.

**Background:** Thalassemia is one of the most common and severe secondary glomerulonephritis (GN). Early detection and good monitoring are essential to provide optimal care, while delay of the appropriate treatment may worsen the outcome. Regarding the pathogenesis of LN, immune and inflammatory responses play an essential role. Several studies have demonstrated cytokines/chemokines in correlation with LN activities. Using a novel LumineX™ assay to detect such changes has maximized its efficiency and clinical advantages by simultaneous measurement of several cytokines within a short period. This study was to demonstrate the correlation of urinary biomarkers with LN activity and its application.

**Methods:** We measured urinary cytokines; monocyte chemotactic protein-1(MCP-1), vascular endothelial growth factor(VEGF), interleukin-6(IL-6), IL-6 soluble (s) receptor (sIL-6R), interferon gamma inducible protein 10(IP-10), platelet derived growth factor(PDGF) and interleukin(IL)-1β using Bioplex MAP Human Cytokine 27plex Panel Kit. These cytokines were measured in controls, patients with active LN and controls. In active LN, we measured these cytokines along two years during Jan 2011 to Dec 2012.

**Results:** 40 biopsy-proven active proliferative LN were compared with 35 inactive LN, 35 other GN and 35 healthy controls. Urinary MCP-1, VEGF, IL-6, IL-10, PDGF and IL-1β were significantly higher in active LN and controls. Among active GN and control groups in active LN, we found the sensitivity of MCP-1 to identify the active LN was better than routine serology. In 40 active LN, the clinical response at 6 months therapy was 12 complete, 15 partial, 9 non-response. Urinary IL-1β, IP-10, PDGF, and VEGF significantly decreased and correlated with the clinical. We described the persistently high level of urinary PDGF at 3 month could be predicting the non-responder to induction therapy at 6th month. During 2 years, renal flare occurred in 5 cases. Increase of IL-1β might be applied as predictor of renal flare.

**Conclusions:** According to our result, urinary biomarkers could be useful to monitor LN activity and might be minimizer kidney biopsy in LN patients.

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

**TH-P0957**

**Soluble CR1 – Could It Be a New Marker of Lupus Nephritis Activity?**

**Authors:** Aleksandra Rochowski, Zofia I. Niemir, Magdalena Poleczyk-Adamczek. Laboratory of Molecular Nephrology, Univ of Medical Sciences, Poznan, Poland.

**Background:** CR1, a membrane receptor for complement components (C3b/C4b), has a soluble form (sCR1) present in the serum and in the urine. The sources of sCR1 are probably erythrocytes and blood leukocytes.CR1 regulates the complement cascade activation and plays an important role in the removal of immune complexes coated with C3b/C4b. Increased serum concentrations of sCR1 were observed in patients with inflammatory diseases and hematologic malignancies. The aim of our study was the analysis of the sCR1 concentration in serum of healthy individuals and patients with primary glomerulonephritides (PGN) and lupus nephritis (LN).

**Methods:** The serum samples were obtained from 147 patients with PGN, 65 with LN and 67 healthy volunteers serving as a control group (C). The activity of the disease was determined by using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). Among patients with LN, 32 were in active phase of the disease (aLN) (SLEDAI score ≥10) and remaining 33 in inactive phase of the disease (inLN) (SLEDAI score <10). Serum sCR1 was evaluated by the standardized enzyme-linked immunosorbent assays.

**Results:** The highest level of serum sCR1 was noticed in patients with aLN compared to the results obtained in C (p<0.01), PGN (p<0.01) and in LN (p<0.05). A significant correlation was observed between sCR1 level and SLEDAI-2K score in LN (r=0.2576; p<0.05), while significant negative correlation appeared between sCR1 level and C3 (r=-0.269; p<0.05) and C4 concentration (r=0.319; p<0.001) in LN. Serum sCR1 did not correlate with C3 and C4 serum level in C and PGN. We also have not found any correlations between sCR1 level and anti-dsDNA concentration in LN, as well as between creatinine serum level and sCR1 in LN and PGN.

**Conclusions:** Increased serum level of sCR1 in aLN and correlations observed between its concentration and C3 and C4, as well as sCR1 and SLEDAI-2K score in LN indicate that serum sCR1 may be a potential marker of lupus nephritis activity.

**Funding:** Government Support - Non-U.S.
Background: Angiogenin (Ang), also known as Ribonuclease 5, is a 123 amino acid protein, involved in stimulating RNA transcription after localisation into the nucleus, leading to angiogenesis and growth stimulation. The presence of Ang in glomerular disease is not known. By the first in relation to activity of lupus nephritis (LN). Treatment of lupus nephritis with the steroid sparing “Rituximab” regimen has published outcomes and all patients were treated in a consistent manner.

Methods: Ang was measured by ELISA on 342 urine samples from 34 patients collected over a 4 year period. During that time all patients had at least 1 episode of biopsy proven ISN/RPS class III/IV/V/LN, for which they received the steroid sparing “Rituximab” regimen. Median age at the time of biopsy 44 years (IQR 27 years). Urine Ang (uAng) levels were normalised for urinary creatinine (creat) level. The relationship between uAng/creat ratios and serum creatinine/urine protein/creat ratio (EdCr) in the samples taken within +/- 5 weeks of biopsy were investigated. Effect of immunotherapy on uAng/creat ratios were +/- 5 weeks of achieving partial remission (PR-uPCR <0.30g/mmol with a >50% reduction from baseline with <15% rise in serum creat) and complete remission (CR-uPCR<0.50g/ mmol with <15% rise in serum creat) were evaluated.

Results: 33, 28 and 30 samples analysed at biopsy, PR and CR respectively. There is a significant correlation between uAng/creat and serum creat at time of active biopsy (p<0.011, Spearman’s correlation R=0.45), but not with uPCR. uAng/creat is significantly reduced in PR and CR by 51% (p>0.05) and 84% (p<0.001) respectively.

Conclusions: In a well described cohort, treated in a consistent manner, uAng is associated with the severity of renal impairment at time of biopsy of active lupus nephritis, and showed significant reduction in patients with remission following immunotherapy. The lack of correlation of uAng with uPCR at presentation suggested that uAng is not a simple consequence of proteinuria. The potential role of Ang in the development of LN will need further investigation.
TH-PO964
Clinical pathological Features and Renal Outcomes of IgA Nephropathy in the Elderly Yusuke Okabayashi, Nobuo Tsboi, Akira Fukui, Yoichi Miyazaki, Iwao Ohno, Tetsuya Kawamura, Makoto Ogora, Takashi Yokoso. Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan.

Background: The number of elderly patients with renal diseases is increasing in parallel with an increased longevity in the general population. However, information is limited regarding characteristics of each disease in the elderly. This study therefore investigated clinico-pathological features of the elderly patients with IgA nephropathy (IgAN), the most common glomerulonephritis worldwide.

Methods: A total of 92 IgAN patients over 60 years old were retrospectively analyzed. Two hundred-fifty IgAN patients of 18 to 59 years of age, from the retrospective cohort of Ministry of Health, Labour and Welfare in Japan, were used as comparison (J Nephrol, 2012). Clinico-pathological features at biopsy, therapies during the follow-up, renal outcomes and extra-renal complications were evaluated.

Results: The average values at diagnosis were age of 65 years, eGFR of 45 ml/min/1.73m, and urinary protein excretion (UPE) of 1.8 g/day. These features were more serious than those of the control group. Consistent with these clinical features, chronic pathological findings including glomerulosclerosis or interstitial fibrosis/tubular atrophy were more advanced than the control group, while degrees of acute lesions such as crescent formations were almost the same as the control group. As the result of appropriate treatments such as diet, RAS inhibitors, statins or steroids, more than 50% of the patients showed clinical remission (UPE<0.3g/day) at the last observation (median 4.1 years). On the other hand, 21 patients (23%) showed a 50% decrease in their eGFR or reached ESRD. The eGFR at biopsy and the proteinuria at one year were identified as independent factors that were associated with the slope of renal function. Extra-renal complications observed during the follow-up were hypertension (79%), diabetes (13%), dyslipidemia (35%), hyperuricemia (33%) and cardiovascular diseases (29%).

Conclusions: In spite of the advanced clinico-pathological features and the presence of various extra-renal complications, therapeutic interventions may lead to better renal outcomes of the elderly patients with IgAN.

TH-PO965

Background: The benefits of tonsillectomy in IgA nephropathy (IgAN) is still debated. Tonsillectomy might remove pathogen sources and reduce the Mucosal Associated Lymphoid Tissue (MALT), limiting dimeric and undergalactosylated IgA1 production.

Methods: In the European network VALIGA 62/1147 IgAN underwent tonsillectomy (TxIgAN), 15 were tested and compared to 45 non-tonsillectomized IgAN (No-Tx) and 30 healthy controls (HC).

Results: Levels of degalactosylated IgA1 were lower in TxIgAN than in No-Tx IgAN (p=0.04); however still higher than in HC (p=0.03). PBMC of TxIgAN, higher than HC and no-Tx IgAN (LMP2/beta1 p=0.01 and LPM7/beta 2 p=0.005), however still higher than in HC (p=0.03). TLR mRNAs were more expressed in PBMC of TxIgAN, higher than HC and no-Tx IgAN (TLR1 23.3 36, TLR2 2.0 2, TLR4 9.0 9, TLR6 2.0 2). Conscriptions: Serum degalactosylated IgA1 was lower in tonsillectomized than non-tonsillectomized IgAN, however significantly higher than controls. Activation of innate immunity via TLRs and ubiquitin-proteasome and pro-oxidative milieu were not affected by tonsillectomy. Tonsillectomized patients had signs of mucosal immunity and oxidative stress higher than non tonsillectomized ones, possibly via extra-tonsilar MALT.

TH-PO966
Analysis of the Correlation between the Oxford Classification and Clinical Indicators of IgA Nephropathy Qiuling Fan, Dept of Nephrology, The First Affiliated Hospital of China Medical Univ, Shenyang, China.

Background: Analyze the correlation and risk factors between clinical indicators and the four main pathological lesions of the Oxford classification in IgAN.

Methods: Clinical and pathological data were collected from 514 patients with biopsy-proven IgA nephropathy who were 18 years or older. Spearman’s coefficient of rank correlation was performed to evaluate associations between the Oxford classification of IgAN and various clinical indicators. The independent risk factors affecting the pathological classification were analyzed by multivariate regression.

Results: For 318A patients, the average age was 35.70, and the average disease duration was 18.31±30.42 months. M0E0S0T0 was the major pathological classification of isolated hematuria. Proteinuria and albuminuria were positively correlated with M lesion, serum albumin, C3 and PFT showed a negative correlation with M lesion. Proteinuria and blood cell count were the independent risk factors for M lesion. The proportion of M1 in cases with proteinuria ≥3.5 g/d is much higher than that in cases with non-nephrotic range proteinuria. Age, SBP, uRBC, proteinuria, albuminuria were positively correlated with E lesion. Duration, serum albumin showed a negative correlation with E lesion. Age and duration of nephritis were independent risk factors for E lesion. 73.3% of patients more than 30 years old showed extraglomerular proliferation. On IgAN, proteinuria were positively correlated with S lesion. Age, CKD stage, SBP, DBP, C4, TC, LDL-C, CRP, Fih, UA, Cys-C and proteinuria were positively associated with T lesion. Hb, serum albumin, IgG showed a negative correlation with T lesion. High CRP levels, DBP >90 mmHg, hypoaalbuminemia, high low density lipoproteinaemia, and anemia were independent risk factors for T lesion.

Conclusions: 1. Proteinuria and blood platelet count were the independent risk factors for M lesion. 2. Age and duration of nephritis were independent risk factors for E lesion. 3. CKD stage, SBP and proteinuria were positively correlated with S lesion. 4. High CRP levels, DBP >90 mmHg, hypoaalbuminemia, high low density lipoproteinaemia, and anemia were independent risk factors for T lesion.

TH-PO967
Prognostic Significance of C1Q Deposition with Renal Outcomes among Patients with IgA Nephropathy Abdulkareem Alsouwai,1 Sufia Husain,1 Noura Aloudah,1 Fayez F. Alhejaili, 2 Khaleed Alsaaad,2 Hala M. Kfoury,3 Mohammed A. Al-Ghonaim.1 1King Saud Univ; Saudi Arabia; 2King Abdulaziz Medical City, Saudi Arabia; 3Prince Salman bin Abdulaziz Chair for Kidney Research, Saudi Arabia.

Background: It has been reported in a study that mesangial C1q deposition in the glomerulus is associated with a poor renal outcome and severe pathologic features in patients with IgAN. The objective was to investigate the predictive power of co-deposition C1q in predicting long term outcome in patients with IgAN.

Methods: Participants with IgAN were divided into two groups based on the renal tissue C1q status and their baseline and long-term outcome of worsening renal function (WRF) were compared. The rate of WRF was defined as increase in serum creatinine of ≥25% from baseline.

Results: Fifty five patients had IgAN and 54.5% had a positive C1q. The baseline proteinuria was significantly higher among those with positive C1q (P=0.03) while serum albumin at baseline was not significantly different (P=0.33). The distribution of mesangial hypercellularity (M), segmental sclerosis (S), endocapillary proliferation (E), tubular atrophy and interstitial fibrosis (Tf) were equally distributed among those with C1q positive and negative groups.

Table 1: Chronic kidney disease risk factors

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>Age (Years) Mean±SD</th>
<th>Serum creatinine</th>
<th>Hyper tension</th>
<th>Dys lipidemia</th>
<th>Hy peruricemia</th>
<th>Type of renal classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47 (11.1)</td>
<td>0.9 (9.2)</td>
<td>64</td>
<td>44</td>
<td>45</td>
<td>18/02/11/01</td>
</tr>
<tr>
<td>2</td>
<td>54 (14.1)</td>
<td>1.4 (12.3)</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>02/11/02/01</td>
</tr>
<tr>
<td>3</td>
<td>55 (21.0)</td>
<td>1.7 (15.0)</td>
<td>30</td>
<td>32</td>
<td>32</td>
<td>02/11/02/01</td>
</tr>
<tr>
<td>4</td>
<td>51 (16.1)</td>
<td>1.9 (16.5)</td>
<td>30</td>
<td>36</td>
<td>36</td>
<td>02/11/02/01</td>
</tr>
<tr>
<td>5</td>
<td>50 (18.1)</td>
<td>1.8 (15.5)</td>
<td>30</td>
<td>36</td>
<td>36</td>
<td>02/11/02/01</td>
</tr>
<tr>
<td>Median [Mean;SD]; All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Among 56 patients whom they follow up greater than one year and a median of 5 years, the rate of WRF was seen in 29.4% for those with C1q positive and 31.6% for C1q negative (P=0.8).

Conclusions: The tissue C1q status among patients with IgAN has no long term prognostic significance.

Funding: Government Support - Non-U.S.

TH-PO968
Renal PLA2R Is a Valuable Biomarker for Idiopathic Membranous Nephropathy Qinghong Xie, Yan Li, Yuecheng Ren, Xiaoye Zhu, Weiyu Zhu, Jianyong Zhong, Jun Xue, Chuan-Ming Hao. Huashan Hospital, Fudan Univ, Shanghai, China.

Background: The present study characterized PLA2R expression in the kidney and examined its role as a biomarker for idiopathic membranous nephropathy (IMN).

Methods: Patients with MN without identifiable secondary causes were included. All renal biopsies were tested by indirect immunofluorescence (IF) and renal PLA2R examined using a specific antibody. PLA2R expression has been optimized by testing different antigen retrievals. Microwaving was used in this study unless specified.

Results: Of 47 tissue samples, 47 samples were positive for PLA2R. PLA2R expression has been optimized by testing different antigen retrievals. Microwaving was used in this study unless specified. We compared paraffin-embedded and frozen section of 40 IMNs, 35 positive and 3 were negative on paraffin but positive on frozen section, suggesting frozen sections are more sensitive.

Funding: Government Support - Non-U.S.
We then examined the correlation of serum autoantibody and kidney PLA2R expression. Of 41 MNS with both serum anti-PLA2R antibody data and renal biopsy PLA2R (paraffin) available, 24 were anti-PLA2R antibody positive (59%) and 17 were negative (41%). Among these 17 negative autoantibody cases, 9 exhibited kidney PLA2R (+) staining. Of 24 serum PLA2R antibody positive cases, only one showed negative for kidney PLA2R.

**Conclusions:** (1) Normally PL2AR is expressed in podocytes, but can only be detected after antigen retrieval (2) In iMN but not non-MN GN, PLA2R immunofluorescence becomes positive. (3) Some serum PLA2R autoantibody negative iMN patients show renal tissue PLA2R staining. (4) Kidney PLA2R can also be detected in lupus nephritis. Conclusion: Renal tissue PLA2R can provide additional information for MN diagnosis.

**TH-PO971**

**Dutch Transplantation in Vasculitis (DUTRAVAS)-Study; Outcome of Renal Transplantation in ANCA-Associated Vasculitis**

Arda Gocergul,1 Chinar Rahmatulla,1 Annelies Evalie Berden,2 Marlies Reinders,2 Marcory van Dijk,2 Aineke A.E. de Joude,3 Carine Peutz-Kootstra,4 Maarten H.L. Christiaans,1 Iris Noorlander,5 Roel Goldschmeding,6 Arjan D. Van Zulien,3 Eric Steenbergen,7 Luuk Hilbrands,8 Lorraine Harper,9 Martijn Alman,10 Ernst C. Hagen,7 Jan A. Buijn,11 Ingeborg M. Bajema,11 Leiden Univ MC,11 Univ MC Groningen,11 Maastricht Univ MC;1 Erasmus MC Rotterdam;1 Radboud Univ MC Nijmegen;1 Univ of Birmingham;1 Trinity College Dublin;7 Meander MC Amersfoort.

**Background:** We present a multi-center study on the outcome of renal transplantation in ANCA-associated vasculitis (AAV) patients focusing on renal disease recurrence and graft survival within 5 years after transplantation.

**Methods:** In total 113 AAV patients (first renal transplantation) were included from 6 university hospitals. Clinical data and transplant biopsies were collected through PALGA (Dutch national pathology database) and a center-specific search. Three patients had immediate graft loss and were excluded from analysis. Transplant biopsies were scored with Banff'09. Renal disease recurrence was scored with the histopathologic classification of ANCA-associated glomerulonephritis. We focused on the first 5 years after transplantation.

**Results:** Sixteen grafts were lost due to acute rejection (3), renal disease recurrence (4), IFTA (4), sepsis (2), infarction (1), cyclosporine toxicity (1), and post-transplant lymphoproliferative disorder (1). Five year graft survival was 82.8%. Thirteen patients had 16 disease relapses; 14 (11 patients) involved the graft. The risk for a first disease recurrence in the graft was 2.8% per patient year within 5 years follow-up. Ten recurrences were classified as: 5 focal, 1 crescentic and 4 mixed class. Four recurrences were clinically diagnosed (no histological confirmation). Of the 4 recurrences that led to graft loss, 3 could be classified: 1 focal and 2 mixed class.

**Conclusions:** This largest cohort study to date shows that a substantial proportion of patients with renal disease recurrence of AAV lost their graft due to the recurrent disease.
TH-PO973

ENT Involvement Is Related to Better Renal Function in Patients with ANCA-Associated Vasculitis (AAV)

Chinar Rahmatullah,1 Robert A. De Lind van wijngaardena,2 Annelies Eavline Berden,1 Herbert Hauer,4 Oliver Flossmann,3 David R.W. Jayne,5 Niels Rasmussen,1 Laure-Helene Noel,1 Franco Ferrario,2 Ruediger Waldherr,6 James S. Ginzler,5 Ernst C. Hagen,2 Jan A. Bruijn,1 Ingeborg M. Bajema,1 Leonid UMC,2 Erasmus MC Rotterdam,3 Bronovo Hospital,4 MC Leiden,5 Leiden UMC,5 Erasmus MC Rotterdam,4 London,3 Medaner MC,3

Background: It has been suggested that ear, nose, and throat involvement (ENT+) can prompt early diagnosis of AAV and that ensuing rapid instigation of therapy can prevent renal impairment. Therefore, this study investigates whether ENT+ AAV patients have better renal function and fewer chronic renal histopathologic lesions at time of diagnosis than ENT- patients.

Methods: 441 newly diagnosed AAV patients with renal involvement from 4 international, prospective, multicenter trials were included. Age, ENT+, ANCA type, interstitial fibrosis and tubular atrophy (IFTA), tubulitis, interstitial infiltrates and the histopathologic class for ANCA-associated glomerulonephritis (AAGN) (n=151) were correlated with eGFR at diagnosis (eGFR0).

Results: Multivariate analysis revealed that ENT+ (n=212) (r=0.25, p<0.001), age (r=0.14, p<0.001), IFTA (r=0.16, p<0.001), tubulitis (r=0.20, p<0.001) and the classification (r=0.24, p<0.001) were associated with eGFR. A prespecified sensitivity analysis including only PR3-ANCA-positive patients showed similar results. ENT+ patients had a higher eGFR0 (60 vs. 44 mL/min, p<0.001), less IFTA (p<0.001) and more often class I/II than class III/IV in their renal biopsies (p<0.001).

Conclusions: In AAV, ENT+ is associated with better eGFR0 and characterized by class I/II on renal histopathology, also in the PR3-ANCA subgroup. These findings indicate that ENT+, possibly because symptoms are clinically overt, leads to a prompt diagnosis of AAV. Reduced diagnostic delay means identifying renal impairment at an early stage, which – with prompt start of treatment – has a known favorable effect on renal outcome.

TH-PO974

Spleen Tyrosine Kinase (SYK) Expression Correlates with Disease Activity and Outcome in Glomerulonephritis

Stephen Paul McAdoo, Gurjeet Bhangal,1 Kevin R. Sperling,1 Surya V. Seshan.1 Weill Cornell Medical College, New York, NY.

Background: Spleen tyrosine kinase (SYK) has a critical role in immunoreceptor signaling. SYK inhibition has shown efficacy in animal models of immune-mediated renal injury, including murine lupus and, in work previously reported by our group, autoimmune disease severity and/or histological class (Fig D,E,F). In anti-GBM and AA V, glomerular sclerosis and tubulitis were more common in ENT+ patients.

Results: Of 6702 total native kidney biopsies, 287 (4%) were obtained from obese patients (mean: weight 122kg, BMI 40.3kg/m2). Associated factors such as insulin resistance (31%), hypertension (60%), and obstructive sleep apnea (9%) were frequent. Immune complex (IC) disease was evaluated. Interestingly, in 14 of 57 (25%) biopsies originally diagnosed as MCD we detected the presence of FSGS lesions. These lesions were typically small and difficult or not detectable in PAS stained sections but could be detected by PEC matrix marker LKIV69.

Conclusions: The clinicopathologic features of 8 non-diabetic patients with long smoking history found in 5139 native kidney biopsies from 2003-2012 showing diffuse mesangial sclerosis and/or nodules indicate that parietal epithelial cells (PECs) are crucially involved in the development of FSGS lesions. In this setting in the absence of nodules, SYK expression in human renal tissue is not well characterised.

Methods: We conducted immunohistochemical analysis for total and phosphorylated SYK in clinical biopsy specimens (thin basement membrane, n=4; minimal change, 4; anti-GBM disease, 12; ANCA vasculitis, 18; lupus nephritis, 16). SYK staining was quantified using automated image analysis software and related to histological class and clinical outcome.

Results: Glomerular staining for total SYK was positive in anti-GBM disease, AAV and lupus nephritis (Fig A,B,C respectively), but not thin basement membrane disease or minimal change. SYK expression appeared to localise to inflammatory lesions (areas of crescent formation or endocapillary proliferation). SYK expression correlated with disease severity and/or histological class (Fig D,E,F). In anti-GBM and AAV, glomerular staining for phosphorylated SYK was positive and localized to areas of crescent formation, demonstrating SYK activation and suggesting a pathogenic role.

TH-PO975

Immuno-Histological Detection of Parietal Epithelial Cells Distinguishes Early FSGS from Minimal Change Disease

Bart Smeets,1 Hermann-Josef Immuno-Histological Detection of Parietal Epithelial Cells Distinguishes Early FSGS from Minimal Change Disease

Background: Recently, we have shown that parietal epithelial cells (PECs) are crucially involved in the development of FSGS lesions. In this setting in the absence of nodules, SYK expression in human renal tissue is not well characterised.

Methods: 95 renal biopsies containing 8 or more glomeruli from 38 adult patients diagnosed with “early” FSGS and 57 patients with newly diagnosed MCD were stained for SYK (PEC marker), and LKIV69 (PE marker). Unaware of the original diagnosis, the glomeruli were evaluated. Biopsies showing staining of one or more of the PEC markers in a visceral location were assigned as FSGS. Those negative for the PEC markers were assigned as MCD.

Results: Evaluation of biopsies with the PEC markers confirmed the original diagnosis (FSGS or MCD) in 76 biopsies (80% of total) and could confirm in 33 of 38 (87%) biopsies diagnosed with FSGS the presence of glomerulocapnia. PECs were involved in the development of FSGS lesions from the earliest stages of disease. In the remaining 5 biopsies stained as FSGS, no PEC marker staining was detected – most likely due to the focal nature of the lesions and because only a single slide of each biopsy was evaluated. Interestingly, in 14 of 57 (25%) biopsies originally diagnosed as MCD we detected the presence of FSGS lesions. These lesions were typically small and difficult or not detectable in PAS stained sections but could be detected by PEC matrix marker LKIV69.

Conclusions: The clinicopathologic features of 8 non-diabetic patients with long smoking history found in 5139 native kidney biopsies from 2003-2012 showing diffuse mesangial sclerosis and/or nodules indicate that parietal epithelial cells (PECs) are crucially involved in the development of FSGS lesions. In this setting in the absence of nodules, SYK expression in human renal tissue is not well characterised.

Methods: We conducted immunohistochemical analysis for total and phosphorylated SYK in clinical biopsy specimens (thin basement membrane, n=4; minimal change, 4; anti-GBM disease, 12; ANCA vasculitis, 18; lupus nephritis, 16). SYK staining was quantified using automated image analysis software and related to histological class and clinical outcome.

Results: Glomerular staining for total SYK was positive in anti-GBM disease, AAV and lupus nephritis (Fig A,B,C respectively), but not thin basement membrane disease or minimal change. SYK expression appeared to localise to inflammatory lesions (areas of crescent formation or endocapillary proliferation). SYK expression correlated with disease severity and/or histological class (Fig D,E,F). In anti-GBM and AAV, glomerular staining for phosphorylated SYK was positive and localized to areas of crescent formation, demonstrating SYK activation and suggesting a pathogenic role.

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

Underline represents presenting author/disclosure.
Results: The patients had similar clinical characteristics, 7/8 were men, age 58-84 years with smoking history of 15-72 pack-years. None of the patients manifested obesity or diabetes, but all had hypertension. Other cardiovascular comorbidities were also present including peripheral vascular disease, heart disease and stroke. At the time of biopsy, the mean creatinine was 1.8mg/dl (range 1.4-5.4) and the mean proteinuria was 3.7g/24hrs. The renal pathologic findings were similar in all patients except mesangial nodules in ING. Global glomerulosclerosis was seen in 6-65% of glomeruli (mean 29%), global endocapillary proliferation in 10-80% (mean 40%). Moderate (25%) and severe (75%) arteriosclerosis and arteriolar hyalinosis (86%) were also observed. Glomerular hilar neovascularization was prominent. Capillary wall double contours, subendothelial widening, endothelial swelling and new basement membrane formation suggesting chronic healing thrombotic microangiopathy (TMA) was noted in 88%. However, no immune complexes were localized.

Conclusions: Kidney biopsies showing either diffuse or nodular mesangial sclerosis from patients with proteinuria and chronic renal insufficiency may be due to prolonged smoking and hypertension. Chronic glomerular endothelial injury may result from smoking and cause a healing TMA appearance in the appropriate setting, even in the absence of mesangial nodule formation.

TH-PO978

Endothelial Cell Injury May Involved in Pathogenesis of Secondary Focal Segmental Glomerulosclerosis Associated with Myeloproliferative Disease

Emiko Fujita, Akira Shimizu, Megumi Fukui, Akiko Mii, Shuichi Tsuruoka.

Department of Nephrology, Nippon Medical School, Bunkyo-ku, Tokyo, Department of Pathology, Nippon Medical School, Bunkyo-ku, Tokyo.

Background: Recently, JAK2V617F mutation may cause myeloproliferative disease (MPD) including polycythemia vera (PV), essential thrombocythemia (ET). The frequency of JAK2 mutation may determine which cell lineages increase possibly due to the diversity of MPD. Several reports describe MPD cases have some degree of proteinuria due to biopsy proven focal segmental glomerulosclerosis (FGS). The pathogenesis of FSGS associated with MPD remains unknown. Endothelial cell abnormalities with mutation of JAK2 in PV patients have been reported. We herein report three cases of FSGS associated with MPD with endothelial cell injury.

Methods: We observed three cases with persistent proteinuria, two of them are nephritic syndrome, after a 8 to 10-year history of MPD. The type of MPD was PV in two patients, unclassifiable MPD in one. Renal biopsy was performed and assessed the pathological characteristics of these cases. We examined serum thrombomodulin (TM) and VEGF to assess endothelial cell injury.

Results: Renal biopsy revealed some glomeruli have segmental sclerosis with foam cell infiltration and podocyte proliferation, double contours, and mesangial sclerosis and hypercellularity on light microscopy. Arteriosclerosis was seen in all cases and ranged from mild in unclassifiable MPD, to severe in PV case which was looks like onion skin thickening. Electron microscopy showed endothelial cell proliferation, loss of fenestrae, and separation of endothelial cells from capillary basement membrane with subendothelial edema. Serum VEGF and TM level was elevated in PV cases accompanied by JAK2V617F mutation, whereas normal in JAK2 mutation—negative unclassifiable MPD. Endothelial cell injuries in glomeruli and small arteries were prominent in the cases with the mutation of JAK2V617F.

Conclusions: We described three cases of glomerulopathy with MPD patients revealed FSGS accompanying endothelial cell injuries in glomeruli and small arteries. Endothelial cell abnormalities with mutation of JAK2V617F may have involvement in pathogenesis in FSGS associated with MPD.

TH-PO997

Histopathologic Findings Associated with APOL1 Risk Variants in Chronic Kidney Disease

Christopher Patrick Larsen, Josephine M. Ambruzz, Larry N. Cossey, Nadia Cordeiro Messias, Patrick D. Walker.

Background: African Americans (AA) have a greatly increased risk of kidney disease which can be explained by the presence of risk alleles in the APOL1 gene. The APOL1 disease spectrum includes primary FSGS, non-diabetic ESKD, and collapsing glomerulopathy. We sought to perform an APOL1 genotype-phenotype correlation in renal biopsies from AA with CKD.

Methods: AA patients with an eGFR<60 ml/min/1.73 m² for 3 months with a diagnosis of arteriopenephrosclerosis on biopsy were included. APOL1 risk allele genotyping was performed using TaqMan assays. 114 biopsies were included including 58 biopsies which had 2 risk alleles and 56 biopsies with 0 risk alleles. A blinded morphologic evaluation of each biopsy was performed by two independent nephropathologists.

Results: We found significantly less obsolescent glomerulosclerosis, more thyroidization-type tubular atrophy and more microcystic tubular dilatation in the patients with 2 risk alleles. There was more arteriosclerosis in the 0 risk allele group. The degree of foot process effacement was not significantly different in these two groups.

Conclusions: We present the first detailed description of the biopsy changes associated with APOL1 risk alleles in the setting of CKD. These findings suggest that APOL1-related CKD may be driven by arteriosclerosis or a primary podocytopathy. Additionally, they allow prediction of the presence of APOL1 risk alleles in this demographic based on renal biopsy findings.

TH-PO980

Prediction of Renal Outcome in Patients with Diabetic Nephropathy Using the Pathological Classification

Yu An, Feng Xu, Yongchen Ge, Cai-Hong Zeng, Zhi-Hong Liu.

Background: In 2010, a pathologic classification of diabetic nephropathy (DN) was launched by Tervaert et al. But its value in the prediction of clinical outcome is largely undefined. Our aim was to evaluate its predictive power in type 2 diabetes mellitus (T2DM).

Methods: We enrolled 414 T2DM patients who had biopsy-confirmed DN and were followed for at least a year after biopsy. All cases were categorized according to the pathological classification of Tervaert et al. Some common pathologic changes of DN were also examined. The relevances between pathological findings and renal outcome were assessed. A renal event was defined as eGFR<15ml/min/1.73m².

Results: Cox regression showed that the glomerular classes, <a class="internal-link" href="#" title="FSGS class-1 type A">FSGS class-1 type A</a>, <a class="internal-link" href="#" title="FSGS class-2 type A">FSGS class-2 type A</a>, <a class="internal-link" href="#" title="FSGS class-3 type A">FSGS class-3 type A</a> and <a class="internal-link" href="#" title="FSGS class-4 type A">FSGS class-4 type A</a> were independent risk factors for renal prognosis, even when adjusted for proteinuria, blood pressure and eGFR.

Conclusions: The glomerular classes and FSGS are significantly associated with renal outcome in patients with T2DM, independently of proteinuria, blood pressure and eGFR. However, the vascular indexes in the classification are incapable of reflect the difference in vascular lesion severity of the patients and can’t be used for renal prognosis, suggesting a necessity to redefine them. Finally, acute tubular injury is also an independent risk factor of the progression of DN to ESRD.

Funding: Government Support - Non-U.S.

TH-PO981

Misdiagnosing Renal Amyloidosis as Adult Minimal Change Disease: Is It a Time for a Change in Practice?


Background: Minimal change disease (MCD) accounts for 10-15% of all adult nephrotic syndrome (NS) cases and diagnosis relies on normal renal light microscopy with foot process effacement on electron microscopy (EM). Renal amyloid deposits (RAD) are identified by red-green birefringence under cross-polarized light after staining with Congo Red (CR) and fibrils seen on EM support the diagnosis further. Late diagnosis and delayed treatment of renal amyloidosis negatively impacts on renal and overall prognosis.

Methods: A retrospective analysis of 2116 patients referred with histologically proven renal amyloidosis to the UK National Amyloidosis Centre (NAC) between 2001 and 2013 was performed. Twenty-nine patients were identified in whom the initial renal histology was reported as MCD before subsequent identification of RAD. All available biopsies from these patients were reviewed by two independent specialists.

Results: Mean age at MCD diagnosis was 58.6 years and median time period between the diagnosis of MCD and amyloidosis was 1 year (range 2 weeks to 10 years). MCD was diagnosed in the absence of EM in 13 of 29 cases. EM pictures were subsequently obtained/ reviewed in 9 such cases, all of which showed fibrils typical of amyloid. MCD was diagnosed in the absence of CR staining in 17 cases which was diagnostic of amyloid in each of 13 cases that were retrospectively stained. The mean number of renal biopsies taken prior to reaching a diagnosis was 1.6. The overriding reason for reviewing or repeating renal biopsies was steroid-resistance of proteinuria, which averaged 7.8 g/24hr at presentation.
Conclusions: This analysis clearly demonstrates the importance of undertaking EM and CR staining in adults with NS and the value of reviewing original biopsies with EM and CR prior to undertaking another renal biopsy. Early diagnosis of amyloid is likely to limit morbidity and mortality associated with a prolonged nephrotic state, progression of untreated amyloidosis and repeated renal biopsies.

Funding: Government Support - Non-U.S.

TH-PO982
Medullary Epithelial Mass Morphometry in Human Renal Biopsies: Progressive Injury and Relationship to Cortical Epithelial Mass

Alton Brad Farm,1 Diane H. Lawson,1 Cynthia Na Cohen,1 Seymour Rosen.2
1Emory Univ; 2Harvard Univ/Beth Israel Deaconess Medical Center.

Background: The outer medulla has two major zones: outer stripe (OS) and inner stripe (IS). OS cellular mass is primarily formed by proximal tubules and is limited in extent. IS consists of an epithelial cell mass (EPCM) formed mostly by thick ascending limbs and collecting ducts. OS and IS zonal delineation depends on recognizing corticomedullary junction connective tissue/vascular components, adjacent OS, and vasa recta. To characterize injury in these regions, we conducted a morphometric study.

Methods: Consecutive native renal biopsies (n=37) were examined; and the sole inclusion criteria was the availability of medulla (primarily outer medulla). Trichrome, PAS, and cytookeratin (CK) immunostained slides were digitally scanned to obtain whole slide images. For the entire cortex and entire medulla, EPCM was quantitated using a positive pixel count algorithm tuned to detect the brown chromogen of the CK stain and the red staining of trichrome. In addition, pathologist visual assessment was recorded for % tubular atrophy (%TA) and % composed of EPCM.

Results: The EPCM (mean±standard deviation [SD]) of the cortex and medulla, respectively, were 61±12% and 45±12% on trichrome; 55±11% and 53±11% on CK, and 46±24%; and 24±15% on pathologist assessment. Cortical and medullary EPCM declined together, with linear regression showing direct relationships between cortical and medullary EPCM by trichrome (r=0.64 between cortex and medulla, p<0.0001) and CK (r=0.87, p<0.0001). The OS and IS width was 1.7±0.9 and 4.7±2.7 mm (mean±SD), respectively. Notably, IS width inversely correlated with trichrome EPCM (r=-0.64, p<0.0001 for all tissue and r=-0.58, p=0.002 for the medulla).

Conclusions: Medullary and cortical EPCM are related, diminishing together. Furthermore, IS expansion is associated with reduced EPCM. Thus, as epithelial cell elements are lost, reactive/fibrotic responses cause interstitial expansion and IS zonal widening. Analyzing and quantitating EPCM in medullary injury may provide a unique perspective to examine human chronic kidney disease.

TH-PO983
The NEPTUNE Digital Pathology Morphologic Profiling of Nephrotic Syndrome L. Barisoni,1 C. Avila-Casado,2 A. Gaism,2 J. Troost,2 S. Bagnasco,2 J.B. Hodgins,2 J. Charles Jennette,2 D.B. Johnstone,2 Jeffrey B. Kopp,2 Catherine M. Conway,2 Stephen M. Hewitt,2 Cynthia C. Nast,2 U Miami, NEPTUNE.

Background: Pathologic classifications of nephrotic syndrome historically have been performed by light microscopy using known diagnostic entities. The Nephrotic Syndrome Study Network (NEPTUNE) has taken a novel approach by a) applying digital pathology review on renal biopsy whole slide imaging (WSI) and immunofluorescence (IF) and electron microscopy (EM) digital images from FSGS, MCD and MN patients; b) morphologically profiling renal biopsies using “descriptors” of injury for all renal compartments. Methods: We defined 49 histologic, 10 IF and 14 EM descriptors. Glomerular histologic descriptors were applied to individually identified, digitally-annotated multilevel-reconstructed glomeruli. As proof of concept and to test descriptor-based profiling reproducibility of WSI and digital EM images, podocyte descriptors (see table) were evaluated in 133 FSGS/MCD/MC biopsies by 3 pathologists: junior, mid-career and senior (P1, P2 & P3). We used Kendall’s coefficient of concordance to measure inter-reader reliability on an ordinal scale across all 3 pathologists as well as pairwise comparisons between each pathologist.

Results:

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Kendall’s coefficient of concordance for each comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effacement</td>
<td>0.6 (P&lt;0.001)</td>
</tr>
<tr>
<td>Cytoskeletal condensation</td>
<td>0.64</td>
</tr>
<tr>
<td>Microvillous transformation</td>
<td>0.74</td>
</tr>
<tr>
<td>von or primary successors</td>
<td>0.94</td>
</tr>
<tr>
<td>P1 vs. P2</td>
<td>0.50</td>
</tr>
<tr>
<td>P1 vs. P3</td>
<td>0.70</td>
</tr>
<tr>
<td>P2 vs. P3</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Conclusions: NEPTUNE descriptor-based morphologic profiling applied to a web-based information system provides comprehensive analysis of renal structures. Preliminary inter-observer reproducibility ranges from excellent (effacement) to good (loss of primary processes), independently from the reader experience. The granularity of morphologic profiling may improve correlation with clinical and molecular signatures, provide more robust information regarding the significance of specific lesions for prognosis and therapeutic response, and set the bases for new classification systems.

Funding: NIHDK Support, Other NIH Support - ORDR, Private Foundation Support

TH-PO984
Granulomatous Interstitial Nephritis Secondary to Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Samih H. Nasr,1 Tait Shanafelt,2 Curtis Hanson,3 Sanjeev Sethi,4 Lynn D. Cornell,5 Mary E. Fidler,6 Nelson Leung.

Mayo Clinic.

Background: Granulomatous interstitial nephritis (GIN) is an uncommon lesion with a native kidney biopsy incidence of 6%. Established causes of GIN include drug hypersensitivity, infection (particularly fungi), sarcoidosis, and TNF® syndrome. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has not been previously recognized as a potential cause of GIN.

Methods: We report the clinicopathologic findings and outcome of 4 CLL/SLL patients who developed GIN.

Results: The cohort consisted of 2 males and 2 females, all Caucasians, with a mean age of 72.8 years at renal biopsy. CLL/SLL was diagnosed concurrently with GIN in 1 patient and 2-8 years prior to GIN in the remaining 3. CLL/SLL stage at the time of GIN diagnosis was 0 in 2 patients, 1 in 3, and 1 on 3. All patients presented with severe renal impairment with mean serum creatinine at renal biopsy of 4.7 mg/dl. Three patients had leukocyturia and 1 hematuria.

Histologically, all cases showed interstitial inflammation (diffuse in 3 and patchy in 1), lymphocytic tubulitis, non-necrotizing granulomas with multinucleated giant cells, and focal acute tubular injury. Interstitial eosinophils were not prominent in any case. In one case, the granulomatous reaction also involved arteries. Focal interstitial involvement by CLL/SLL was noted in 3 cases. One patient also had granulomatous reaction in skin lesions and lymph nodes.

GIN was treated with steroids alone in 2, steroids and cyclophosphamide in 1, and sequential treatments with steroids, cyclophosphamide, rituximab, vincristine, and alemtuzumab in 1. Duration of follow up ranged from 2 to 66 months. All 4 patients had a partial response to therapy (mean follow up serum creatinine 2.6 mg/dl, mean decrease in serum creatinine 5.1 mg/dl). One patient had multiple relapses of GIN occurring during CLL/SLL flares which responded to lymphoma chemotherapy.

Conclusions: We report a novel association between GIN and CLL/SLL. GIN secondary to CLL/SLL may occur with or without interstitial lymphomatous infiltration and extranodal granulomatous reaction. Steroids (with or without lymphoma directed chemotherapy) leads to partial improvement of kidney function.

TH-PO985
Day Case Renal Biopsy: Single Centre Experience Roshni Rathore, Renal Medicine, Royal Preston Hospital, Preston, United Kingdom.

Background: There has been an increase in number of renal biopsies being performed on an outpatient basis in recent years. Day case renal biopsy offers advantage of patients being discharged home same day. We aim to look at our practice in the last 3 years at Royal Preston Hospital, specifically looking at minor and major complications, biopsies with adequate tissue yield, patients discharged home same day and mean length of stay if admission was required.

Methods: We retrospectively analysed 312 renal biopsies done between 2010-2012. Data was gathered using Quadramed system and histopathology database. Percutaneous renal biopsies were performed under ultrasound guidance using spring loaded biopsy gun. Data was gathered using Quadramed system and histopathology database. Percutaneous renal biopsies were performed under ultrasound guidance using spring loaded biopsy gun. Data was gathered using Quadramed system and histopathology database. Minor complications included death, loss of kidney or life-threatening haemorrhage. If complication occurred for transfusion or intervention was regarded as major complication. Serious complications included death, loss of kidney or life-threatening haemorrhage. If complication occurred after discharge, it was regarded as a delayed complication.

Results: Number of biopsies has increased with each consecutive year. In more than 93% of biopsies, adequate tissue yield was obtained. While minor complications increased as data was gathered using Quadramed system and histopathology database. Percutaneous renal biopsies were performed under ultrasound guidance using spring loaded biopsy gun. Data was gathered using Quadramed system and histopathology database. Minor complications included death, loss of kidney or life-threatening haemorrhage. If complication occurred for transfusion or intervention was regarded as major complication. Serious complications included death, loss of kidney or life-threatening haemorrhage. If complication occurred after discharge, it was regarded as a delayed complication.

Conclusions: If patients suitable for day case renal biopsy are selected using set criteria, there are more likely to be safely discharged from day case unit on the same day. If haematuria warrants inpatient admission, overnight stay is sufficient for most of the patients. With ultrasound guided technique using automated biopsy gun, number of complications is small and the diagnostic yield is reasonably good. Therefore, day case renal biopsy remains a safe procedure in majority of patients.
Critical Analysis of the Pseudocapsule after Robotic Assisted Enucleation Partial Nephrectomy

Mari M. Picken,1 Gopal N. Gupta,2 Pathology, Loyola Univ Medical Center, Maywood, IL; 2Urology, Loyola Univ Medical Center, Maywood, IL.

Background: The optimal surgical margin for small renal masses (SRMs) is 5 mm. Enucleation of SRMs is gaining acceptance as it maximally preserves nephrons and allows for zero warm ischemia time. However, there remains a concern about the oncologic adequacy of enucleated nephromas. Our objective was to critically examine the pseudocapsule of 7 consecutive SRMs treated with robotic assisted off clamp enucleation.

Methods: We retrospectively examined 7 consecutive SRMs that were enucleated utilizing a robotic assisted enucleation partial nephrectomy technique without hilar clamping. The tumor pseudocapsule was used to guide the extirpation. Specimens were reviewed by a genitourinary pathologist with particular attention to pseudocapsule characteristics.

Results: Mean pathologic tumor size was 3.1 cm (range 1.2–5.6 cm); clear cell RCC x4, papillary type II RCC x2, renal oncocytoma x1. Surgical margins were negative on all patients. The mean thickness of the pseudocapsule was 0.05 mm (range 0.02-0.15 mm). The pseudocapsule is made of compressed kidney tissue which creates a plane of dissection that can be seen microscopically.

Conclusions: The ideal treatment of a SRM would be maximally nephron sparing with no warm ischemia time and be performed with minimally invasive techniques. Robotic assisted enucleation partial nephrectomy accomplishes these goals. It is important for surgeons and pathologists to understand the characteristics of the pseudocapsule which constitutes the oncological margin. Further study is warranted.

Angiotensin II-Regulated Proteins in Human Kidney Cells as Markers of renal AngII activity and a Potential Biomarker of Early Diabetic Nephropathy

Ana Konvalinka,1 Susan B. Gurley,3 Thomas M. Coffman,1 Shao-Ling Zhang,4 Rohan John,5 Eleftherios P. Diamandis,2 Pathology, Loyola Univ Medical Center, Maywood, IL; 2Pathology, Loyola Univ Medical Center, Maywood, IL.

Background: Angiotensin II-Regulated Proteins in Human Kidney Cells as Markers of renal AngII activity and a Potential Biomarker of Early Diabetic Nephropathy

Methods: We utilized stable isotope labelling with amino acids (SILAC) in PTECs to compare proteomes of AngII-treated and control cells. Our top hits were validated in decreased AngII-exposed cell lines and in vivo in wild type and AT-1R knock-out mice. Furthermore, HO-1 kidney expression and urinary exosomes were examined in diabetic patients.

Results: Mean pathologic tumor size was 3.1 cm (range 1.2–5.6 cm); clear cell RCC x4, papillary type II RCC x2, renal oncocytoma x1. Surgical margins were negative on all patients. The mean thickness of the pseudocapsule was 0.05 mm (range 0.02-0.15 mm). The pseudocapsule is made of compressed kidney tissue which creates a plane of dissection that can be seen microscopically.

Conclusions: Our in vitro approach identified novel markers of AngII activity and the animal studies demonstrated that these markers are relevant in vivo. These interesting proteins hold promise as specific markers of renal AngII activity in patients and in experimental models.
TH-PO990

**Plasma Pro-Enkephalin Is Associated with Acute Kidney Injury in Critically Ill Patients and Is Not Influenced by Sepsis**
Joachim Streck,1 Rossella Marino,2 Olle Melander,3 Andreas Bergmann,1 Salvatore Di Somma,2 Sphingotec GmbH, Hennigsdorf, Germany; 3‘Sant’Andrea Hospital, Rome, Italy; 1‘Skåne Univ Hospital, Malmö, Sweden.

**Background:** Novel biomarkers for the detection of Acute Kidney Injury (AKI) in critically ill patients have not been established in clinical routine, as they are not sufficiently accurate, influenced by inflammation and/or detectable only in urine. Opioid receptors are highly expressed in the kidney, but it is not known, whether Enkephalin is associated with kidney function.

**Methods:** 101 consecutive ED patients with the final diagnosis sepsis, severe sepsis or septic shock were enrolled. Plasma samples were obtained on ED admission and on the following day. The 7 day mortality rate was monitored. Patients were categorized for severity of AKI according to the RIFLE criteria. Plasma Pro-Enkephalin (pro-ENK), a stable surrogate marker of the unstable Enkephalin stemming from the same precursor peptide, was measured by a novel immunoenassy. For comparison, pro-ENK was measured in a large general population cohort (n=4453).

**Results:** In the general population the mean pro-ENK concentration was 44 pmol/L and the 99th percentile was 80 pmol/L. Pro-ENK was negatively correlated with eGFR (r=-0.33, p<0.0001). Key characteristics of the ED cohort were: median age: 78 y; final diagnosis severe sepsis or septic shock: 29%; 7 day mortality rate: 28%. Pro-ENK was negatively correlated with creatinine clearance (r=-0.74, p<0.0001) and was associated with 7 day mortality rate (survivors: 75 [47-124] pmol/L; non-survivors: 209 [77-499] pmol/L; p<0.001), whereas creatinine clearance was only borderline significant (p=0.071). Multivariate analysis revealed creatinine clearance to be by far the strongest determinant of pro-ENK (partial R^2=0.17). Pro-ENK increased with severity of AKI (RIFLE staging; ANOVA p<0.0001). Importantly, pro-ENK levels in patients without kidney dysfunction or only risk were essentially in the normal range. In contrast, NGAL was markedly elevated over normal already in patients without kidney dysfunction.

**Conclusions:** Pro-ENK is a new plasma biomarker for AKI severity and independent from SIRS and infection.

---

**TH-PO991**

**The Proteome-Transcriptome-Combined Database of Kidney Distal Tubular Proteins for Novel Urinary Biomarker Discovery**
Hidehiko Fujinaka,1 Tadashi Yamamoto,2 1Institute for Clinical Research, Niigata National Hospital, Kashiwazaki, Niigata, Japan; 2Structural Pathology, Institute of Nephrology, Niigata Univ, Niigata, Japan.

**Background:** Several proteins have been proposed as new urinary biomarkers of kidney injuries, but they do not always identify the injured sites of kidney nephron segments. The aim of the present study is to discover new urinary biomarkers which identify the injured sites as distal tubule cells.

**Methods:** The proteome-transcriptome combined database was developed with 3 databases; the human protein atlas (immunohistochemistry, http://www.proteinatlas.org/), the microarray database of human kidney (Fujinaka, Nephropathy 2010), and the urinary proteome database (http://141.61.102.16/urine/). By the atlas database, kidney proteins of distal tubules of mouse and humans were collected. Then, kidney expressions of the human protein atlas were compared between proximal tubules and distal tubules. By the microarray database, expression patterns of the urinary proteome database were observed. Through this combined database, a large number of bands were compared with urinary protein expressions. By combining this database, new urinary biomarkers for kidney distal tubule injuries were targeted.

**Results:** In rat kidney cortices of UUO, mRNA expressions of 8 genes such as CAGP and ANXA3 were decreased, while 3 genes such as CALB1 were increased. Among them, the % change of the CALB1 mRNA was the most prominent. CALB1 protein expression in the kidney distal nephron segment was decreased extremely in UUO and gradually in rat anti-GBM GN. The urinary CALB1 protein levels of the anti-GBM GN rats were decreased concomitantly with the reduction in the kidney cortices. The human IgAN patients displayed decreased CALB1 protein expression in their distal tubules, and some patients displayed decreased urinary calbindin 1 levels.

**Conclusions:** Our proteome-transcriptome combined database may be a good tool to discover new urinary biomarkers which identify distal tubule injuries.

---

**TH-PO992**

**Galectin-3, a Biomarker of Cardiovascular Risk, Inversely Correlates with eGFR**
George Tidmarsh,1 Pablo E. Pergola,2 Bhuipinder Singh,1 James RoIke,1 Stacey Ruiz,1 Gerard John Smits,2 Geoffrey A. Block,1 La Jolla Pharmaceutical Company, Inc, San Diego, CA; 2Clinical Advancement Center, San Antonio, TX; 3Southwest Kidney Institute, Tempe, AZ; 4Balboa Nephrology Medical Group, La Mesa, CA; 5CSC, Inc, Santa Barbara, CA; 6Denver Nephrology, Denver, CO.

**Background:** Galectin-3 is an important fibrosis mediator, is clinically regarded as a marker of CV risk. It has been proposed to correlate with kidney function in patients with CV disease, however, alterations in patients without CV disease have not been studied.

**Methods:** We evaluated the relationship between galectin-3 and kidney function in a retrospective study of 99 subjects with an eGFR <20 to >90 mL/min/1.73m^2 and in a prospective study of 26 patients with an eGFR of 15 to 50 mL/min/1.73m^2. Galectin-3 was measured using an ELISA that exhibits no cross-reactivity with collagens or other galectin family members.

**Results:** In the retrospective study, galectin-3 and eGFR showed a significant inverse correlation (Figure 1A; r=-0.74, p<0.001). In the prospective study, a significant inverse correlation was also observed (Figure 1B; r=-0.56, p=0.003). No statistically significant difference between galectin-3 and eGFR was observed when comparing both retrospective and prospective data. Mean galectin-3 levels in subjects with eGFR >90 were 15±3.8 ng/mL. Using a threshold of 24 ng/mL (2 SD above the mean), 43% of subjects with eGFR 40-49 had elevated galectin-3 while 93% with eGFR <20 had elevated galectin-3. For reference, congestive heart failure patients are considered to be at highest risk when serum levels are >25.9 ng/mL.

**Conclusions:** We find that serum galectin-3 is substantially elevated in the setting of even mildly reduced eGFR. Mean values of galectin-3 were markedly elevated in individuals with eGFR <50. Prognostic utility of measuring galectin-3 remains to be validated in CKD and interventions aimed at reducing galectin-3 are of critical interest.

---

**TH-PO993**

**Plasma α-Klotho Levels and Its Clinical Implications in Patients with IgA Nephropathy**
Hidenori Yamazaki,1 Fumihiro Tomoda,2 Kota Kakeshita,1 Taizo Nakagawa,1 Tsutomu Koike,1 Satoshi Kagitani,2 Hiroshi Inoue.2 The Second Dept of Internal Medicine, Univ of Toyama, Toyama, Japan.

**Background:** α-Klotho has protective actions against renal injury and its renal expression has been demonstrated to decrease in many experimental models of kidney disease. However, circulating α-Klotho levels and its clinical implications remained to be elucidated in human renal disease. In the present study, plasma α-Klotho levels in patients with IgA nephropathy and its relationship to disease severity were evaluated.

**Methods:** Twenty-seven patients with IgA nephropathy were enrolled into the study. Plasma circulating α-Klotho was measured using that commercial assay kit (Immuno-Biological Laboratories Co., Ltd., Gunma, Japan). The disease severity was estimated by effective GFR (eGFR), urinary protein excretion and histological injury score using Oxford classification.

**Results:** Plasma α-Klotho correlated negatively with eGFR (r= 0.438, p=0.022) and positively with urinary protein excretion (r=0.549, p=0.003). Thus, the decrease in plasma α-Klotho was associated with reduced renal function and worsening of proteinuria in IgA nephropathy. Stepwise multiple regression analysis identified plasma α-Klotho as independent determinant factor for urinary protein excretion (R^2= 0.706), but not eGFR.

**Conclusions:** Plasma α-Klotho showed circulating α-Klotho as a novel surrogate marker for severity of IgA nephropathy.

---

**TH-PO994**

**Near-Infrared Fluorophore ZW800-1: A Potential Marker of Glomerular Filtration Rate (GFR)**
Michael Hutchens,1 Mizuko Ikeda,1 Hak Soo Choi,1 Sharon Anderson.2 1Anesthesiology & Perioperative Medicine, OHSU, Portland, OR; 2Nephrology & Hypertension, OHSU, Portland, OR; 3Hematology/Oncology, BIDMC, Boston, MA.

**Background:** Noninvasive measurements of GFR using clearance of fluorescein-isothiocyanate–inulin (FITCI) and -sinistrin have been reported, but FITC use in injured animals may be limited by temperature- and pH-dependent fluorescence and hemoglobin absorption.2 ZW800-1 is a stable, zwitterionic fluorophore, MW 943Da, which is eliminated almost entirely in urine.3 We hypothesized that elimination of ZW800-1 would be similar to elimination of FITC.

**Methods:** C57BL/6 mice were used. Group 1: procedurally naïve mice received a jugular catheter under isoflurane anesthesia. On the imaging stage of a whole-animal imager, mice were injected with 11.5 μg of ZW800-1 and 10 mg of FITC diluted in 300 μL of 0.9% saline. Images were acquired via the 800nm filter every 5m for 120m. Blood was collected via tail artery at 55,75,95, and 120m and analyzed for FITC fluorescence.
after physiologic buffering. Groups 2&3: the above was performed 24h after cardiac arrest and cardiopulmonary resuscitation (CA/CPR) or in naïve controls. FITC and ZW800-1 disappearance curves were fit. Results: ZW800-1/FITC coinjection was well tolerated. FITC and ZW800-1 disappearance curves were similar. clearance is correlated with inulin clearance in mice with and without renal injury. ZW800-1 Garcia-Buitrago, 3 Phillip Ruiz, 3 Gaston E. Zilleruelo. 1

studied the expression of these proteins in human glomerulonephritis. von Willebrand factor (vWf) are implicated to renal scaring and glomerulosclerosis, and matrix expansion, increased expression of PAI-1 is an ominous finding for renal function, as transforming growth factor-β1 (TGF-β1) were measured by colorimetric assays. Prussian blue was used to identify intracellular hemosiderin in urine. Albuminuria was associated to the urine biomarkers by Pearson and Spearman correlation. Results: Participants were classified into two groups based on the presence or absence of albuminuria. Significant differences between two groups by t-test is noted in the table. Patients with albuminuria were more likely positive for urine hemosiderin, and had significantly higher KIM-1 and NAG to urine creatinine ratios.

<table>
<thead>
<tr>
<th>Parameter, units</th>
<th>Albuminuria (N=19)</th>
<th>No albuminuria (N=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin urine creat, mg/dl</td>
<td>0.33±0.73</td>
<td>0.3±0.21</td>
<td>0.004</td>
</tr>
<tr>
<td>NAG urine creat, unit/g</td>
<td>3.32±2.96</td>
<td>2.76±1.94</td>
<td>0.008</td>
</tr>
</tbody>
</table>
| ET-1 urine creat, pg/ml | 3.02±2.96 | 1.0±1.94 | 0.01 destructive inflammatory fibrosis. Serum creatinine level, 24-H urinary protein excretion and other laboratory data were also collected. PAI-1 and vWf intraglomerular deposition was assessed immunochemically and expressed semiquantitavely on a 0-3 scale (normal, mild, moderate and severe respectively). 11 normal kidney samples were used as controls. Results: Glomerular PAI-1 and vWf staining scores in glomerulonephritic samples were markedly higher compared to controls. Samples with moderate deposition of PAI-1 had higher levels of glomerulosclerosis (4.0±1.813%), compared to samples with no (1.1±16.5%) or mild (2.1±14.7%) staining (p<0.001). Moderate/intense level of interstitial fibrosis was found in all specimens with moderate staining for PAI-1, but in only 18.8% of samples with normal staining (p<0.001). Serum creatinine level was significantly higher (3.4±2.173 mg/dl) in patients with moderate deposition of PAI-1, comparing to patients with no (1.4±1.3 mg/dl) or mild (1.5±0.6 mg/dl) deposition (p<0.001).

Conclusions: PAI-1 and vWf are deposited intraglomerularly and probably cooperate at human GN. Increased expression of PAI-1 is an ominous finding for renal function, as it is implicated to matrix expansion, fibrosis and glomerulosclerosis.

TH-P0996

Urinary Screening for Kidney Injury Biomarkers in Children and Adults with Sickle Cell Disease with and without Albuminuria Ofelia A. Alvarez, 1 Dima Hamidi, 1 Vimal Master Sankar Raj, 1 Thomas Harrington, 1 Monica T. Garcia-Buitrago, 1 Phillip Ruiz, 2 Gaston E. Zilleruelo. 1 Dept of Pediatrics, Univ of Miami, Miami, FL; 1 Dept of Internal Medicine, Univ of Miami, Miami, FL; 1 Dept of Pathology, Univ of Miami, Miami, FL.

Background: Renal involvement in sickle cell disease (SCD) manifest in several forms. Presence of albuminuria is considered a hallmark of sickle cell nephropathy. The objective of this study was to evaluate kidney injury (KI) biomarkers in urine which could predict onset of sickle cell nephropathy.

Methods: We measured KI biomarkers in random urine samples of 38 children and adults with SCD with or without albuminuria in a cross-sectional analysis. Kidney injury molecule 1 (KIM-1), N-acetyl-b-D-glucosaminidase (NAG), endothelin-1 (ET-1), and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Circulating suPAR in Japanese Patients with Glomerular Diseases: A Multicenter Cross-Sectional Study
Takehiko Wada,1,2 Masaomi Nagakura,1,2 Shoichi Maruyama,1,3 Enyu Imai,1 Kumi Shoji,1 Sawako Kato,1 Tomomi Endo,1 Eri Murao,1 Kouju Kamata,1 Hitoshi Yokoyama,1 Keiji Fujimoto,1 Yuko Oba,1 Tomoya Nishino,1 Hideki Kato,1 Shunya Uchida,1 Yoshiie Sasamoto,1 Takao Saito,1 Seiichi Matsuo,3 1Division of Nephrology and Endocrinology, Univ of Tokyo, Tokyo, Japan; 2Japanese Renal Nephrotic Syndrome Study Investigators, Japan.

Background: Elevated serum soluble urokinase receptor (suPAR) levels have been described in several glomerular diseases (FGSD) patients in several different cohorts. However, it still remains to be determined if this is the case for Japanese patients and if circulating suPAR can be clinically useful as a diagnostic marker.

Methods: We measured serum suPAR levels in 70 Japanese patients with biopsy-proven glomerular diseases from 8 hospitals in a cross-sectional manner, using a commercially-available ELISA kit. We also analyzed the association between the suPAR levels and clinical/histological parameters obtained from medical record.

Results: The suPAR levels show a significant positive correlation with age (R=0.15, p=0.001) and negative correlation with eGFR (R=-0.32, p=0.0001). After excluding patients with low eGFR (<60 mL/min/1.73m2), the difference in suPAR levels between the diseases was not significant. Analyses based on receiver operating characteristics (ROC) curve revealed that the serum suPAR level was not a potent clinical measure as a diagnostic marker. In a different cohort, patients with ANCA-associated glomerulonephritis had remarkably higher levels of serum suPAR (679±1153 pg/mL) compared with all of the primary glomerular diseases, which may be associated with inflammation and renal impairment.

Conclusions: Data in the current study suggest that suPAR may be accumulated in the serum with renal functional decline. For patients with normal renal function, the difference of suPAR values was not significant among primary glomerular diseases. Assessment of statistical measures based on ROC curve analysis showed that the suPAR level has little value as a diagnostic biomarker.

Fund: Government Support - Non-U.S.

The Role of Inflammatory Marker MRP8/14 in CKD Patients
Tatsuki Minamata,1 Sansa Minamata,1 Yoshinori Taniguchi,1 Yoshiko Shimamura,1 Koike Inoue,1 Taro Horino,1 Kazu Hamada,1 Yoshio Terada,1 Kenji Yuasa,2 Shinpei Fujimoto,1 Koji Oga,1 1Kochi Univ, Nankoku, Japan; 2Kochi-Takasui Hospital, Kochi, Japan.

Background: Myeloid-Related Protein 8/14 complex (MRP8/14) is an endogenic ligand of toll-like receptor (TLR)-4, and is considered to be an inflammatory marker. Although it has been reported that MRP8/14 related to arteriosclerosis and coronary lesion in type 2 diabetes, there are no reports about the relationship between MRP8/14 and chronic kidney disease (CKD).

We studied the association between MRP8/14 levels and renal function or the other parameter in CKD.

Methods: A total of 432 patients (mean age 60±17) with CKD were enrolled. Serum samples were collected, and MRP8/14 levels were measured by using ELISA kit. Serum creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), urine protein/Cr ratio, and the patient's history of diabetes were collected. MRP8/14 levels were inversely associated with serum Cr (p=0.007, r=0.135), BUN (p=0.011, r=0.135), UA (p=0.011, r=0.137), and body mass index (BMI) (p=0.001, r=0.212), and Body Mass Index (BMI) (p=0.001, r=0.189).

Results: MRP8/14 levels were inversely associated with serum Cr (p=0.007, r=0.135), BUN (p=0.011, r=0.135), UA (p=0.011, r=0.137), and body mass index (BMI) (p=0.001, r=0.212), and Body Mass Index (BMI) (p=0.001, r=0.189).

Conclusions: MRP8/14 levels were positively associated with serum Cr (p=0.007, r=0.135), BUN (p=0.011, r=0.135), UA (p=0.011, r=0.137), and body mass index (BMI) (p=0.001, r=0.212), and Body Mass Index (BMI) (p=0.001, r=0.189).

We have demonstrated that increased expression of LMW, and especially MRP8/14, is a reliable quantitative and non-invasive marker which may independently predict the extent of interstitial fibrosis. The aim of our study was to evaluate the diagnostic performance of the measurement of urinary concentration of low and high molecular weight proteins in estimating the extent of interstitial fibrosis.

Methods: The urine of 189 consecutive patients who underwent renal biopsy in the Nephrology Department of the Georges Pompidou European Hospital were analyzed. Kidney transplant recipients or patients with acute kidney injury were excluded. The percentage of IF was assessed using a numerical quantification software based on the colorimetric analysis of fibrosis areas. Urinary biochemical analyses were performed to determine total proteinuria, albuminuria, microalbuminuria, as well as urinary levels of retinol binding protein (RBP), alpha-1-microglobulin (α1MG), beta 2 microglobulin (β2MG), transferrin, and Igα/μmuglobulins.

Results: We found a significant correlation between the degree of IF and RBP/creat ratio (R2=0.11, p<0.0001). In a lesser extent IF was associated with urinary β2MG and α1MG, but not with total proteinuria or with high molecular weight proteinuria. The correlation of interstitial fibrosis with RBP/creat remained significant after adjustment with estimated glomerular filtration rate, age, body mass index, α1MG and β2MG. The RBP/creat ratio was significantly higher in patients with IF> 30% when compared with patients with FI<30% (16.6 ± 3.6 mg vs 4.8 mg/gj1.g, p<0.0007).

Conclusions: We have demonstrated that increased expression of LMW, and especially MRP8/14, is a reliable quantitative and non-invasive marker which may independently predict the extent of kidney IF. The fact that urinary RBP dosage is available in nearly all clinical chemistry departments is appealing for its implementation in the routine care of CKD patients.
**TH-PO1003**

Combined Cyclosporine and Prednisolone Therapy in Adult Patients with New-Onset Minimal-Change Nephrotic Syndrome

- **Authors:** Lawrence B. Holzman, Crystal A. Gadegbeku, John R. Sedor, J. Troost, Peter Ichikawa, Kayori Tsuruoka, Naohiko Imai, Yugo Shibagaki, Tsutomu Sakurada, Enyu Imai, Sayuri Shirai, Daisuke Sakagami, Shido Inoue, Masahiro Ishii, and Ichiro Okazaki

- **Methods:** Patients with new-onset of MCNS were randomly assigned to two groups, namely, the CyA group (about 2mg/kg; C2:600-1200 mg/dL) + PSL (0.5 mg/kg/d day) group (n = 10) and the PSL alone (PSL: 0.8 mg/kg/d day) group (n = 10), and the clinical characteristics were compared between two groups. All patients used C2 for CyA monitoring.

- **Results:** There were no significant difference of relapse rates among both group. The duration of a single dose of rituximab administered in the CyA group (CR) preservation was longer than that in the PSL group (565 days). CyA was lower than that in relapsing group (829ng/ml) in the CyA+PSL group. Incidence rate of side effect in the CyA+PSL group was higher than that in the PSL group.

- **Conclusions:** The combined cyclosporine and prednisolone therapy obtained longer CR preservation and reduced the PSL dose and side effects in adult patients with new-onset MCNS.

<table>
<thead>
<tr>
<th>Results:</th>
<th>18 yrs</th>
<th>18 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34(0-35)</td>
<td>32(0-35)</td>
</tr>
<tr>
<td>Black*</td>
<td>4(0-29)</td>
<td>4(0-29)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8(0-50)</td>
<td>8(0-50)</td>
</tr>
<tr>
<td>Disease duration (m)</td>
<td>3(1-19)</td>
<td>3(1-19)</td>
</tr>
<tr>
<td>Relapse</td>
<td>8(0-35)</td>
<td>8(0-35)</td>
</tr>
<tr>
<td>CyA + PSL</td>
<td>605(490-1119.9)</td>
<td>389(320.2-95)</td>
</tr>
<tr>
<td>PSL</td>
<td>25(12-422)</td>
<td>25(12-422)</td>
</tr>
<tr>
<td>C</td>
<td>32(24-41)</td>
<td>33(24-41)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.9(2.4-3.7)</td>
<td>2.9(2.4-3.7)</td>
</tr>
</tbody>
</table>

---

**TH-PO1004**

Study of Single-Dose Rituximab at an Interval of 6 Months during 24-Month Period on Steroid-Dependent Minimal-Change Nephrotic Syndrome in Adults

- **Authors:** Yuko Iwabuchi, Takashi Takei, Takahito Moriyama, Kosaku Nitta, Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan.

- **Background:** Steroid dependent minimal-change nephrotic syndrome (MCNS) necessitates administration of prolonged courses of prednisolone, therefore, a paradigm shift from such toxic "non-specific" therapies to selective immunomodulating regimens is necessary for these cases.

- **Methods:** To assess the therapeutic effects of rituximab (an anti-CD20 antibody) in adult patients with steroid-dependent MCNS, we performed a prospective trial of the effects of a single dose of rituximab administered at an interval of 6 months in 27 MCNS patients. We evaluated the biochemical parameters and compared the clinical findings between the 24-month period before and 24-month period after the first rituximab infusion.

- **Results:** Significant reduction in the total number of relapses was observed during the 24-month period after the first rituximab infusion as compared with the findings during the 24-month period before the first rituximab infusion (110(100%) vs 8(7%), p<0.001). Twenty-one of 25 patients with prednisolone at the first rituximab were able to discontinue prednisolone after 24-month period (p=0.001). Complete remission was induced/maintained in all patients under ongoing B-cell depletion.

- **Conclusions:** Our results revealed that rituximab therapy was associated with reduction in the number of relapses and in the total dose of prednisolone needed. Therefore, rituximab appears to be a useful therapeutic agent for adult patients with steroid-dependent MCNS.

**TH-PO1005**

Nephrotic Syndrome Study Network Baseline Cohort

- **Authors:** Debbie S. Gibson, Lawrence B. Holzman, Crystal A. Gadegbeku, John R. Sedor, Peter Troost, Peter X.K. Song, Daniel C. Catran, Fernando C. Fervenza, Patrick H. Nachman, Frederick J. Kaskel, Marva M. Moxey-Mims, Matthias Kretzler. Nephrotic Syndrome Study Network.

- **Background:** The Nephrotic Syndrome (NS) Study Network (NEPTUNE) is an ongoing longitudinal observational study. Here we introduce the NEPTUNE cohort.

- **Methods:** Eligibility: proteinuria >500 mg/d and initial renal biopsy. Comparison of the initial 361 subjects with baseline data and histology are compared between children and adults using two-sample t or chi-square tests. Continuous variables are presented as mean (25,75th 'interile' and frequencies as n(%) of cases. HTN is defined as BP>140/90 for adults and >95th %tile for children. eGFR was calculated using CKD-Epi or CKiD equations.

**TH-PO1006**

Clinicopathological Characterization of Minimal Change Disease with Glomerular Foam Cell Infiltration

- **Authors:** Emiko Fujita, Akira Sairou, Akiko Miwa, Megumi Fuku, Shuichi Tsuruoka, Dept of Nephrology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan; Dept of Pathology, Nippon Medical School, Bunkyo-ku, Tokyo.

- **Background:** Minimal change disease (MCD) is a major idopathic nephrotic syndrome. It is defined pathologically as glomerular disease with minimal or no glomerular alterations, no glomerular immune deposits, and extensive effacement of podocyte foot processes.

- **Methods:** In the present study, we examined renal biopsies of MCD in our department between 1990 and 2013, selected the cases of MCD with or without glomerular FC infiltration, and assessed the clinicopathological characteristics of these cases.

- **Results:** In 312 biopsies with a diagnosis of MCD, glomerular FC infiltration was detected in 10 cases (3.2%) (FC+ group). In histopathology, glomerular endothelial cell injuries were present in all FC+ cases that were characterized by narrowing capillaries, increased number of endothelial cells, swelling of endothelial cells with loss of fenestra, separation of endothelial cells from capillary basement membrane with subendothelial edema, and macrophage infiltration in subendothelial and mesangial areas. In clinical findings, compared to FC- group, FC+ group showed that age of biopsy was older (46.2±22.0 vs 21.7±17.6, p<0.01), the selectivity index of urinary protein was lower (0.15±0.12 vs 0.07±0.10, p<0.05), systolic blood pressure was higher (134.4±26.0 vs 118.0±7.2, p<0.05), high frequency of complications including diabetes mellitus (2 cases), hypertension (40% vs 17%), and limited response to steroid therapy (partial remission in 2 cases), but there was no significant in serum LDL-cholesterol level between two groups.

- **Conclusions:** FC infiltration in MCD may be associated with the presence of glomerular endothelial cell injuries and macrophage infiltration into subendothelial and mesangial areas in milieu of nephrotic syndrome. MCD cases with glomerular FC infiltration may include the cases of incomplete remission after steroid therapy.

**TH-PO1007**

Resistance to Immunosuppressive Therapy in Patients with Primary Nephrotic Syndrome: Japan Nephrotic Syndrome Cohort Study (JNSCS)

- **Authors:** Kyohsei Yamamoto, Shoichi Maruyama, Hiroshi Yokoyama, Seichi Matsumoto, Enyu Imai. Geriatric Medicine and Nephrology, Osaka Univ, Suita, Osaka, Japan; Nephrology, Nagoya Univ, Nagoya, Aichi, Japan; Nephrology, Kanazawa Medical Univ, Uchinada-Cho, Ishikawa, Japan.

- **Background:** In primary nephrotic syndrome (NS), little information is available about the prevalence of resistance to immunosuppressive therapy (IS) and the optimal time to diagnose the resistance to IS.

- **Methods:** Study design and setting: A nationwide prospective cohort study including 57 nephrology centers in Japan. Patients: Between 2008 and 2010, 396 primary NS patients were diagnosed by kidney biopsy as primary NS and were registered in JNSCS. The present study included 281 JNSCS participants with >3.5 g/day of the baseline urinary protein

---

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

Underline represents presenting author/disclosure.
(UP) at initiating IS. Outcome: Partial remission (PR) defined as UP <3.5 g/day. Statistics: 90% and 95% distribution of time to PR in minimal change disease (MCD), membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS) and others were assessed.

Results: Median baseline ages of MCD (n=134), MN, (n=98), FSGS (n=30) and others (n=16) were 39 (range 12-81), 65 (14-84), 59 (20-83) and 49 (14-83) year, respectively. During median 13 days (range 2-1122) of the observational period, 100%, 88%, 83% and 84% achieved PR, and their cumulative probabilities of the resistance to IS at the final observation were 0.00, 0.08, 0.13 and 0.14.

Among 261 patients with PR, 90% (95%) time to PR were 29 (59), 207 (242), 66 (207) and 30 (60) days. Initial immunosuppressive drugs administered within 1 month were corticosteroid and, in some patients, cyclosporin (11%, 46%, 40% and 32%). Only 5 MN patients received cyclophosphamide.

Conclusions: Approximately 10% of primary NS were resistant to IS except MCD. Optimal time to diagnose the resistance may be 1-2, 7-8, 2-7, and 1-2 months in MCD, MN, FSGS and others.

Funding: Government Support - Non-U.S.

TH-PO1008

Oxidative Stress Markers in the Urine from Pediatric Patients with Nephrotic Syndrome Yaeko Motoyoshi, Tomohiro Udagawa, Eriko Tanaka. Pediatrics, Tokyo Medical and Dental Univ, Bunkyo-ku, Tokyo, Japan.

Background: Oxidative stress has been shown to be involved in the renal damage especially in diabetes mellitus (DM). Beside DM, we previously found that massive urinary protein is reabsorbed by proximal tubule cells via megalin, and induces Heme oxygenase-1 (HO-1) in a mouse model of nephrotic syndrome (Kidney Int 74: 1262). However, oxidative stress in human patients with nephrotic syndrome has not yet been well studied. The aim of this study is to show that when large amount of protein is filtrated through glomeruli, proximal tubule cells require a great deal of energy to decompose the protein, and oxidative stress is produced according to the dose of urinary protein.

Methods: Urine was collected from 9 nephrotic syndrome patients (one to ten years old), every day from development or relapse of the disease until remission. 2 steroid sensitive, 4 steroid dependent, and 3 steroid resistant patients were included to this study. Their peak urinary protein /creatinine ratio (g/g) was 20.0-136.5. Oxidative stress markers and urinary protein/cre ratio. In contrast, urinary L-FABP/Cre ratio was 1.8-fold higher and urinary SOD activity/Cre ratio was 2.0-fold higher in steroid resistant group compared with steroid dependent group. 3 markers were elevated in nephrotic syndrome patients with massive proteinuria. L-FABP excretion increased, then decreased at almost the same time as total protein change. Value of 8-OHdG and SOD activity ascended after urinary protein started to decrease in most patients.

Conclusions: Although there was no correlation between 3 markers and the dose of urinary protein, we speculate that L-FABP excretion increased, reflecting tubular damage induced by massive urinary protein. SOD activity elevated to neutralize oxidative stress caused by urinary protein, and 8-OHdG excretion increased at last to repair DNA damage.

Funding: Private Foundation Support

TH-PO1009

Nephrotic Range Proteinuria Has No Significant Effect on Probability of CD19 Depletion following Rituximab Treatment Emily Glover, Alan D. Salama, Aine Burns. 1 Centre for Nephrology Royal Free NHS Trust; 2Univ College London.

Background: Rituximab is used to treat an increasing number of autoimmune conditions. It is an expensive treatment and different units use different frequency and dosing regimens.

In our unit, circulating CD19 counts are routinely checked following first infusion to assess effective depletion (CD19 ≤5 x 10^9) and to decide if a further dose is indicated. We have previously demonstrated that response to and duration of depletion using this protocol is similar to other published series in vasculitis patients using much higher doses, such as 1g twice weekly for 4 weeks (Little M, et al. 2013).

We investigated whether there were any factors that could predict who would deplete following our 1st and 2nd doses of Rituximab treatment (375 mg/m²) and importantly whether nephrotic range proteinuria reduced the chance of depletion.

Methods: 101 patients with different diagnoses and ethnicities were treated according to our standard protocol. Age, sex, ethnicity, diagnosis, proteinuria, serum albumin and serum IgG were analysed for predictors of first dose depletion. Of the 79 patients with data on proteinuria, 12 had nephropic range (mean 5.88 g/l; range 4.21 to 13.38 g/l).

Results: Of the 101 patients analysed, 54 depleted (CD19 ≤5 x 10^9) on the 1st infusion, 14 on the 2nd infusion, 18 did not deplete with either the 1st or 2nd infusion and 15 did not deplete on the 1st infusion and did not receive a 2nd infusion. There were 3 adverse drug reactions of which two involved respiratory distress. There was no statistically significant effect of age, sex, ethnicity or diagnosis on depletion. Critically, nephrotic range proteinuria, albumin and IgG had no predictive value for depletion following rituximab treatment.

Conclusions: The finding that nephrotic range proteinuria has no significant effect on probability of CD19 depletion following rituximab treatment is valuable information for reducing the cost of administration as higher doses or longer courses of rituximab would not appear to be indicated in these patients. Little, M et al. 2013. Induction treatment of ANCA associated vasculitis with a single dose of rituximab. Rheumatology (Submitted).

TH-PO1010

Tacrolimus Monotherapy after Short Term Steroid Treatment in Treating Adults with Idiopathic Minimal Change Nephropathy: A Pilot Study Heng Li, Xiayu Li, Jianghua Chen. Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.

Background: Although steroids therapy leading to complete remission in most of patients with minimal change nephropathy (MCN), the wide range side effects of steroids make steroids therapy difficult to be accepted by the patients. This study aimed to observe the efficacy and tolerance of tacrolimus monotherapy after ten days’ steroids treatment in patients with MCN caused nephrotic syndrome.

Methods: In this observational study, 25 patients with MCN were treated with tacrolimus monotherapy (Group A, n = 6) from the beginning or after 10 days’ steroids therapy (Group B, n = 19). Data on serum albumin, proteinuria, serum creatinine, GFR and other biochemical results were collected during the at least 12 months’ follow-up period.

Results: Three of six patients in Group A and all 19 patients in Group B achieved complete remission. Acute renal failure was occurred in two patients in Group A and one patient in Group B. One patient in Group A has no response to tacrolimus monotherapy for more than two months and achieved complete remission after treated with steroid. The adverse effects including gastrointestinal symptoms and pulmonary infections were mild and tolerated by the patients. One patient in Group A and 6 patients in Group B underwent 9 relapses during follow-up period.

Conclusions: Tacrolimus monotherapy after short-term steroid therapy is effective and safe in treating patients with MCN. It may become a novel method to treat MCN patients.

TH-PO1011

Efficacy and Safety of Low-Dose Rituximab on Steroid-Dependent Minimal Change Nephrotic Syndrome in Adults Susumu Uda,1 Keiko Kanemoto,1 Eijin Ashikaga.2 1Div of Nephrology, Kanto Rosai Hospital, Kawasaki, Kanagawa, Japan; 2Div of Nephrology, Yokohama Municipal Citizen’s Hospital, Yokohama, Kanagawa, Japan.

Background: Recently, B cell depleting therapy by rituximab (RTX) has been used successfully to treat therapy for steroid-dependent minimal change nephrotic syndrome (MCN) in adults. However, the most unexpected side-effects and the lack of knowledge regarding the optimal dosage of RTX to MCN patients, it would be useful to limit treatment to these patients. We investigated the effect of low-dose RTX and clinical response in adults with steroid-dependent MCN.

Methods: Data on 7 adults patients receiving single dose of RTX (200mg (range 104-133 mg/m²) IV) for biopsy-proven steroid-dependent MCN after a steroid-induced complete remission and followed over 6-months is presented. Therapy with prednisone and other immune-suppressive drugs was tapered.

Results: To date a total of 8 cases included 1 relapsed patient had been studied (mean age 34±12 years, 6 male and 1 female, mean follow-up time 13±8 months). B cell depletion was found in all cases. At <6 months post-RTX, 7 (88%) cases maintained complete remission, allowing rapid prednisone & immunosuppressive agents taper or discontinuation (100%). Only one B cell depleted case (<5x10^9/L) before RTX infusion relapsed under B cell depletion at 3 week. Two cases (25%) relapsed at 7-12 months after complete recovery of B cell. B cell recovery tendency from depleted state was detectable after 3 to 8 months. Two cases (25%) reached long term remission over 18 months without relapse. An increase of B cells but was not always associated with relapse. No serious side effects were noted.

Conclusions: A single low-dose RTX was effective and safe for sustained complete remission in adult patients with steroid-dependent MCN and maintained 6-months remission in about 90% cases.

Funding: Private Foundation Support
TH-PO1012
Initial Steroid-Sensitivity Is A Highly Sensitive Predictor for Post-Transplant Recurrence of Steroid-Resistant Nephrotic Syndrome
Wen Y. Ding,1 Ania Koziel,1 Agnieszka Bierzynska,1 Hugh J. McCarthy,1 Corinne Antignac,2 Olivia Beyer,2 Moin Saleem.1 1Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom; 2Nephrology, Evelina Children's Hospital, London, United Kingdom; 1Hôpital Necker - Enfants Malades, INSERM, Paris, France.

Background: The post-transplant recurrence risk of paediatic patients with a primary diagnosis of steroid-resistant nephrotic syndrome (SRNS) is between 30 to 50%. Accumulating evidence suggests that SRNS resulting from single gene mutations has no more than an 8% chance of responding to treatment but a significantly reduced risk of post-transplant recurrence. We therefore hypothesised that SRNS that progresses to end-stage renal failure (ESRF) could be classified into 2 categories: 'likely-genetic' - cases treatment-resistant from the outset and resulting from single gene mutations, and 'likely-circulating factor', - cases presenting at times with initial steroid sensitivity before treatment resistance developed. We posed the question whether these two categories might be linked.

Methods: We studied 153 consecutively transplanted patients with SRNS at 3 large paediatric centres in Europe. We compared a number of phenotypic factors including initial steroid-sensitivity, genetic mutations, extra-renal abnormalities and family history.

Results: 55 of 153 children (36%) with SRNS who were transplanted suffered from recurrence. Recurrence occurred in 26/28 (93%) patients who showed initial steroid-sensitivity (p<0.001; OR = 130, 95% CI=6.7 to 2533.3) and 29/125 (23%) patients with primary steroid resistance. No patients with identified genetic mutations, extra-renal abnormalities or a positive family history (n=30) manifested initial steroid sensitivity or recurrence.

Conclusions: Our data indicates that initial steroid-sensitivity is the strongest predictor for post-transplant recurrence described to date, whereas SRNS associated with initial steroid resistance and documented or clinical features of a genetic mutation is highly protective. Clear early differentiation of these patient groups from the outset would enable accurate patient stratification for immunosuppression and transplantation strategies.

TH-PO1013
The Efficacy of Adrenocorticotropic Hormone in Steroid-Dependent Nephrotic Syndrome: Old and New Therapy
Masao Kikuchi,1 Yuji Sato,1 Kazuo Kitamura,1 Shouichi Fujimoto.2 1First Dept of Internal Medicine, Univ of Miyazaki, Miyazaki, Japan; 2Dept of Hemovascular Medicine and Artificial Organs, Univ of Miyazaki, Miyazaki, Japan.

Background: Recently, it has been reported that tacrolimus, mycophenolate mofetil and rituximab are effective therapies for patients with steroid-dependent nephrotic syndrome (SDNS). But, these drugs are off-label use in Japan as well as many countries. Adrenocorticotropic hormone (ACTH), widely used for nephrotic patients in the 1950s, has come under the spotlight for its antiinflammatory, lipid-lowering and renoprotective properties, which are not fully explained by its steroidogenic effects. In addition, ACTH might have the potential to recover adrenocortical suppression with long-term exogenous glucocorticoid therapy. We have reported the efficacy of ACTH in SDNS.

Methods: We treated with ACTH (tetracosactide acetate) for three patients who were diagnosed with minimal glomerular abnormality on the basis of renal biopsy. Although they were treated with steroid pulse therapy, cyclosporine, cyclophosphamide, mizoribine and LDL-apheresis, they relapse easily after the steroid tapering. 0.5-1 mg ACTH was weekly given for them intramuscularly. We assessed their adrenocortical function before and after ACTH therapy.

Results: During the follow up (average 10 months), all three cases achieved complete remission after starting ACTH therapy. Their prednisolone dose could taper from 60.7 mg/day (before ACTH therapy) to 14.3 mg/day (after ACTH therapy). Their remission maintenance percentage of follow-up period increased from 12.3% (before ACTH therapy) to 85.3% (after ACTH therapy). There was no obvious adverse effect. Their responses to the rapid ACTH stimulation test after ACTH therapy recovered 2.8 times compared with those before ACTH therapy.

Conclusions: For ACTH helps steroid tapering and produces a recovery of adrenocortical function, ACTH is an effective therapy for steroid-dependent nephrotic syndrome.

TH-PO1014
The Efficacies of Cyclosporine Combination Therapy on the First Attack of Minimal-Change Nephrotic Syndrome in Adults
Akira Fujiwara,1 Nobuhito Hirawa,2 Muri Katsurama,1 Saana Saha,3 Keisuke Yatsu,1 Yoshiyuki Toy,1 Gen Yasuda,2 Satoshi Umemura.1 1Medical Science and Cardireoan Medicine, Yokohama City Univ School of Medicine, Yokohama, Kanagawa Prefecture, Japan; 2Div of Nephrology and Hypertension, Yokohama City Univ Medical Center, Yokohama, Kanagawa Prefecture, Japan.

Background: A combination of cyclosporine with prednisolone therapy (CPT) has been used as the treatment of frequently relapsing, steroid-dependent, or steroid-resistant minimal-change nephrotic syndrome (MCNS). However, few reports have examined the efficacy of CPT as first line treatment. Therefore, we conducted a retrospective clinical research to evaluate the efficacies and their safety by using CPT in new-onset MCNS in adults.

Methods: Forty-six adult patients with biopsy-proven MCNS, diagnosed for the first time, were analyzed retrospectively. We divided the patients into three groups. In the CPT group (n=17), they were treated with cyclosporine orally (2–3 mg/kg/day) with prednisolone (30 mg/day) after methylprednisolone pulse therapy (0.5 or 1.0 g/day for three days). In the MPF group (n=15), prednisolone (30 mg/day) after intravenous methylprednisolone pulse therapy was employed. The PSL group (n=14) was treated with prednisolone (40–60 mg/day) alone.

Results: Complete remission was obtained in all patients except one in the CPT group. Length of hospitalization was shorter in the CPT group (p<0.05). The average maintenance dosage of prednisolone at 6 months from the start of therapy was significantly low in the CPT group. During the nine months of following up, the CPT group experienced no relapse, whereas the MMP group and the PSL group experienced some relapses. Moreover, the adverse effects were mild and infrequent in the CPT group.

Conclusions: Cyclosporine combination therapy led to shorten the length of hospital stay and reduction of daily prednisolone dosage without severe adverse effects for the first attack adult-onset MCNS patients. Moreover, this combination therapy may be useful in reducing the complete remission in terms of the speed, and in reducing the relapse rates. Cyclosporine combination therapy may be a new treatment option for new-onset MCNS in adults.

TH-PO1015
Clinicopathological Correlates in FSGS: A Single Tertiary Center Study
Maria I. Story,1 Daniele Gomes Holanda,1 Fadi Tohme,2 Ramesh Nair,3 Manish Suneja.2 1Internal Medicine, Univ of Iowa Hospital and Clinics, Iowa City, IA; 2Pathology, Univ of Iowa Hospital and Clinics, Iowa City, IA.

Background: Focal Segmental Glomerulosclerosis (FSGS) is a common pathological finding in kidney biopsies done to evaluate proteinuria. Distinguishing different FSGS pathological variants is helpful in guiding treatments. Guidelines for treating primary and secondary FSGS exist; however, heterogeneity abounds in practice. We investigated the clinical-pathological correlation in adult onset FSGS.

Methods: A retrospective analysis of biopsy proven FSGS between 10/2001 and 12/2009 was done. Patients with recurrent FSGS after transplant, age <16, immune complex glomerulonephritis, and on known nephrotic medications were excluded. All the remaining biopsies were classified according to the Columbia classification. Patients were then classified as either primary or secondary FSGS based on the presence of nephrotic syndrome (serum albumin<3.5, urine P/C ratio>3.5, edema, and hypercholesterolemia) and the pathology was correlated.

Results: 80 patients were initially identified with FSGS based on biopsy reports. After exclusion criteria were applied, we were left with 28 cases. 21 were classified as FSGS NOS, 3 perihilar, 3 collapsing, 1 cellular and 1 tip lesion variant. There were 5 cases of primary FSGS based on presence of nephrotic syndrome (3 collapsing, 1 cellular and 1 tip lesion). All secondary cases were either perihilar (n=3) or FSGS NOS (n=21). Of the cases of secondary FSGS 54% had BMI >30 and 17% had a single kidney. Serum albumin of <3.0 was significantly associated with primary FSGS (p < 0.001). 4 of the 5 primary cases and 3 of the 24 secondary cases were treated with steroids. One of the primarries and eight of the secondaries progressed to ESRD.

Conclusions: At our institution, primary/idopathic FSGS is far less common than secondary FSGS (17% of FSGS biopsies). FSGS NOS, similar to perihilar lesions, is strongly associated with secondary FSGS. This observation is not reported previously. Low albumin is the strongest predictor of primary FSGS (< 0.001). It is important to distinguish between primary and secondary FSGS to avoid unnecessary treatment with immunosuppressive therapy.
Han, Hyung Jung Oh, Seung Hyeok Han, Shin-Wook Kang, Tae-Hyun of FSGS. However, these are not well de or partial remission (PR).

the onset of ESRD. Secondary outcome included the rates of complete remission (CR) was the composite of doubling of baseline serum creatinine concentrations (D-SCr) or

Chandigarh, India.

Glomerulosclerosis

Tacrolimus Therapy in Adults with Steroid Resistant Focal Segmental

TH-PO1017

Clinical Features and Outcomes of Focal Segmental Glomerulosclerosis Pathologic Variants in Korean Adult Patients Young, Eun Kwon, Ji Suk Han, Hyung Jung Oh, Seung Hyoek Han, Shin-Wook Kang, Tae-Hyun Yoo. 1Dept of Internal Medicine, College of Medicine; 2Brain Korea 21, Yonsei Univ, Seoul, Korea.

Background: Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome (NS) and ESRD, particularly in African-Americans. Many studies have shown that clinical characteristics and outcomes differ depending on pathologic variants of FSGS. However, these are not well defined in Asian populations.

Methods: We conducted a retrospective cohort study to evaluate clinical features and outcomes according to pathologic variants of FSGS in 111 adult patients. Primary outcome was the composite of doubling of baseline serum creatinine concentrations (D-SCr) or the onset of ESRD. Secondary outcome included the rates of complete remission (CR) or partial remission (PR).

Results: Not otherwise specified (NOS), tip, perihilar, cellular, and collapsing variants were present in 70 (63.1%), 29 (18.0%), 17 (15.3%), 3 (2.7%), and 1 (0.9%) patients, respectively. Fifty patients (45.0%) presented NS, and among them 47 patients (94.0%) were treated with immunosuppressants. NS were more prevalent in patients with tip lesion than in those with other variants. The overall 5-year and 3-year renal survival rates were 76.8% and 56.3%, respectively. During a median follow-up duration of 34.5 months, only 1 patient (5.0%) with tip lesion reached the composite outcome compared to 2 (11.8%) and 12 patients (17.1%) with perihilar and NOS variants, respectively, but this difference did not reach statistical significance. CR and PR were achieved in 29 (26.1%) and 32 patients (28.8%), respectively. Tip lesion was associated with a significantly increased probability of achieving CR (P = 0.044).

Conclusions: Similar to other populations, Korean adult patients with FSGS had distinct clinical features with the exception of a rare frequency of cellular and collapsing variants. Although pathologic variants were not associated with the overall outcome, tip variant exhibited favorable outcome in terms of achieving CR. Further studies with a larger sample size are required to delineate the long-term outcome and response to treatment according to the pathologic variants.

TH-PO1018

Tacrolimus Therapy in Adults with Steroid Resistant Focal Segmental Glomerulosclerosis Raja Ramachandran, Harbir Singh Kohli, Manish Rathi, Vivekanand Jha, Krishan L. Gupta, Vinay Sachkha. Nephrology, PGIMER, Chandigarh, India.

Background: Management of adults with steroid resistant (SR) focal segmental glomerulosclerosis (FSGS) steroids is a challenging task. Is tacrolimus (Tac) effective in this situation without serious adverse effects? This prospective study was done to answer this question.

Methods: This prospective observational study was done from January 2011 to April 2013. Patients with adult onset (≥18 yrs) FSGS with SR (prednisolone 1 mg/kg/day for at least 16 weeks) were enrolled. In patients with SR-FSGS, oral Tac was started targeting a trough level of 5-10 ng/ml along with oral prednisolone (0.15mg/kg/day). In patients with complete remission at 24 weeks, Tac dose was reduced to target 3-6ng/ml for next 24 weeks and hiked again if there was a relapse, while in partial responders Tac trough levels were kept at 5-10ng/ml for next 24 weeks. However, in patients with no remission at 24 weeks Tac was discontinued. Outcome viz. complete remission (CR) (reduction of proteinuria to <0.3 g/dl and albumin ≥ 3.5g/dl), partial remission (PR) (reduction of proteinuria to 0.3-3.5 g/dl and albumin ≥ 3.5g/dl) were assessed at the end of 24 and 48 weeks. Relapses defined as increased proteinuria after complete or partial remissions were recorded. Adverse effects viz. nephrotoxicity (>25% rise in creatinine), cosmetic effects, infections and impaired fasting glycose were recorded every month and analysed at the end of 48 weeks.

Results: A total of 34 SR-FSGS completed the study. Of 34 patients CR and PR was achieved in 12 (35%) and 05 (15%) patients respectively. Tac resistance was seen in 17 (50%) patients. Time taken to achieve remission was 21.2±12.4 weeks. Two patients had relapse on tapering the dose after 24 weeks. Of 34 patients reversible nephrotoxicity was seen in 6 (17.6%), irreversible nephrotoxicity in 2 (5.8%), Tac related diabetes in 6 (17.6%), infections in 12 (35.2%), impaired glucose tolerance /DM in 10 (29.4%), tremors in 4 (11.7%) and gum hypertrophy in 2 (5.8%).

Conclusions: Tac is a very effective agent in the management of SR-FSGS. However, strict renal function and blood sugar monitoring is required due to its nephrotoxicity and diabetogenic potential.

TH-PO1019


Background: Serum suPAR was recently proposed as a specific biomarker of primary FSGS. However, subsequent studies have shown that eGFR is a major determinant of serum suPAR level in patients with FSGS and non-FSGS CKD. suPAR has a MW of 20-60kDa, which implies free glomerular filtration. Urinary suPAR excretion has been demonstrated. We studied kidney handling of suPAR in patients.

Methods: serum and urine samples of patients with FSGS (n=6) and MN (n=4) were obtained using a standardized protocol for measurement of urinary proteins. Urinary beta-2-microglobulin (b2m) was only measured if pH was >6.0. suPAR was measured with the Quantikine Human suPAR Immunoassay (R&D Systems, Minneapolis, MN). We compared fractional excretions (FE) of suPAR with b2m and albumin. eGFR was calculated with the 4 variable MDRD Study Prediction Equation.

Results: Median eGFR was 50 (IQR 23-71) ml/min/1.73m2, and median proteinuria was 9.3 (IQR 6.6 -15.8) g /10mmol creatinine. Median serum suPAR was 6185 (IQR 343-2150) ng/mmol creatinine in patients with FSGS and 636 (IQR 423-833) ng/mmol creatinine in patients with MN, a non-significant difference. FE-suPAR did not correlate with FE-b2m, a marker of tubular reabsorption (figure). There was also no correlation of FE-suPAR with either FE-albumin or FE-IgG.

Conclusions: suPAR can be detected in urine. There was no evidence for tubular reabsorption of suPAR. FE-suPAR did not correlate with FE-albumin, which suggests that urine suPAR is also not simply a marker of glomerular permeability defect.

TH-PO1020

Soluble Urokinase Receptor Levels in Serum and Urine of Patients with Primary Focal Segmental Glomerulosclerosis and Controls Rutger J. Maas, Jeroen Deegens, Jack F. Wetzels. Nephrology, Radboud Univ Nijmegen Medical Centre, Nijmegen, Netherlands.

Background: Serum suPAR was proposed as a diagnostic marker for primary FSGS and post-transplant FSGS recurrence. However, previous studies have shown a correlation between serum suPAR and eGFR, which is a potential source of bias. We investigated if serum or urinary suPAR levels can distinguish between primary FSGS and controls with comparable eGFR.

Methods: Serum suPAR was measured with the Quantikine Human suPAR Immunoassay (R&D Systems, Minneapolis, MN) in serum and urine of patients with primary FSGS (n=10) and membranous nephropathy (MN); n=5) with nephrotic syndrome, and in dialysis patients with a history of recurrent (n=3) FSGS, and controls (n=7). eGFR was calculated with the 4 variable MDRD Study Prediction Equation.

Results: Median eGFR was 36 (IQR 15-69) ml/min/1.73m2 in patients with primary FSGS and 37 (IQR 22-69) ml/min/1.73m2 in patients with MN. Serum suPAR di did not discriminate between patients with primary FSGS and MN (fig. 1). Median urinary suPAR was 822 (IQR 343-2150) ng/mmol creatinine in patients with FSGS and 636 (IQR 423-833) ng/mmol creatinine in patients with MN, a non-significant difference. In patients on dialysis, serum suPAR did not discriminate between patients with previous posttransplant FSGS recurrence and controls (fig. 1).

Conclusions: Serum and urinary suPAR levels were similar in patients with primary FSGS compared to eGFR-matched controls.
TH-PO1021

Circulating Soluble Urokinase Receptor Levels in Primary Nephrotic Syndrome Predict the Response to Therapy


Background: Circulating soluble urokinase receptor (suPAR) speculated to produce proteinuria and focal segmental glomerulosclerosis (FSGS). However, no studies have investigated the involvement of suPAR in the development of primary nephrotic syndrome (NS) in Japan.

Methods: Circulating suPAR levels were measured by ELISA (R & D system in 36 primary NS cases including 8 FSGS (4 with tip lesion, 2 with NOS type, and 2 with collapsing type), 14 minimal change nephrotic syndrome (MCNS), 12 membranous nephropathy (MN) and 2 membranoproliferative glomerulonephritis (MPGN), and 15 normal controls. Circulating suPAR levels and clinical parameters during the 6 months after immunosuppressive therapy were analyzed. In this study, refractory NS was defined as daily proteinuria did not decrease to < 1 g after 6 months therapy.

Results: Circulating suPAR levels before therapy were significantly higher in NS patients than in normal controls (P <0.05), but not significantly different among those with FSGS, MCNS, MN, or MPGN. There was a significant negative correlation between the circulating suPAR levels and eGFR in the total NS, FSGS, and MCNS groups (total, r = -0.54, p <0.001, n=107; FSGS, r = -0.61, p=0.002, n=31; MCNS, r = -0.54, p=0.003, n=41) and a significant positive correlation between the circulating suPAR levels and CRP (r = 0.79, p<0.001, n=24) or age (r = 0.68, p=0.002, n=21) in MN. In addition, circulating suPAR levels decreased significantly in MCNS from 3,288 to 2,723 pg/ml after 2 months therapy (p<0.03), but not in FSGS or MN. Patients with refractory NS showed higher circulating suPAR levels with a tendency to increase during therapy. ROC analysis showed that refractory NS was defined by more than 3,324 pg/ml and the increase of circulating suPAR levels more than 226 pg/ml at 2 months after therapy (AUC 0.89, p=0.012, AUC 0.85, p=0.027, respectively).

Conclusions: These results suggested that alteration of circulating suPAR level and the levels at 2 months after the therapy reflected the response to therapy in patients with primary NS, even in MCNS.

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

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

Underline represents presenting author/disclosure.

3 patients with FHIMN (19%) developed secondary causes (SLE in 2 patients within 2 years; disseminated Esophageal malignancy in 1 - within 6 months of presentation). One patient with TIMN (2%), developed Esophageal malignancy, 25 months after presentation, whilst in partial remission (p=0.02). A-PLA2Rab was measured in 41 prevalent patients – positive in 5/10 patients with FHIMN (50%) and 21/31 with TIMN (68%) (p=0.029). Development of systemic diseases was recorded. Where archived serum was available, A-PLA2Rab was tested.

Results: 16 patients with FHIMN presented with preserved renal function. Renal survival at median follow up of 50 months was 87%. In comparison to 46 patients with TIMN, there was no significant difference in presentation or renal outcome.

<table>
<thead>
<tr>
<th></th>
<th>Full House IMN</th>
<th>Typical IMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Male %</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Abstract %</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Immunosuppression (%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>63</td>
<td>51</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: FSGS is the most common diagnosis in PR biopsies, but does not appear to be associated with worse long term renal outcomes compared with controls. It is unclear whether pregnancy reveals or causes FSGS, or whether lesions are primary or secondary. Further work is needed to explore this, and to define risk factors for progression in order to optimise antenatal and postpartum management.

TH-PO1023

Clinical Relevance of “Full House Idiopathic Membranous Nephropathy”
Shiv Bhutani, Durga A.K. Kanigicherla, Patrick Hamilton, Rosnithi Rathore, Muntau Patel, Paul E. Brenchley, Michael Venning. Manchester Institute of Nephrology and Transplantation, Central Manchester Univ Hospitals NHS Foundation Trust, Manchester, United Kingdom.

Background: Idiopathic Membranous Nephropathy is typically characterised by IgG and C3 deposits (Typical IMN, TIMN). Variants that include C1q, IgM, IgA (Full House IMN, FHIMN) without secondary causes at presentation are seen. Outcome in this subset is unclear.

Methods: Retrospective analysis of 62 consecutive adult patients with first diagnosis of IMN made by biopsy between 2003 & 2009 at our single center. Remission, CKD-5, and development of systemic diseases was recorded. Where archived serum was available, A-PLA2Rab was tested.

Results: 16 patients with FHIMN presented with preserved renal function. Renal survival at median follow up of 50 months was 87%. In comparison to 46 patients with TIMN, there was no significant difference in presentation or renal outcome.

<table>
<thead>
<tr>
<th></th>
<th>Full House IMN</th>
<th>Typical IMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Male %</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Abstract %</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Immunosuppression (%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>63</td>
<td>51</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: FSGS is the most common diagnosis in PR biopsies, but does not appear to be associated with worse long term renal outcomes compared with controls. It is unclear whether pregnancy reveals or causes FSGS, or whether lesions are primary or secondary. Further work is needed to explore this, and to define risk factors for progression in order to optimise antenatal and postpartum management.

TH-PO1024

Low Serum Albumin and Elevated Serum Creatinine Levels Are Predictors for Thromboembolic Complications in Patients with Membranous Nephropathy
Eliom Hoxha, Ina Ellen Thiele, Gunther Zahnier, Ulf Panzer, Sigrid Harendza, Rolf A. Stahl. III. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

Background: Patients with Membranous Nephropathy (MN) have a high risk to experience thromboembolic complications (TEC). It is currently unclear whether there is a level of albuminuria or serum albumin which predict an increased risk of TEC. Secondly it is also unclear whether there exist differences in the risk for TEC between primary and secondary MN.

Methods: We analyzed in a prospective multicenter study 263 adult patients with MN up to 24 months (64.6% primary MN with PLA2R-Ab positivity; 35.4% secondary MN). Patients were seen every three months for analysis of proteinuria, serum albumin and serum creatinine. TEC were assessed at each visit and categorized in embol of lung arteries, thrombosis of leg veins, central veins, the dialysis fistula or renal venous thrombosis.

<table>
<thead>
<tr>
<th></th>
<th>Full House IMN</th>
<th>Typical IMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Male %</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Abstract %</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Immunosuppression (%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>63</td>
<td>51</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: 3 patients with FHIMN (19%) developed secondary causes (SLE in 2 patients within 2 years; disseminated Esophageal malignancy in 1 - within 6 months of presentation). One patient with TIMN (2%), developed Esophageal malignancy, 25 months after presentation, whilst in partial remission (p=0.02). A-PLA2Rab was measured in 41 prevalent patients – positive in 5/10 patients with FHIMN (50%) and 21/31 with TIMN (68%) (p=0.029). Development of systemic diseases was recorded. Where archived serum was available, A-PLA2Rab was tested. In addition, circulating suPAR levels were measured by ELISA (R & D system) and significantly higher in NS patients than in normal controls (P <0.05), but not significantly different among those with FSGS, MCNS, MN, or MPGN. There was a significant negative correlation between the circulating suPAR levels and eGFR in the total NS, FSGS, and MCNS groups (total, r = -0.54, p <0.001, n=107; FSGS, r = -0.61, p=0.002, n=31; MCNS, r = -0.54, p=0.003, n=41) and a significant positive correlation between the circulating suPAR levels and CRP (r = 0.79, p<0.001, n=24) or age (r = 0.68, p=0.002, n=21) in MN. In addition, circulating suPAR levels decreased significantly in MCNS from 3,288 to 2,723 pg/ml after 2 months therapy (p<0.03), but not in FSGS or MN. Patients with refractory NS showed higher circulating suPAR levels with a tendency to increase during therapy. ROC analysis showed that refractory NS was defined by more than 3,324 pg/ml and the increase of circulating suPAR levels more than 226 pg/ml at 2 months after therapy (AUC 0.89, p=0.012, AUC 0.85, p=0.027, respectively).

Conclusions: These results suggested that alteration of circulating suPAR level and the levels at 2 months after the therapy reflected the response to therapy in patients with primary NS, even in MCNS.

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

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

Underline represents presenting author/disclosure.
Membranous Nephropathy after Allogeneic Hematopoietic Stem Cell Transplantation
Rikako Hiramatsu, Yoshifumi Ubara, Keiichi Sumida, Tatsuya Suwabe, Junichi Hoshino. Nephrology Center, Toranomon Hospital, Tokyo, Minato-ku, Japan.

Background: Renal involvement in patients with chronic graft-versus-host disease (cGVHD), presenting as nephritic syndrome, is rare following hematopoietic stem cell transplantation (HSCT). The most frequent form of post-HSCT glomerulonephritis is membranous nephropathy (MN); but data on its clinicopathological features and long-term outcome are scarce.

Methods: From 2000 to 2012, the clinical characteristics, pathological features, and long-term outcome were evaluated in 5 patients with MN after HSCT. Kidney biopsies were analyzed by light microscopy (LM), immunofluorescence (IF), electron microscopy (EM), and IgG subclasses in glomerular deposits were identified.

Results: All patients had a history of cGVHD, with active cGVHD prior to MN diagnosis. Mean time between HSCT and diagnosis of MN was 21.8 months (range: 9–33). Serum creatinine was 1.0 mg/dl (0.8 to 1.3). Discoid IgG4 nephritidic immunosuppressants prior to MN onset was a consistent feature, occurring at a median of 12.6 months (range: 2–25) before onset. Significant proteinuria (mean; 8.40 g/day, range; 5.93–13.0) was common. LM did not detect definite spike formation in capillary lumens. EM revealed subepithelial and intramembranous deposits, as well as mesangial deposits with extensive podocyte foot process effacement. Subepithelial deposits were segmental, small and electron-lucent. If showed that IgG1 and IgG4 were the predominant IgG subclasses in glomerular deposits, which were negative for C3. All MN cases were initially treated with corticosteroids, resulting in complete remission (CR) at a median of 12.2 months (range: 5–24). Long-term follow up at a median of 92.4 months (range; 38–144) showed that relapse of MN paralleling the evolution of cGVHD occurred in 2 patients at 43 and 27 months after initial CR. One patient developed end-stage renal failure requiring hemodialysis.

Conclusions: This series of 5 patients with post-HSCT MN is the largest study so far. Initial response to treatment was favorable, but careful observation for MN relapse parallel to cGVHD evolution, and long-term renal monitoring, are necessary.

Funding: Government Support - Non-U.S.
determine risk factors, competing risk regression analysis was performed with relevant covariates at baseline. A severity score of nephrotic syndrome (NS) determined by proteinuria (≥3.5 g/day) and/or hypoalbuminemia (≤2.5 g/dL) at each visit was used as a time-dependent variable.

Results: 32 CVE occurred in a median of 8 m (IQR 3-29), 69% within 2 years. Cumulative incidence rates of CVE, ESKD, and death in the entire cohort were 5.7%, 8.9%, and 2.2%, respectively, at 2 years and 9.1%, 19.4%, and 4% at 5 years, respectively. Among patients with baseline eGFR ≥60 ml/min, the risk of CVE [4.2% (95% CI 1.5-6.8)] exceeded that of ESKD [2.5% (0-5)] by 2 years; but not when eGFR <60 ml/min, [8% (3.6-12.4)] vs. 18.6% (12-25), respectively. The severity of NS (HR 2.19), previous CVE, diabetes mellitus and age were significant risk factors of CVE after adjusting for smoking and UKD stages.

Conclusions: Early after diagnosis, the risk for CVE is similar to that of ESKD, and is greater than ESKD in patients with preserved renal function. CVE are an important complication of MN and may be as relevant an outcome measure as ESKD. CVE are associated with the severity of NS and traditional risk factors.

TH-PO1030
Development and Evaluation of a Patient-Reported Outcome (PRO) Measure for Idiopathic Membranous Nephropathy (IMN): The Membranous Nephropathy Quality of Life Tool (MNQoL)
Christine Barrett,1 Jane E. De Vries,1 Rachel B. Jones,2 Lynda C. Doward,1 Patrick Hamilton,1 Michael Venning,1 GlaxoSmithKline plc,1 Vasculitis Unit, Addenbrooke’s Hospital, Cambridge; 2RTI-Health Solutions, Manchester; 3Manchester Institute of Nephrology and Transplantation, Manchester Royal Infirmary, United Kingdom.

Background: Regulators such as the FDA recognise that the patient perspective is important in evaluating new treatments for IMN. No PRO measures currently exist specific for nephrotic states including IMN. Our objective was to develop a new PRO tool, for use in IMN studies as an exploratory endpoint alongside the Kidney Disease Quality of Life 36 item survey (KDQoL-36), and to evaluate content validity of both tools.

Methods: Patient interviews (n=4) and a literature review yielded 12 key symptoms of IMN. A 14-item MNQoL was developed with 5 response levels asking the degree of bother associated with each symptom, treatment side effects and the quantity of medicines taken to treat IMN. Cognitive debriefing was conducted with a new IMN patient sample (n=9) to determine content validity and ease of completion of the MNQoL and KDQoL-36 (study HO-12-955).

Results: Patients debriefed were 6M/3F, with median age=51/range 39-68, 4 active disease/5 remitted (partial or complete), mean years since diagnosis=6.3/SD 6.7 and mean serum creatinine was 1.07mg/dl. Six studies used western blot and four used immuno fluorescence. Sensitivity of anti-PLA2R testing ranged from 66-98% and specificity from 84-100%. Using the median value of IMN incidence in patients with nephrotic range proteinuria obtained from published literature (2%), PPV and NPV ranged from 92%-100% and 78-96%, respectively.

Conclusions: Our findings indicate that serum testing for anti-PLA2R is an important diagnostic tool in the evaluation of patients with nephrotic range proteinuria with a high sensitivity, specificity, and at expected incidence levels, a high positive and negative predictive value for IMN.

TH-PO1032
Cirulating TNF Receptors Is a Significant Prognostic Biomarker for Idiopathic Membranous Nephropathy with Nephrotic Syndrome
Seun Mi Lee,1 Hyun Seop Cho,2 Dong Ki Kim,2 Yun Kyu Oh,2 Chun Soo Lim,3 Shin-Wook Kang,1 Jung Pyo Lee,1 Yun So Kim.1 1Seoul National Univ Hospital; 2Cheju Halla General Hospital; 3Cheju National Univ Boramae Medical Center; 4College of Medicine, BK21, Yonsei Univ.

Background: Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. There is no secure biomarker that can indicate the severity and predict the long-term prognosis of the MN. The aim of this study is to evaluate the clinical significance of TNF receptors (TNFRs) as a prognostic marker.

Methods: 94 patients had MN with nephrotic range proteinuria at the time of biopsy were enrolled. Circulating TNFR levels were measured using serum samples stored at the time of biopsy. The primary clinical endpoint was a remission. Secondary outcome was the decline of estimated glomerular filtration rate (eGFR; ≥30% decline compared to baseline).

Results: At the time of biopsy, eGFR and proteinuria worsened proportionally as circulating TNFR1 and TNFR2 increased (p<0.001). 73 of 94 patients reached primary outcome. Compared to non-responder group, responder group had significantly lower TNFR levels (TNFR1: 1.07±0.67 vs. 2.37±1.54, P=0.033). However, there was no significant difference of TNFR2 between responder and non-responder (475±10.2 vs 2215.38 ± 7865.10 =2106.0, P=0.074). The risk of reaching the secondary endpoint was significantly higher in the in the highest quartile of TNFR1 or TNFR2 compared with other quartiles by the Kaplan Meier method (P=0.001 and P<0.001, respectively). Highest TNFR1 was a significant risk factor for the secondary endpoint after adjusting for age, sex, amount of proteinuria, eGFR, treatment, and presence of remission (Hazard Ratio [HR] 1.51, 95% confidence interval [CI] 1.4-2.02, P=0.005). Highest TNFR2 was also statistically significant (HR 1.50, 95% CI 1.2-2.00, P=0.007).

Conclusions: This study showed circulating TNFR1 could predict remission. In addition, circulating TNFR1 and TNFR 2 could predict progression of CKD in patients with MN. Further studies would be needed to establish the role of circulating TNFRs to reflect the responsiveness of specific treatment.

TH-PO1033
Tacrolimus in Membranous Nephropathy
Paula Jara Caro Espada, Elena Gutierrez-Solis, Jorge Enrique Rojas-Rivera, Manuel Praga. GLOSEN (Spanish Group for Study of Glomerular Diseases).

Background: Tacrolimus (TAC) monotherapy has shown to be effective in the treatment of idiopathic membranous nephropathy (IMN), but observational studies involving a larger number of patients have not been published.

Methods: We performed a retrospective analysis of all IMN patients treated with TAC in 12 Spanish Hospitals. Primary outcomes were complete (CR) or partial (PR) remission. Secondary outcomes were relapses after TAC withdrawal and safety and tolerance to treatment.

Results: 122 patients were included. Median interval between renal biopsy and TAC treatment was 9 months (7-30). 43 patients (35%) had received other immunosuppressive treatments. Initial TAC dose was 0.0489±0.12 mg/kg/day and only 10 patients were treated simultaneously with corticosteroids (CS). Mean duration of TAC treatment was 17±7 months, including a full-dose TAC period (12±5 months) and a tapering period (5±4). CR
or PR were achieved in 103 patients (84%). Non-responder patients (n=19) showed a non-significant trend for higher proteinuria and worse renal function at the onset of TAC than responders. Among responders, 60 patients (58%) achieved PR and 43 (42%) CR. Patients who achieved CR had a significantly higher percentage of females (44 vs. 21%; p<0.015), a shorter time to remission (3 v 6 mos; p<0.018), and a lower proteinuria (6.7±3.2 vs 8.8±3.9 g/day; p<0.005) and serum creatinine (9.0±2 vs 11±3 mg/dl; p<0.0001) at baseline than PR patients. No influence of Cs on the rate of remission was observed. TAC was well tolerated. Nephrotoxicity, leading to TAC withdrawal, was observed in 4 cases (3%), and minor/transient side effects in 21 patients (17.2%). After 30 (14-66 month) months of follow-up, 44% of patients who had achieved CR/PR, relapsed. Median time to relapse after TAC withdrawal was 9.5 months (3-62). Relapses were significantly more common among patients who had received Cs (8% vs 0%). Patients who relapsed showed a higher although non-significant proteinuria (1.96±1.76 vs. 1.19±1.16 g/day; p=0.051) at the onset of TAC tapering.

**Conclusions:** TAC monotherapy induced a high number of remissions in IMN and was well tolerated. New strategies for avoiding frequent relapses after TAC withdrawal should be investigated.

**TH-PO1034**

**Tacrolimus in Treating Hepatitis B Virus Associated Membranous Nephropathy with Nephritic Syndrome Who Failed Antiviral Monotherapy**

**Jianghua Chen. The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Kidney Disease Center, Hangzhou, Zhejiang Province, China.**

**Background:** Hepatitis B virus associated membranous nephropathy (HBV-MN) may lead to renal failure in a significant proportion of patients and spontaneous remission is rare. Although antiviral treatment such as lamivudine is considered to improve renal outcome, its potential therapeutic impact on HBV-MN has not been characterized. When a proportion of patient with HBV-MN are resistant to antiviral therapy, it is a challenge to find other therapies that are effective.

**Methods:** This prospective observational study enrolled 14 adult patients with HBV-MN and nephrititic syndrome who were no response to therapy with at least 3 months of lamivudine therapy. All had rise in Scr.

**Results:** Following 24 weeks of therapy, Eight of 14 patients (57.1%) had complete remission (CR) and 4 of 14 patients (28.6%) had complete remission (PR). The mean time to partial remission and complete remission was 6.8 ± 4.7 weeks and 11.5 ± 6.6 weeks, respectively. Two patients developed resistance to TAC therapy due to no response with persistent severe proteinuria after 16 weeks of TAC therapy 3 (25%) of 12 patients who achieved remission experienced relapses during follow-up. Renal function remained stable in all patients with complete remission or partial remission. 1 of 2 non-responder progressed to doubling their baseline Scr. Elevation of AST occurred in 2 (14.3%), and 2 (14.3%) of 14 patients. The marker for HBsAg of all patients did not change during follow-up.

**Conclusions:** The regimen of tacrolimus combined with low dose prednisone seems to be effective and safety in treating patients with HBV-MN and nephrititic syndrome who failed lamivudine monotherapy.

**TH-PO1035**

**Efficacy and Safety of Rituximab Plus Cyclosporine in Idiopathic Membranous Nephropathy: Results of an Ongoing Prospective Trial**

**Meryl A. Waldman, Michelle Braun, Howard A. Austin. NIDDK/Kidney Disease Section, National Institute of Health, Bethesda, MD.**

**Background:** Cyclosporine (CsA) has efficacy in reducing proteinuria in idiopathic membranous nephropathy (IMN) but partial remissions (PR), rather than complete (CR) are more common and relapse upon drug withdrawal is problematic. Extending treatment may increase remissions and reduce relapses but potential for nephrotoxicity exists. Rituximab (RTXx) monotherapy has shown promise in IMN but PRs are more common and effect on proteinuria tends to be delayed. We are conducting a prospective phase 2 trial in 30 pts with IMN to investigate whether “induction” with RTX + CsA for 6 mos followed by “maintenance” RTX may achieve greater reduction in proteinuria than either agent alone, increase number of remissions (especially CR) & reduce relapse rates. Here we report interim data.

**Methods:** Patients with IMN, persistent high grade proteinuria despite conservative rx for min 6 mos & eGFR ≥40 ml/min/1.73 m² receive RTX (1 gm d 1, 15) + CsA 6 mos, then tapered. A 2nd course of RTX is given after min of 6 mos & evidence of B cell recovery.

**Results:** To date, 11 pts are enrolled. Mean CrCl61 ml/min/38 ±90; Mean proteinuria 11.9 g/d. Of 8 pts with minimum of 12 mos follow up, all showed response; 4 (50%) CR (defin:protein reduction ≥50% & ≤3.5 g/d); 4 (50%) CR (≤0.3 g/d), 1 pt relapsed after achieving PR.

<table>
<thead>
<tr>
<th>n</th>
<th>Baseline proteinuria ≤24hr</th>
<th>12 mos</th>
<th>12 mos</th>
<th>12 mos</th>
<th>18-20 mos</th>
<th>24 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>10.5</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>4.1</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>3.9</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>9.9</td>
<td>5.1</td>
<td>5.1</td>
<td>5.1</td>
<td>5.1</td>
<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td>9.8</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>9.6</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>12.6</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>12.6</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>5.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>0</td>
<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Regimen was well tolerated.

**Conclusions:** “Induction” with RTX + CsA followed by “maintenance” RTX may be a treatment approach for IMN to achieve a greater number of remissions and may obviate the need for long term immunosuppression. It appears to be well tolerated. Enrollment continues and longer term follow up is needed.

**Funding:** NIDDK Support

**TH-PO1036**

**Thrombotic Microangiopathy in Metastatic Melanoma Patients Treated with Adoptive Cell Therapy and Total Body Irradiation**

**Meryl A. Waldman, Jennifer Tseng, Michael S. Ring, Howard A. Austin, James Yang, James E. Balow. NIDDK/Kidney Disease Section, National Institute of Health; NCRI, National Institute of Health.**

**Background:** Adoptive cell therapy (ACT) using ex-vivo expanded autologous tumor infiltrating lymphocytes can mediate the regression of bulky metastatic melanoma when administered with high-dose IL-2 following a lymphodepleting preparative regimen of cyclophosphamide & fludarabine. A series of trials showed that addition of total body irradiation (TBI) 12 Gy to regimen led to improved response rates & survival. However a complication encountered after TBI was thrombotic microangiopathy (TMA). Here we report incidence & course of TMA after TBI.

**Methods:** In the pilot trial, all pts received ACT with TLI + IL2 following non-myeloablative chemo & 12 Gy TBI. The RCT randomizes patients to ACT/ chemo regimen with or without TBI. Dxs of TMA made by kidney bx in 3 pts; subsequently dx based on clinical presentation (new onset hemolytic anemia, rise in Scr &LDH, dec pltts & haptoglobin).

**Results:** 25 pts enrolled in the pilot trial. To date, 89 pts enrolled in the RCT, 44 in TBI arm. Of 69 pts exposed to TBI in both trials, 16 (23%) were dx’d with TMA. No pts without exposure to TBI dev TMA. Median time to dx was 8 mos after TBI (range 4-12). All had rise in Scr.

**Conclusions:** Thrombotic microangiopathy is a complication of total body irradiation and occurred in almost 25% of pts exposed to 12 Gy dose. Although hematologic abnormalities are self limiting, most are left with residual renal dysfunction, proteinuria and persistent hypertension.

**Funding:** NIDDK Support, Other NIH Support - National Cancer Institute

**TH-PO1037**

**Rituximab-Induced Continuous B Cell Depletion for Durable Remission in 28 Consecutive Patients with Idiopathic Membranous Nephropathy**

**William Franklin Pendergraft, Charles T. Owens, Andrew P. Murphy, Colin M. Berry, Karen A. Laliberte, John Niles. Joint Nephrology Fellowship Program, Massachusetts General Hospital (MGH) and Brigham and Women's Hospital, Boston, MA; Div of Nephrology, MGH, Boston, MA; Vasculitis and Glomerulonephritis Clinic, MGH, Boston, MA.**

**Background:** Great strides have been made with respect to the pathogenesis of idiopathic membranous nephropathy, and numerous groups are now actively working to develop an optimal strategy for induction and maintenance of remission. Induction therapy
with chlorambucil and corticosteroids appears to be more effective than with calcineurin inhibitors; however, rituximab may be more efficacious. We report here our experience to date with the management of the disease.

Methods: We performed a retrospective analysis of clinical data from patients with biopsy-proven idiopathic membranous treated by our group with continuous B cell depletion.

Results: 28 patients (50% women) received induction of remission therapy for idiopathic membranous nephropathy. All patients received corticosteroids. 15 patients received cyclophosphamide and rituximab. Mean duration of therapy was 172 days (S.D. 139). Mean spot urine protein to urine creatinine ratios went from 9.0 (S.D. 4.8) at the start of therapy to 2.5 (S.D. 2.8). 13 patients received rituximab without concomitant cyclophosphamide. Mean duration of therapy was 361 days (S.D. 117). Mean spot urine protein to urine creatinine ratios went from 5.1 (S.D. 3.3) at the start of therapy to 2.3 (S.D. 3.1). One patient in the rituximab and corticosteroids group died five months into therapy after being institutionalized for advanced Alzheimer’s. One patient developed GCSF-responsive neutropenia.

Conclusions: Over the past year, our group has seen a dramatic rise in the number of new cases. Induction therapy with cyclophosphamide, corticosteroids and rituximab was more effective than corticosteroids and rituximab alone in reducing proteinuria despite shorter overall duration of continuous B cell depletion. These preliminary results suggest that induction therapy with cyclophosphamide in the setting of B cell depletion may provide more rapid and complete induction of remission.

Funding: Clinical Revenue Support

TH-PO1038
Rituximab Therapy in Idiopathic Membranous Nephropathy with Poor Response to Tacrolimus: Long Term Follow Up
Montserrat M Diaz Encarnacion, Nephrology, Fundacion Puigvert, Barcelona, Spain.

Background: It is still unknown in which patients with idiopathic membranous (MN) Rituximab (RTX) could be a useful therapy.

Methods: In this study 17 patients with MN were included and met the following criteria: persistence of nephrotic syndrome (NS) after 6-8 months treatment with angiotensin II blockade and poor response to tacrolimus (Tc) (target level: 5-7ng/ml). RTX is introduced in case of persistence of NS after 4 months period of treatment with Tc (6 patients), partial response (PR) (at 46±26 meses; 9 patients) and relapse or renal failure during Tc treatment (2 patients). 1 g of RTX was administered on day 1, 15 and every 6 months according to the response. Antibodies anti-PLA2R, B lymphocytes, renal function, proteinuria and serum albumin were evaluated at entry and at months 3, 6, 12, and 24.

Results: 11/17 patients were available at the end of the follow up (5 deaths and 2 patients lost follow up). 6/7 patients with a GFR<60ml/mn/1,73m2 improved their GFR (16±11ml/mn/ 1,73m2) in 5/9 patients with PR achieved CR

Conclusions: At the end of follow up 8 patients presented a CR, 8 a PR (proteinuria = 0.7±0.4 g/d), 1 a NS. RTX achieved a P or CR in 90% of patients with poor response to Tc. This response is still persisting after 16 months of follow up.

TH-PO1039
Long-Term Treatment of Idiopathic Membranous Nephropathy Based on Cyclosorine and Steroid-Free Regime: A Single Center Experience
Camila Barbosa L. Oliveira, Alline S. A. Oliveira, Carla Queiroz Neves, Clarissa Jacobo, Bernadette Carvalho, Luis H.B.C. Sette, Giselle Vajgel Fernandes, Maria Alina Cavalcante, Lucila Maria Valente. Nefrologia, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil.

Background: Cyclosporine A (CyA) is an effective treatment for idiopathic membranous nephropathy (IMN) but the optimal dose and duration remains controversial. We aim to evaluate the effect of CyA as induction and long-term treatment for nephrotic patients with IMN.

Methods: Adult patients with IMN and nephrotic syndrome (NS) between 1997 and 2012 were evaluated. CyA was used for patients: NS > 6 months or proteinuria > 8 g/day or deteriorating renal function, at a dose of 3 mg/Kg/day without steroids.

Results: Demographic, clinical and prognostic characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Treated N= 33</th>
<th>Not Treated N= 12</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, year</td>
<td>39.7 ± 17.4</td>
<td>48.0 ± 17.4</td>
<td>1.68</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>21 (63.6)</td>
<td>(58.3)</td>
<td>0.503</td>
</tr>
<tr>
<td>UPCR (mg/dL)</td>
<td>1.1 (0.5)</td>
<td>1.9 (0.4)</td>
<td>1.279</td>
</tr>
<tr>
<td>SCR, mg/dL</td>
<td>1.3 (0.8)</td>
<td>1.9 (1.3)</td>
<td>0.330</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td>0.722</td>
</tr>
<tr>
<td>Proteinuria, g/day</td>
<td>3.2 ± 6.4</td>
<td>8 ± 3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>23 (69.7)</td>
<td>(58.8)</td>
<td>0.722</td>
</tr>
</tbody>
</table>

Conclusions: RTX could be a useful therapy for patient with poor response or resistant to calcineurins inhibitors therapy.

TH-PO1040
A Retrospective Analysis of Patients with Idiopathic Membranous Nephropathy Treated with Steroids and Intravenous Cyclophosphamide in the Modified Ponticelli regimen
Robin Ramphul, Raja Mohammed Kaja Kamal, David Makanjuola, Rebecca Suckling, Fiona E. Harris, Bhrijiraj Roy Sood. Renal Unit, St. Helier Hospital, Carshalton, Surrey, United Kingdom.

Background: The use of steroids and oral Cyclophosphamide in the modified Ponticelli regimen is a recognised treatment for patients with idiopathic membranous nephropathy however the role of intravenous cyclophosphamide for this indication is poorly described.

Methods: Data on creatinine, albumin and urine protein to creatinine ratio (UPCR) were collected. All patients included were followed-up for at least 6 months. Treatment failure was defined as ESRD, doubling of serum creatinine, switch to, or introduction of alternative immunosuppression. Complete remission (CR) was defined as a reduction in UPCR to < 50mg/mmol. Partial remission (PR) was defined as a reduction in UPCR to < 350mg/mmol and a 50% or greater reduction in UPCR.

Results: There were 12 men, age 68yrs (range 37 – 79); 1 died within 12 months. 10 patients had stable renal function, 2 doubled their serum creatinine and progressed to ESRD after 24 months. The mean UPCR reduced over the course of follow-up (mean UPCR at baseline = 1128.2 mmol/mmol, 6 months = 849.2, 12 months = 615.3, 24 months = 93.5). 2 patients achieved CR of proteinuria and 3 had PR. 12 patients were switched to calcineurin inhibitor (CNI), 2 after 12 months and 1 after 18 months for worsening of UPCR - all 3 maintained stable renal function.

Conclusions: In our cohort of patients, the immunosuppressive regimen reduced the proteinuria and stabilised the decline in renal function. This suggests that pulsated intravenous Cyclophosphamide may be a viable alternative to oral Cyclophosphamide in the treatment of idiopathic membranous nephropathy.

TH-PO1041
Safety and Tolerability of Intravenous Cyclophosphamide as an Alternative to Oral Cyclophosphamide in Patients Treated for Idiopathic Membranous Nephropathy – A Single Centre Experience
Robin Ramphul, Raja Mohammed Kaja Kamal, David Makanjuola, Rebecca Suckling, Fiona E. Harris, Bhrijiraj Roy Sood. Renal Unit, St. Helier Hospital, Carshalton, Surrey, United Kingdom.

Background: The role of the modified Ponticelli regimen in managing idiopathic membranous nephropathy (IMN) is well recognised. With pulsated intravenous (iv) Cyclophosphamide, the total dose is reduced, but it is not clear whether this is safer, or better tolerated than oral Cyclophosphamide.

Methods: We retrospectively analysed the medical records for adverse events in 13 patients treated between January 2003 and April 2012 for IMN with immunosuppressive treatment according to the following treatment protocol: Prednisolone - 40 mg/day for 30 days - months 1, 3 and 5. Cyclophosphamide - day 1 - months 2, 4 and 6 (dose shown in table).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Creatinine (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>300</td>
</tr>
<tr>
<td>300+</td>
<td>350</td>
</tr>
<tr>
<td>400</td>
<td>450</td>
</tr>
<tr>
<td>500+</td>
<td>550</td>
</tr>
</tbody>
</table>

Methods: Onset of therapy was defined as ESRD, doubling of serum creatinine, switch to, or introduction of alternative immunosuppression. Complete remission (CR) was defined as a reduction in UPCR to < 50mg/mmol. Partial remission (PR) was defined as a reduction in UPCR to < 350mg/mmol and a 50% or greater reduction in UPCR.

Results: There were 12 men, age 68yrs (range 37 – 79); 1 died within 12 months. 10 patients had stable renal function, 2 doubled their serum creatinine and progressed to ESRD after 24 months. The mean UPCR reduced over the course of follow-up (mean UPCR at baseline = 1128.2 mmol/mmol, 6 months = 849.2, 12 months = 615.3, 24 months = 93.5). 2 patients achieved CR of proteinuria and 3 had PR. 12 patients were switched to calcineurin inhibitor (CNI), 2 after 12 months and 1 after 18 months for worsening of UPCR - all 3 maintained stable renal function.

Conclusions: In our cohort of patients, the immunosuppressive regimen reduced the proteinuria and stabilised the decline in renal function. This suggests that pulsated intravenous Cyclophosphamide may be a viable alternative to oral Cyclophosphamide in the treatment of idiopathic membranous nephropathy.
Results: The adverse events are tabulated below. 8/13 had no complications. In the 5 remaining patients, the majority of complications were infective. In 1 patient Chronic Lymphocytic Leukemia (CLL) was diagnosed 5 years after treatment of the IMN. Subsequent treatment of the CLL with Chlorambucil resulted in remission of proteinuria. One patient died of a myocardial infarction.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Creatinine (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td>30-70</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group</th>
<th>Creatinine (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td>30-70</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td></td>
</tr>
</tbody>
</table>

Results: 48/125 were immunosuppressed; 26 male;22 female. 7/48 (14.6%) were on maintenance therapy; 5/7 P+AZA, 2/7 P+MMF. 2 male;5 female with median age 54 years. No significant difference in creatinine or eGFR between the groups. Maintenance immunosuppression had a significant sustained improvement in albumin at 2, 5 and 10 years compared with baseline(p<0.05, p<0.001, p<0.01 respectively). Improvement in albumin was seen at 2 years compared to baseline and in those with maintenance(p<0.001). Maintenance immunosuppression had 100% survival and remained dialysis independent at 10 years. In contrast 11 of those on immunosuppression with no maintenance became dialysis dependent, 4 died within 2 years.

Conclusions: Those on maintenance therapy had 100% survival rates and remained dialysis independent. The cohort size on maintenance therapy is small and larger studies would be required to determine possible benefit of long term maintenance immunosuppression.

TH-PO1044

Immunosuppression for Idiopathic Membranous Nephropathy in North East England

Background: Membranous nephropathy is the most common cause of adult-onset nephrotic syndrome in Europe, with an incidence of 5-10 per million population per year. The majority of cases are idiopathic (IMN) and it is now understood that IMN is an autoimmune disease. The current immunosuppressive (IS) protocol used for IMN patients is Prednisolone alone (P) and Cyclophosphamide (C). There is no consensus on the best approach in the management of IMN. There are two groups; those who receive maintenance IS and those who do not receive IS. The aim of this study was to assess the outcomes in patients with IMN treated with maintenance IS to the a group that did not require such therapy.

Methods: Patients with biopsy-proven IMN who had started IS before January 2013 were included in this retrospective cohort study. The following disease markers were recorded: serum creatinine and albumin, eGFR and urine protein:creatinine ratio (uPCR). Measurements of these markers were then repeated at completion of IS (or 6 months after commencing if they did not complete) and again at 6 months after completion of IS. Any reason for non-completion and adverse events were recorded.

Results: 25 patients were included in the study. 17 (68%) were male and 8 (32%) were female. The mean age was 65.5 years. Of the 25 patients, 13 (52%) completed IS, 10 (40%) did not complete and 2 (8%) were currently undergoing treatment. Of those that completed, 3 (23%) completed as per protocol and 9 (69%) completed on a reduced dose. Of those that did not complete, 8 (80%) abandoned due to adverse effects and 2 (20%) died whilst on the regime. No patients achieved total remission (uPCR<20mg/mmol). 11 patients achieved partial remission (uPCR<200mg/mmol) by the end of IS and 13 patients were in partial remission 6 months after finishing treatment. There were 4 cases of sepsis and 3 cases of neutropaenia during IS.

Conclusions: The rates of remission in this study do not match the success of immunosuppression reported by Ponticelli and the high incidence of adverse events, non-completion and adverse deaths suggest that the safety of chlorambucil use in this population may warrant more concern than previously expected.

TH-PO1043

Maintenance Immunosuppressive Therapy in Membranous Nephropathy

Background: Immunosuppressive therapy has been shown to be beneficial in the treatment of Membranous Nephropathy (MN). The benefits of maintenance immunosuppression therapy are unknown. Aim is to assess outcome and progression of MN with different maintenance immunosuppressive regimens.

Methods: Patients with biopsy proven MN in single centre from 1995-2010 had demographic data, urine protein creatinine ratio (UPCR in mg/mmol), baseline eGFR at 2, 5 and 10 years, onset of renal replacement therapy (RRT) and patient survival collected. Initial immunosuppressive regimens were: Prednisolone alone (P), P+Cyclophosphamide (P+CYP), Maintenance therapy was; P+Azathioprine (AZA) or P+Mycophenolate mofetil (MMF).

Results: 48/125 were immunosuppressed; 26 male;22 female. 7/48 (14.6%) were on maintenance therapy; 5/7 P+AZA, 2/7 P+MMF. 2 male;5 female with median age 54 years. No significant difference in creatinine or eGFR between the groups. Maintenance immunosuppression had a significant sustained improvement in albumin at 2, 5 and 10 years compared with baseline(p<0.05, p<0.001, p<0.01 respectively). Improvement in albumin was seen at 2 years compared to baseline and in those with maintenance(p<0.001). Maintenance immunosuppression had 100% survival and remained dialysis independent at 10 years. In contrast 11 of those on immunosuppression with no maintenance became dialysis dependent, 4 died within 2 years.

Conclusions: Those on maintenance therapy had 100% survival rates and remained dialysis independent. The cohort size on maintenance therapy is small and larger studies would be required to determine possible benefit of long term maintenance immunosuppression.
Conclusions: Complement mediated glomerulonephritis was 4.3% among previously diagnosed as MPGN cases. All cases of complement mediated GN developed to progressive renal dysfunction although the numbers were small. Decreased GFR, hypertension and hypoalbuminemia at the time of diagnosis may be factors predicting progressive renal dysfunction in MPGN patients.

TH-PO1046
Factors Involved in the Progression of Membranoproliferative Glomerulonephritis: Retrospective Cohort of 74 Patients
Alline S.A. Oliveira, Camila Barbosa L. Oliveira, Carla Queiroz Neves, Clarissa Jacob Barros Carvalho, Luis H.B.C. Sette, Giselle Vaijel Fernandez, Maria Alina G.M. Cavalcante, Lucila Maria Valente. Nefrologia, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil.

Background: Prognosis of membranoproliferative glomerulonephritis (MPGN) is generally considered unfavorable and it is not clear which factors are involved in long-term progression. Reports suggest that the prognosis is worse in cases of nephrotic syndrome compared with non-nephrotic proteinuria but some authors observed that although the trend is less favorable for the patients with nephrotic syndrome in the first years, this difference disappears later during the follow-up.

Methods: We evaluated the medical records of patients treated at the ambulatory of Nephrology diagnosed with MPGN between 1995 and 2013. Patients were considered with controlled blood pressure when at least 80% of measurements were below 140 and 90 mmHg.

Results: Seventy-four were patients were evaluated, 55% male with a median age of 44 ± 15 and mean follow-up time of 42.5 months. Initial assessment showed hematuria (70%), hypertension (58%) and 24-hour proteinuria (P24h) ≥ 3.5 g/day (61%). Blood pressure control was associated with a lower chance of developing CICr < 50 (OR 0.34 p-value 0.04) and ESRD (OR 0.18 p-value 0.03). Moreover, for each additional gram on P24h, there was a 20% increase chance of duplicating serum Cr (p-value 0.03). Patients with P24h > 3.5, interstitial fibrosis and tubular atrophy were also correlated to a higher chance of doubling Cr (p-value of 0.018, 0.03 and 0.05, respectively). Male sex was associated with progression to ESRD (OR 8.79, p-value 0.03).

Conclusions: Failure to control blood pressure, male sex and high P24H as well as findings of tubular atrophy and interstitial fibrosis were related to poor renal outcomes in patients with MPGN.

TH-PO1047
Phenotypic and Genotypic Characteristics of C3 Predominant Glomerulonephritis

Background: C3 predominant glomerulonephritis is the pathological designation used to distinguish the C3 Glomerulopathies (C3G) – a group of diseases defined by their immunofluorescent renal biopsy pattern and by an association with dysregulation of the alternative pathway (AP) of complement. The two major subcategories are dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). A portion of postinfectious glomerulonephritis patients will also present with a predominant C3 pattern on IF, however their clinical course will distinguish them from the C3Gs (hypocomplementemia less than 12 weeks and general renal recovery). We present the phenotypic and genotypic characteristics of the C3 dominant glomerulonephritis cases seen in our practice.

Methods: We performed a review of all patients seen and biopsied in our practice from 2007-2013 that met the criteria of C3 predominant staining on IF (C3 staining with a magnitude of 2 greater than other stains - except IgM) and at least 6 months of data for review.

Results: 26 patients met the criteria for review: 4 DDD, 17 C3GN and 4 PIGN. 100% of DDD pts and approximately 50% of C3GN and PIGN pts had hypertension at biopsy. The level of urinal protein was not statistically different at presentation between the groups; however was different at followup: DDD>3GN>PIGN. 40% of DDD, 18% of C3GN and 0% of PIGN pts required dialysis during their course with a trend toward worse eGFR for DDD pts at followup. 77% of pts had an abnormal C3 at presentation with 43% at 60 week followup (N = 18). All pts suspected of PIGN resolved their hypocomplementemia by 12 weeks. An AP genetic assessment was available on 15 of the 26 pts and DNA variants were found in 53%. No genetic abnormalities were found in the PIGN pts.

Conclusions: C3GN was the most common C3 dominant glomerulonephritis. Four of four PIGN patients who were biopsied for disease severity had a C3 dominant glomerulonephritis on biopsy. C3 dominant glomerular lesions of the non-PIGN type often follow a chronic glomerular disease course with nearly half of patients continuing to have hypocomplementemia. To our knowledge, this is the largest reported American cohort of C3Gs.

TH-PO1048
Bortezomib Is Highly Efficient in Monoclonal Immunoglobulin Deposition Disease

Background: Monoclonal immunoglobulin deposition disease (MIDD) is a rare complication of plasma cell disorders. Recent data from small case series suggest that novel anti-myeloma agents may improve patient and renal survival.

Methods: Thirty-patients with LCD and 3 with HCD, all treated with bortezomib plus dexamethasone (BD)-based chemotherapy, were retrospectively analyzed. Data were recorded at baseline and at completion of chemotherapy. Hematologic response was defined according to International Myeloma Working Group. Renal response was defined as a ≥ 50% decrease in 24H proteinuria (at least 0.5 g), in the absence of a reduction in eGFR ≥ 25% or an increase in serum creatinine ≥ 0.5 mg/dL.

Results: Median age at diagnosis was 57 years. Serum and/or urine monoclonal gammopathy was found in 32 patients (97%), 26 of whom (67%) had multiple myeloma and 1 had Waldenstrom macroglobulinemia. Serum free light chain (FLC) ratio was abnormal in all 32 patients tested, with raised kappa (28, 84%) or lambda (4, 12%) FLCs. At diagnosis, median serum creatinine was 213 mmol/L, with 24H proteinuria of 1.27g. Seven patients (21%) required hemodialysis at diagnosis. Patients received a median of 4 courses of BD, alone or reinforced with cyclophosphamide (n = 11), thalidomide (n=2), or lenalidomide (n–1). In 14 patients (42%), treatment was followed by HDT/SCT. Hematologic response (partial response or above) was achieved in 24 patients (73%), including very good partial response in 19 cases, and complete response in 2 patients. After a median follow up of 27 months, 2 patients had died. In 23 patients with renal involvement, 11 (48%) had renal response, all of whom showed improved renal function. Two patients progressed to end stage renal disease. Out of 7 patients requiring hemodialysis dialysis at diagnosis, 1 died, and dialysis was withdrawn after BD in 1 case. Four patients had severe adverse effect including 1 encephalopathy.

Conclusions: BD-based regimens appear to be associated with high hematologic and renal response rates in MIDD. Further prospective studies are required to confirm these data.

TH-PO1049
Primary AL-Amyloidosis – Retrospective Study of 54 Patients, One Center Experience
Elena Zakharyova. Nephrology, City Clinical Hospital n.a. S.P. Botkin, Moscow, Russian Federation.

Background: “Primary” AL-amyloidosis is a plasma-cell dyscrasia characterized by overproduction of monoclonal Ig light chains, most commonly affecting kidneys with nephrotic syndrome (NS) and renal failure (RF). Satisfactory treatment does not exist, current options include high-dose melphalan with autologous stem cell transplantation (TASC), melphalan-prednisone (MP), melphalan-dexamethasone (MD), bortezomib (B) containing regimens, and immunomodulators. We aimed to evaluate treatment results in our cohort.

Methods: Using electronic database for we searched patients with biopsy-proven “primary” AL-amyloidosis, treated in 1998-2013. Work-up included serum and urine immunoochemistry, kidney biopsy with light microscopy and immunofluorescence electron microscopy, and bone marrow aspiration and/or biopsy with immunohistochemistry. Treatment regimens were TASC, MP, MD, B, and supportive treatment (ST) only.

Results: Study group included 54 patients, 29 (53.7%) male and 25 (46.3%) female, median age 57 [34;78] y.o. Clinical presentation and treatment are shown in table.

Conclusions: Failure to control blood pressure, male sex and high P24H as well as findings of tubular atrophy and interstitial fibrosis were related to poor renal outcomes in patients with MPGN.

TH-PO1047
Phenotypic and Genotypic Characteristics of C3 Predominant Glomerulonephritis

Background: C3 predominant glomerulonephritis is the pathological designation used to distinguish the C3 Glomerulopathies (C3G) – a group of diseases defined by their immunofluorescent renal biopsy pattern and by an association with dysregulation of the alternative pathway (AP) of complement. The two major subcategories are dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). A portion of postinfectious glomerulonephritis patients will also present with a predominant C3 pattern on IF, however their clinical course will distinguish them from the C3Gs (hypocomplementemia less than 12 weeks and general renal recovery). We present the phenotypic and genotypic characteristics of the C3 dominant glomerulonephritis cases seen in our practice.

Methods: We performed a review of all patients seen and biopsied in our practice from 2007-2013 that met the criteria of C3 predominant staining on IF (C3 staining with a magnitude of 2 greater than other stains - except IgM) and at least 6 months of data for review.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Among 29 patients, treated with chemotherapy, 14 (48.2%) achieved hematological remission, 11 (37.9%) – also organ remission, in 15 (51.7%) cases treatment failed, no significant differences between treatment groups was found.

Conclusions: Majority of patients in our cohort were diagnosed late and presented with nephrotic syndrome, notably about a half of them - with renal failure and multiorgan involvement, which limited chemotherapy choice and was associated with 33% of mortality. Treatment results in chemotherapy subgroup showed 48% of hematological and 38% of organ remissions, and did not depended on chemotherapy regimen.

TH-PO1050

Alchemy – A Large Prospective Study of Chemotherapy in Systemic AL Amyloidosis Jennifer H. Pinney, Helen J. Lachmann, Ashutosh Wechalekar, Philip N. Hawkins, Julian D. Gillmore. UK National Amyloidosis Centre, Div of Medicine, Royal Free Hospital, London, United Kingdom.

Background: There are no large prospective clinical trials in AL amyloidosis. Methods: ALchemy is a prospective observational study of chemotherapy in patients with AL amyloidosis. All patients with newly diagnosed AL amyloidosis requiring chemotherapy in the UK were eligible for study entry from September 2009. Study participants underwent assessment of their disease at baseline, after 3 cycles of chemotherapy and 6, 12, 18 and 24 months from baseline. Clonal disease was assessed after each cycle of chemotherapy and monthly thereafter. Details about tolerability and toxicity of chemotherapy were collected via a case record form.

Results: This the largest prospective study in AL amyloidosis worldwide; recruitment is ongoing. Here we present data from the first 616 patients. A primary renal presentation was seen in 49% and 24% had isolated renal disease. Median survival was best in patients after each cycle of chemotherapy and monthly thereafter. Details about tolerability and toxicity of chemotherapy were collected via a case record form.

Conclusions: This study illustrates the need for and barriers to knowledge translation (KT) of the recent KDIGO GN guidelines into clinical practice. Methods: We surveyed nephrologists in British Columbia, Canada, using a 40 question survey addressing physician characteristics, GN exposure, care gaps, barriers to guideline use and support for a regional GN registry. Results: The response rate was 64% (47 of 73 nephrologists). Biannually a median of 6 (IQR 5,10) new cases of idiopathic GN are seen per physician, which is similar in urban vs rural and academic vs private practices. Self-reported treatment of GN is shown in the table. There are no large prospective clinical trials in AL amyloidosis.

TH-PO1051

Glomerular Toxicity of Two Therapies Targeting the Vascular Endothelial Growth Factor Result from Distinct Mechanisms Mario Ollero,1 Hassane Izzeddine,2 Melanie Mangier,3 André Pavlak,3 Djillal Sahali,3 1INSERM, U 935, Equipe 21, Univ Paris-Est Creteil Val-de-Marne, Creteil, France; 2Pitie-Salpetriere Hospital, Paris, France.

Background: Renal toxicity constitutes a dose-limiting side effect of antinecancer therapies targeting the vascular endothelial growth factor (VEGF), including anti-VEGF ligands and receptor tyrosine kinase inhibitors (RTKI). Methods: We studied 29 patients having followed this kind of treatment. Eight of them developed minimal change nephropathy (MCN), focal segmental glomerulosclerosis (FSGS), and/or thrombotic microangiopathy (TMA). MCN/FSGS-like lesions developed mainly under RTKI, whereas TMA complicated anti-VEGF therapy. We performed immunohistochemical and immunoultrastructural studies on kidney biopsies displaying TMA or MCN/FSG-like lesions and compared them with idiopathic forms. In parallel, we investigated molecular mechanisms underlying these glomerular syndromes. The RTKI Sorafenib was tested in vitro on wild-type and ReA- deficient mouse embryonic fibroblasts (MEF), on a podocyte cell line, and on lymphocytes from healthy donors.

Results: TMA sorafenib induced high ReA expression in endothelial cells and podocytes, whereas MCN/FSG was not altered. Conversely, c-mip was highly abundant in MCN/FSG-like lesions, whereas ReA was scarcely detected. Electron microscopy showed marked alterations in TMA glomeruli, including duplication of glomerular basement membrane, loss of fenestrations, detachment of endothelial cells and marked effacement of visceral epithelial cell foot processes in some areas. ReA gold particles where increased in podocyte nuclei, as well as in endothelial cells as compared with controls. Sorafenib upregulated c-mip at both transcript and protein levels in vivo and in vitro, at least partly due to inhibition of NF-κB activity. Notably, Sorafenib induced a profound cytoskeleton disorganization with depletion of stress fibers and impressive production of F-actin-rich membranes.

Conclusions: These results suggest that renal toxicity of anti-VEGF and RTKI therapies results from distinct mechanisms operating in podocytes and endothelial cells, in which ReA and c-mip play an antagonistic and mutually exclusive role.

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

TH-PO1052

Care Gaps and Barriers to Guideline-Based Management of Glomerulonephritis: A Survey of Nephrologists Sean Barbour,1 Monica C. Beaulieu,2 Jagbir Gill,3 Heather N. Reich,3 Adeera Levin,3 1Div of Nephrology, Univ of BC; 2BC Provincial Renal Agency; 3Div of Nephrology, Univ of Toronto.

Background: There is substantial variability in the treatment of glomerulonephritis (GN) that contributes to poor patient outcomes and historically may be due to a lack of accepted guidelines. As such, we sought to better understand the need for and barriers to knowledge translation (KT) of the recent KDIGO GN guidelines into clinical practice. Methods: We surveyed nephrologists in British Columbia, Canada, using a 40 question survey addressing physician characteristics, GN exposure, care gaps, barriers to guideline use and support for a regional GN registry. Results: The response rate was 64% (47 of 73 nephrologists). Biannually a median of 6 (IQR 5,10) new cases of idiopathic GN are seen per physician, which is similar in urban vs rural and academic vs private practices. Self-reported treatment of GN is shown in the table. Most treat ANC and membranous GN per KDIGO guidelines; however, treat FSGS and 2g/proteinuria with immunosuppression and only 56% treat FSGS and 5g/d proteinuria with prednisone (less often in those with >15 vs fewer years in practices, 21% vs 64-73% p=0.03). Over 90% feel that standardized care tools would improve patient care yet they are available to only 19-27%. Patient education tools and decision support are unavailable to 93% and 57%. Insurance for immune therapies is poorly accessible to 86% yet 98% feel this would improve care. Almost all physicians support a regional GN registry that would provide achievable benchmarks in GN clinical care.

TH-PO1053

Proteinuria Does Not Need to Be Standardized to Body Surface Area in Adults with Glomerulonephritis Sean Barbour,1 Daniel C. Cattran,1 Gabriela Espino-Hernandez,2 Michelle A. Hladunewich,3 Adeera Levin,1,2 Heather N. Reich.3 1Div of Nephrology, Univ of BC; 2BC Provincial Renal Agency; 3Div of Nephrology, Univ of Toronto.

Background: Baseline proteinuria (Prot) is an important but poorly determined determinant of renal outcome in glomerulonephritis (GN). While it is conventional in children to adjust traditional unadjusted proteinuria.

Methods: We analyzed an adult cohort with IgA nephropathy (IgAN N=445), focal segmental glomerulosclerosis (FSGS N=472) and membranous nephropathy (MN N=434) from the Toronto GN Registry followed for a median of 54 months. The primary outcome (ESRD or 50% drop in eGFR N=385) was analyzed using Cox regression to compare model fit between Prot and ProtBSA at biopsy, which were log-transformed due to non-linearity.

Results: The median baseline Prot was 3.7g/dl and ProtBSA was 3.5g/dl/1.73m². As shown in the table, in MN and IgAN both Prot and ProtBSA were associated with a similar and increased risk of renal progression (p<0.001 for all HR). The R², AIC, and C-statistic were similar between Prot and ProtBSA and the continuous (c)NRI and IDI were very

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
small or not different from zero. As in previous studies neither baseline Prot nor ProtBSA were associated with renal progression in FSGS (HR=1.11; 95%CI 0.94-1.32, HR 1.12 95%CI 0.95-1.33 both p>0.2).

Conclusions: In a large cohort of adults with GN, Prot and ProtBSA similarly predict the risk of renal outcome. BSA adjustment does not improve the prognostic value of baseline proteinuria measurements.

TH-PO1054

Immunohistochemical Staining of IgG4 in Gomeruli for a Range of Renal Biopsies Shinya C. Wolford, Xu Zeng, Michele T. Rooney, Wei Li, Ping L. Zhang. 

1Anatomic Pathology, William Beaumont Hospital, Royal Oak, MI; 2Bostwick Laboratories, Orlando, FL.

Background: Immunohistochemical (IHC) staining for IgG4 became available in our lab due to the discovery of a systemic autoimmune inflammatory disease. Other labs have used immunofluorescent (IF) methods to stain IgG4 to differentiate idiopathic membranous glomerulopathy (MGN) from lupus membranous nephritis (LMN). In this study, we used IHC methods to stain IgG4 for a range of renal biopsies with known IgG staining by IF method to determine the presence of IgG4 in various glomerulopathies.

Methods: Monoclonal IgG4 antibody was purchased from Cell Marque (dilution: 1:100). Four control groups including normal renal tissue (C1 normal renal tissue n=5), LMN (C2, n=9), monoclonal light chain nephropathy without heavy chain deposition (C3, n=24), and ANCA-associated crescentic glomerulonephritis (C4, n=8). Four study groups were composed of MGN (S1, n = 14), heavy chain nephropathy with or without monoclonal light chain (S2, n = 3), mixed group (S3, post-infectious glomerulonephritis, n = 2), thrombotic microangiopathy, n=5, membranoproliferative glomerulonephritis n =2), and acute glomerulonephritis (S4 n =13). All cases were stained for IgG4 and their expression in each was graded from 0 to 3+ depending on staining intensity.

Results: All 4 control groups (C1 – C4, total n = 46) are entirely negative for IgG4 in glomeruli. In group S1, 64 % (9/14) of MGN showed granular membranous staining for IgG4. One of three glomeruli from group S2 (33%) revealed linear IgG4 (3+) along glomerular loops and along tubular basement membranes, similar to its IgG pattern by IF method. Group S3 stained negatively for IgG4. In one of 13 cases in group S4 (7.7%), linear IgG4 (2+) was identified in all 7 glomeruli, similar to the pattern of IgG linear staining by IF method.

Conclusions: Our data using IHC staining for IgG4 has confirmed specific IgG4 staining in the glomeruli of a majority of MGN cases as reported by others using IF methods. In addition, heavy chain deposition disease and anti-GBM CGN can be IgG4 positive in the glomeruli but with differing staining patterns as compared to MGN.

Funding: Clinical Revenue Support

TH-PO1055

Histopathological Analysis of IgG4-Related Kidney Disease: Hints from an Autopsy Series of 5 Cases Ichiro Mizushima, 1Mitsuhiro Kawano, 1Takako Oshima, 1Takashi Takei, 1Kosaku Nitta.

1Rheumatology, Kanazawa Univ Hospital, Japan;

Background: IgG4-related disease (IgG4-RD) is a systemic disease characterized by marked lymphoplasmacytic infiltrates with abundant IgG4-positive plasma cells (PCs), fibrosis, and obstructive phlebitis. Plasma cell-rich tubulointerstitial nephritis is a typical renal manifestation of this disease. However, histopathological evaluation of the whole kidneys in autopsy cases has not been previously reported.

Methods: We analyzed 5 autopsy cases using Hematoxylin and eosin, Periodic acid Schiff, Periodic acid methenamine silver, and elastic Van Gieson stains. Immunohistochemical staining was performed using anti-IgG4 antibodies (Abs) and anti-CD138 Abs.

Results: Two patients died of associated cancer and they had undergone chemotherapy without corticosteroid (CS). Two patients were receiving maintenance CS treatment (Tx) and the remaining one was not. All patients had typical extrarenal involvement by IgG4-RD. Two patients fulfilled the criteria for IgG4-RD: increased IgG4+ > 30/high power field (HPF); IgG4/CD138 > 40%, while one patient, who underwent long-term CS Tx, showed few lymphoplasmacytic infiltrates but marked periarterial fibrosis of interlobular arteries. Three patients without CS Tx or with only short-term CS Tx who had bird’s eye pattern fibrosis, dense lymphoplasmacytic infiltrates around arteriolar wall or interlobular artery segments (width ≥ 200-500μm) and vein. In contrast, another patient with long-term CS Tx had mild patchy infiltration of lymphocytes and PCs, but had a large fibrotic area with disappearance of almost all tubules with scattered glomeruli and arteries remaining.

Conclusions: Periarterial and perivenous lesions with marked lymphoplasmacytic infiltrates are additional characteristic features of IgG4-related kidney disease.

TH-PO1056

Diffuse Effacement of Foot Processes of Podocytes in Stage I Membranous Nephropathy Kavori Tsurouka, Yuusuke Kajimoto, Seicho Higo, Go Kanzaki, Shinya Nagasaka, Akira Shimizu. Analytic Human Pathology, Nippon Medical School, Tokyo, Japan.

Background: Idiopathic membranous nephropathy (MN) is widely characterized pathologically by the spike formation in glomerular basement membrane in light microscopy (LM), glomerular capillary pattern of IgG4 and C3 deposition in immunofluorescence study (IF), and glomerular subepithelial electron dense deposits (EDD) in electron microscopy (EM). However, in stage I (Ehrenreich T and Chu J) of MN, we sometimes experience the cases that did not have typical features of these MN findings.

Methods: In the present study, in order to clarify the clinicopathological characteristics of MN stage I, we selected 33 cases (22.3%) of stage I of MN from 148 cases of idiopathic MN that we diagnosed in our department from 2001 to 2013. We assessed clinical and pathological characteristics including LM, IF, EM, and IHC-findings.

Results: The 33 cases of stage I of MN were consisted of 22 males and 11 females. Ages at the time of biopsy ranged from 3 to 80 years (56.0 ± 20.1 years). Renal dysfunction was not detected in all cases. In addition, stage I MN was characterized by the presence of nonglomerular IgG4-positive IgA and IgG (4.8 ± 2.57g/dl), nonglomerular IgM (2.4±1.0 g/dl), and nonglomerular IgG4-positive IgG (4.8 ± 3.27g/dl), and short interval from disease onset (3.6 ± 4.1 months). In the pathology, the formation of spike on GBM was not detected in all cases. In EM, segmental subepithelial EDD was detected in all MN cases, but only a segmental and small subepithelial EDD was noted on GBM in 13 cases (39%). In these 13 cases, weak IgG deposition was evident with the degree of deposition of IgG4 > C3 in IF. The IgG subclass showed the predominant deposition of IgG4 > IgG1. In addition, IgG4 was only noted on subepithelial EDD on GBM in immuno-EM. Interestingly, diffuse effacement of foot process of podocytes was evident in stage I MN, even in the segmental and small subepithelial EDD on GBM. Subepithelial EDD and podocyte injury may be mediated heavy proteinuria in stage I MN.

TH-PO1057

Prognosis in IgA Nephropathy: 30-Year Analysis of 1,012 Patients at a Single Center in Japan Takahito Moriyama, Kaiyu Tanaka, Chihiro Iwasaki, Yasuko Oshima, Takashi Takei, Kosaku Nitta. Medicine, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan.

Background: Little is known about the long-term prognosis of patients with IgA nephropathy (IgAN). We therefore assessed the prognosis over 30 years of 1,012 patients with IgAN treated at our center since 1982.

Methods: This retrospective cohort analysis evaluated clinical and histological findings at the time of renal biopsy, initial treatment, patient outcome over 30 years, and risk factors associated with progression.

Results: Of the 1,012 patients, 40.5% were male. Mean patient age was 32.9±12 years and mean blood pressure was 122±17/75±13 mmHg. Mean serum albumin was 3.9±0.5 g/dl, and mean estimated glomerular filtration rate (eGFR) was 71.1±23.5 ml/min/1.73m2. Mean proteinuria was 1.19±1.61 g/day, and number of mean urinary red blood cells was 36.6±35.3 per high powered field. Histologically, mesangial hypercellularity was present in 47.6% of patients, endothelial hypercellularity in 44.3%, segmental sclerosis in 74.6%, and tubular atrophy/interstitial fibrosis in 28.8% by Oxford classification. Initial treatment consisted of corticosteroids in 26.9% of patients, immunosuppressive agents in 1.5%, RAS inhibitors in 28.9%, and tonsillectomy plus steroids in 11.7%. The 10-, 20-, and 30-year renal survival rates were 84.3, 66.6, and 50.3%, respectively.

Cumulative renal survival rate from renal biopsy until ESRD in all 1,012 patients with IgAN.

Conclusions: IgAN is not a benign disease, with over 50% of patients progressing to ESRD within 30 years despite treatment.

Cox multivariate regression analysis showed that higher proteinuria (HR 1.28, 95%CI 1.02-1.62, P=0.0372), lower eGFR (HR 1.36, 95%CI 1.43-2.43, P<0.0001), and higher uric acid concentration (HR 1.28, 95%CI 1.05-1.62, P=0.0372) at the time of renal biopsy were independent risk factors for the development of end stage renal disease (ESRD).

Conclusions: IgAN is not a benign disease, with over 50% of patients progressing to ESRD within 30 years despite treatment.

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

Underline represents presenting author/disclosure.
Neonatal Kidney Size and Function in Preterm Infants: What Is a True Estimate of Glomerular Filtration Rate? 
Carolyn L. Abitbol, 1 Wacharee Seeherunvong, 1 Marta G. Galazar, 2 Marissa J. Defreitas, 3 Teresa C. Cano, 4 Chryso P. Katsouflis, 5 Alicia E. Edwards- Richards, 6 Vimal Master Sankar Raj, 7 Jayanthi Chandler, 1 Shahnaz Dura, 8 Sahil Y. Yasin, 3 Gaston E. Zilleruelo. 2

1Pediatric Nephrology, Univ of Miami/ Holtz Children’s Hospital, Miami, FL; 2Obstetrics & Perinatology, Univ of Miami/ Holtz Children’s Hospital, Miami, FL; 3Obstetrics & Perinatology, Univ of Miami/ Holtz Children’s Hospital, Miami, FL; 4Obstetrics & Perinatology, Univ of Miami/ Holtz Children’s Hospital, Miami, FL

Background: Preterm birth is associated with early and late renal insufficiency that may be related to low nephron mass and altered maturation of renal function.

Methods: Sixty preterm and 40 term infants were enrolled at birth. Serum creatinine(Cr) and cystatin-C(CysC) were used to calculate estimated glomerular filtration rate (eGFR). Renal ultrasounds assessed kidney dimensions with calculation of total kidney volume (TKV) as a surrogate of nephron mass. Multiple regression analysis was applied to assess the relative impact of neonatal parameters on eGFR including TKV, gestational age (GA) and mean arterial pressure (MAP).

Results: Renal lengths correlated with GA and were within reference values for fetal ultrasound at each GA. Estimation equations for GFR based on Cr, CysC and combined CysC+Cr demonstrated that Cr-based equations underestimated GFR; whereas, CysC and combined equations were consistent with the reference inulin clearance studies. TKV, GA and MAP correlated positively with eGFR; though, only MAP and GA remained significant when other measures were held constant.

Conclusions: Primary determinants of GFR in preterm infants are gestational age and mean arterial blood pressure. Serum creatinine is unreliable as a marker of renal function in preterm infants. Until more reliable markers are available, CysC should be used as the primary assessment of GFR in preterm infants.

Funding: Pharmaceutical Company Support - Gerber Foundation

Tubular Dysfunction in Extremely Low Birth Weight Survivors
Kazuya Matsumura, Mariko Hida, Midori Awazu. Dept of Pediatrics, School of Medicine, Keio Univ, Tokyo, Japan.

Background: Extremely low birth weight (ELBW) survivors are known to develop glomerulonephrosclerosis due to low nephron number. Microalbuminuria is regarded as an early marker of glomerular injury. Tubular damage may also occur, but little is known other than increased urine calcium excretion. We therefore studied tubular function of ELBW survivors.

Methods: Fifty-three subjects (30 boys and 23 girls, aged 7 months-19 years, median 42 months) were studied. The median gestational age and birth weight were 26 (22-32) weeks and 745 (316-999) g, respectively. Normal values were defined as urine calcium:creatinine ratio (Ca/Cr) >0.3 mg/mg, N-acetyl-glucosaminidase:creatinine ratio (NAG/Cr) >0.5 U/mg, glucose:creatinine ratio (glu/Cr) >250 mg/g, uric acid:creatinine ratio (UA/Cr) >reference values by age, and microalbumin:creatinine ratio (malb/Cr) >30 mg/g. We assessed the association between urine markers and factors thought to predict renal injury such as asphyxia, nephrotic drugs, chronic lung disease etc. Univariate and logistic regression analyses were used to compare variables.

Results: Three subjects who had overt proteinuria were excluded. Ninety percent of subjects had at least one tubular dysfunction. Frequencies of elevated values were; NAG/Cr 75.5%, UA/Cr 51.3%, 2M/Cr 38.2%, malb/Cr 28.2%, Ca/Cr 21.1%, and glu/Cr 20.5%. Urine 2M/Cr and glu/Cr were negatively correlated with the gestational age. No association was observed between urine markers and the birth weight. There was a significant negative correlation between the current age and Ca/Cr, NAG/Cr, glu/Cr, and UA/Cr, suggesting a maturation of tubular function. On the other hand, 2M/Cr and malb/Cr did not correlate with the current age, which may indicate persistent kidney injury. Significant correlations were observed between malb/Cr and 2M/Cr, and malb/Cr and NAG/Cr. There was no association between urine markers and putative risk factors for renal injury.

Conclusions: Tubular dysfunction is quite common in ELBW survivors. Microalbuminuria is paralleled by increases in urine 2M and NAG, which may suggest that it is, at least in part, tubular in origin.

Funding: Government Support - Non-U.S.

Epidemiology of Acute Kidney Injury in Hospitalized Children: A Comparison of ICU and Non-ICU Patients
Elizabeth A.K. Hunt, 1,2 Michael A. Ferguson, 1,2 Sushrut S. Warker. 1,2 Div of Nephrology, Boston Children’s Hospital, Boston, MA; 3Harvard Medical School, Boston, MA; 4Renal Div, Brigham and Women’s Hospital, Boston, MA.

Background: Acute kidney injury (AKI) in children has been primarily studied in intensive care units and following cardiac surgery. Less is known about the epidemiology of AKI in hospitalized, non-critically ill children.

Methods: We obtained clinical, demographic, and laboratory data from all children hospitalized at a large pediatric tertiary care center in 2011 who had at least one serum creatinine (Scr) measurement. Primary determinants of GFR in preterm infants are gestational age and mean arterial blood pressure.

Results: We studied 12,090 admissions of 8,706 patients. 6,599 patients had no Scr measurement and 5,485 had one Scr measurement. The incidence of AKI in ICU patients was 35% (23% R, 7% I and 23% F); 3.3% of patients with pRIFLE F required renal replacement therapy (RRT). Overall mortality in ICU patients was 2.8%, and ranged from 0.9% with no AKI to 8.6% in pRIFLE F. Length of stay (LOS) increased with higher stages of AKI. In non-ICU patients, the incidence of AKI was 25% (13% R, 3% I and 9% F); 2.7% of patients with pRIFLE F required RRT. Overall mortality was 0.15%, and ranged from 0.07% with no AKI to 0.9% in pRIFLE F. LOS increased with higher stages of AKI.

Funding: Other NIH Support - T32 training grant

Tubular Dysfunction in Extremely Low Birth Weight Survivors
Kazuya Matsumura, Mariko Hida, Midori Awazu. Dept of Pediatrics, School of Medicine, Keio Univ, Tokyo, Japan.

Background: Extremely low birth weight (ELBW) survivors are known to develop glomerulonephrosclerosis due to low nephron number. Microalbuminuria is regarded as an early marker of glomerular injury. Tubular damage may also occur, but little is known other than increased urine calcium excretion. We therefore studied tubular function of ELBW survivors.

Methods: Fifty-three subjects (30 boys and 23 girls, aged 7 months-19 years, median 42 months) were studied. The median gestational age and birth weight were 26 (22-32) weeks and 745 (316-999) g, respectively. Normal values were defined as urine calcium:creatinine ratio (Ca/Cr) >0.3 mg/mg, N-acetyl-glucosaminidase:creatinine ratio (NAG/Cr) >0.5 U/mg, glucose:creatinine ratio (glu/Cr) >250 mg/g, uric acid:creatinine ratio (UA/Cr) >reference values by age, and microalbumin:creatinine ratio (malb/Cr) >30 mg/g. We assessed the association between urine markers and factors thought to predict renal injury such as asphyxia, nephrotic drugs, chronic lung disease etc. Univariate and logistic regression analyses were used to compare variables.

Results: Three subjects who had overt proteinuria were excluded. Ninety percent of subjects had at least one tubular dysfunction. Frequencies of elevated values were; NAG/Cr 75.5%, UA/Cr 51.3%, 2M/Cr 38.2%, malb/Cr 28.2%, Ca/Cr 21.1%, and glu/Cr 20.5%. Urine 2M/Cr and glu/Cr were negatively correlated with the gestational age. No association was observed between urine markers and the birth weight. There was a significant negative correlation between the current age and Ca/Cr, NAG/Cr, glu/Cr, and UA/Cr, suggesting a maturation of tubular function. On the other hand, 2M/Cr and malb/Cr did not correlate with the current age, which may indicate persistent kidney injury. Significant correlations were observed between malb/Cr and 2M/Cr, and malb/Cr and NAG/Cr. There was no association between urine markers and putative risk factors for renal injury.

Conclusions: Tubular dysfunction is quite common in ELBW survivors. Microalbuminuria is paralleled by increases in urine 2M and NAG, which may suggest that it is, at least in part, tubular in origin.

Funding: Government Support - Non-U.S.
outcomes in a single center tertiary pediatric intensive care unit (PICU) and cardiothoracic unit (PCTU) population.

Methods: Electronic health records for all discharges (N=1213) from 07/2011-02/2013 were extracted, validated and analyzed. The KDIGO creatinine (Cr) based criteria (Cr must be greater than 0.5 mg/dl) were used to stage AKI. Outcomes were ICU length of stay (LOS) and ICU mortality. Exclusion: ESRD, renal transplant or missing PRISM score (N=191). A priori, one discharge was utilized Chi Squared tests (N=0.01). AKI Stage III was associated with increased odds of ICU mortality (OR 4.2, 95% CI 2.4-7.6.)

With increased mortality. The KDIGO criteria adequately describes clinically meaningful prevalence of AKI, AKI is associated with increased ICU LOS and stage III AKI is associated with increased mortality. The KDIGO criteria adequately describes clinically meaningful AKI in a broad pediatric critical care population.

Conclusions: Using the KDIGO criteria to define AKI we show there is a high prevalence of AKI, AKI is associated with increased ICU LOS and stage III AKI is associated with increased mortality. The KDIGO criteria adequately describes clinically meaningful AKI in a broad pediatric critical care population.

**TH-PO1063**

**Acute Kidney Injury (AKI) in Non-Cardiac Neonates in the Pediatric Intensive Care Unit (PICU)**


**TH-PO1066**

**Hyperuricemia Is Associated with Hypertension and Progression of Chronic Kidney Disease in Children**

George J. Schwartz,1 Michael F. Schneider,2 Kyle Rodenbach,1 Vikas R. Dharnidharka,3 Donald J. Weaver,4 Sahar A. Fathallah-Shaykh,5 Marva M. Moxy-Mims,5 Bradley A. Warady,5 Susan L. Furth,5 Mark Mitsnefes.6


**Background:*** There is little data on the relationship of uric acid [Ur] to pediatric CKD. Methods: We quantified the relationship between [Ur] and GFR, hypertension (Htn), and obesity among 617 subjects of the CKD study. Htn was defined as systolic or diastolic BP>95% or 90% and was separated from those whose BP was <95%ile or <90%ile. GFR was measured by iohexol plasma disappearance or estimated from CKID-published formulas. From [Ur] distributions subjects were divided into 2 groups: 1) girls and boys<13 years old, and 2) boys>13 years. 432 kids with >2 GFR measurements were studied by multivariate analysis of the effect of initial [Ur] on risk of a decline in GFR.

**Results:** There was no significant difference in mean [Ur] between two groups. From [Ur] distributions subjects were divided into 2 groups: 1) girls and boys<13 years old, and 2) boys>13 years. 432 kids with >2 GFR measurements were studied by multivariate analysis of the effect of initial [Ur] on risk of a decline in GFR.

The [Ur] distribution at the time of the initial measurement in these groups was as follows: Group 1: [Ur] >7 mg/dl, SBP >95th percentile, and diabetes, or obesity, or hypertension or proteinuria, or pre-existing CKD or any other factors. Group 2: [Ur] <7 mg/dl, SBP <95th percentile, and no diabetes, or hypertension, or proteinuria, or pre-existing CKD or any other factors. Group 1: [Ur] >7 mg/dl, SBP >95th percentile, and diabetes, or obesity, or hypertension or proteinuria, or pre-existing CKD or any other factors. Group 2: [Ur] <7 mg/dl, SBP <95th percentile, and no diabetes, or hypertension, or proteinuria, or pre-existing CKD or any other factors.

**Conclusions:** Group 1 had higher [Ur] and lower GFR and more obesity, hypertension, diabetes, and pre-existing CKD. Group 2 had lower [Ur] and higher GFR and less obesity, hypertension, diabetes, and pre-existing CKD.

**Funding:** NIDDK Support

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

_341A_
TH-PO1067
Prediction of Chronic Kidney Disease (CKD) Progression in Children by Urinary Neutrophil-Associated Lipocalin (NGAL). Anke Dooyen,1,2 Aysoon Karabay Bayazit,2 Daniela Kracht,2 Rene Zeller,2 Ali Anarat,2 Anja Christine Sander,2 Anette Melk,2 Uwe Querfeld,2 Franz S. Schaefer.1,2 "Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany; 4C Study Group.

Background: NGAL, a novel biomarker of acute kidney injury, has been suggested in animal studies and work in adult patients to be predictive also of CKD progression. The aim of this work was to evaluate whether NGAL provides useful information about progression risk in children with CKD.

Methods: Urinary NGAL was measured in 385 children with CKD (mean age 12.5±3.3 yrs, eGFR 31±10 ml/min/1.73 m²) followed in the 4C Study for a mean of 20±7 months. NGAL/creatinine ratio was calculated and log-transformed (NGAL-log). Short-term CKD progression was defined as either attainment of end-stage renal disease (ESRD) or >10% eGFR loss within the first year of follow-up. Long-term CKD progression was defined as ESRD or >50% eGFR loss at any time during the observation period.

Results: NGAL-log was correlated inversely with eGFR (r=-0.4, p<0.0001) and positively with albuminuria (r=0.3, p<0.0001) and CRP (r=0.2, p<0.0001). There was no association to age, BMI or blood pressure (BP).

Conclusions: NGAL is an independent predictor of short-term progression of CKD in children, independent of baseline eGFR and other classic risk factors. There was no additional impact of NGAL on prediction of long-term CKD progression.

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

TH-PO1068
Serum Hepcidin Is a Superior Indicator of Functional Iron Status in Children with Chronic Kidney Disease (CKD). Anke Dooyen,1,2 Franz S. Schaefer.1,2 "Pediatric Nephrology, Univ of Heidelberg, Germany; 4C Study Group.

Background: Hepcidin inhibits intestinal iron uptake as well as release from internal iron stores. It is upregulated in CKD and may thereby contribute to the initiation of diabetic nephropathy. In children with T1D, the interaction between hyperfiltration and inflammation remains unknown. Our objective was to determine whether renal hyperfiltration is associated with increased levels of urinary cytokines/chemokines in adolescents with T1D.

Methods: Blood pressure, estimated glomerular filtration rate using cystatin C and a panel of 41 urinary cytokines/chemokines using a Luminex platform were measured in individuals recruited to the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AddIT). T1D patients with hyperfiltration (DM-H, n=81, GFR ≥135 ml/min/1.73 m²) or normofiltration (DM-N, n=98, GFR<135 ml/min/1.73 m²) were compared to a group of healthy controls (n=59).

Results: Compared to controls and after correcting for age, gender and weight, DM-H and DM-N exhibited elevated levels of urinary FGF-2, IL-6, IL-12 and -15, TNFα and TNFβ (p<0.042). These factors were not different in the two T1D groups. In contrast, some markers were higher in control vs. DM-H and DM-N, including eotaxin, GM-CSF, IL-7 and -17, PDGF-AA and PDGF-AB/BB, RANTES, VEGF and MCP-3 (p<0.031). Other interleukins, IFN, IP-10, MCP-1, TGF, MDC and MIPβ were similar in the three groups. Conclusion: Normotensive, nonalbuminuric T1D children exhibit differences in urinary cytokines/chemokines compared to healthy controls. In contrast with previous work in adults, hyperfiltration in T1D children is not associated with increased urinary cytokine/chemokine excretion. Further work is warranted to determine if this early biomarker profile changes over time; 2) whether these factors respond to drug therapy; 3) the correlation between these factors and longer term outcomes.

Funding: Private Foundation Support

TH-PO1070

Background: Children with vitamin D deficiency are treated with either ergocalciferol or cholecalciferol. Vitamin D treatment is standard fixed dose and duration as per serum 25(OH)D levels, irrespective of age and weight. That means, the same dose might be sub therapeutic for some patients and toxic for other patients. However, limited studies are available looking at response of 25(OH)D level post treatment.

Methods: We enrolled 144 patients aged 2 to 19 yrs, 34 Primary Hypertension (PH), 95 Chronic kidney disease (CKD) 23 Control (C). Among CKD, 58 were (CKD I-IV), available looking at response of 25(OH) D level post treatment.

Results: Mean age (yrs) was (13.02±4.73). 76% African american. eGFR (ml/135 ml/min/1.73 m²) or 135 ml/min/1.73 m²) was significantly lower among CKD (61.23±44.10) than PH and C. Mean post treatment 25(OH) D didn’t correlate with PTH, eGFR, BMI, SBP z-score, serum cholesterol. Mean post treatment 25(OH) D (>30 ng/ml) was (24±9/11.16). After completion of standard treatment almost 76 % patients had 25 (OH) D level <30 ng/ml, mean 25 (OH) D (24±11.16); PH (24±5.71) and CKD (24±9.93) and control (21.8±5.67). None were in toxic range.

Conclusions: The standard treatment dose of Vitamin D doesn’t normalize 25(OH) D level in majority of patients. Newer treatment guidelines may be needed to optimize the treatment.

TH-PO1071
Prevalence and Determinants of 25-Hydroxyvitamin D Deficiency in the Chronic Kidney Disease in Children Cohort. Juhi Kumar,1 Lisa Aronson Friedman,2 Alison G. Abraham,2 Valerie L. Johnson,2 Frederick J. Kaskel,2 Bradley A. Warady,1 Susan L. Furth,2 Michal L. Melamed,2 Anthony A. Portale.1 "Pediatrics, Weill Cornell Medical College, New York, NY; 2-Medicine, Albert Einstein College of Medicine, Bronx, NY; 3-Chronic Kidney Disease in Children(CKD) Investigator.

Background: Deficiency of 25-hydroxyvitamin D (25OHID) is highly prevalent in healthy children. Children with chronic kidney disease (CKD) are at higher risk for 25OHID deficiency, although the risk factors are poorly defined.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents present author/disclosure.
Methods: We measured 250HD levels at baseline and after 1.5 years and 3.5 years of follow-up in 504 children with CKD stages 2-4 enrolled in the Chronic Kidney Disease in Children (CKiD) study. We used generalized estimating equations to determine the associations of demographic, nutritional, anthropometric and biochemical factors with 250HD deficiency, defined as level <20 ng/ml; 250HD sufficiency was defined as level ≥30 ng/ml.

Results: Median participant age was 12.2 years, and 22 % were African-American. Overall, 64 % of participants were 250HD deficient at one or more visits. The prevalence of deficiency decreased with subsequent visits; 28 % were deficient at baseline, 24 % at 1.5 and 23 % at 3.5 years of follow-up. Nutritional vitamin D supplement use was low, 1.5% at baseline, 3 % at 1.5, and 15 % at 3.5 years of follow-up. By multivariable analysis, 250HD deficiency was significantly associated with older age (OR=1.1, p <0.05), African-American race (OR=4.4, p <0.001), higher BMI (OR=1.1, p <0.001), less than daily milk intake (OR=2.6, p <0.001), insufficient sunlight exposure (winter season/higher latitude of blood draw, OR=2.8, p <0.001), lower serum albumin (OR=2.5, p <0.01), baseline vs. 1.5 year follow up visit (OR=2.0, p<0.05) and absent use of nutritional vitamin D supplements (OR=6.6, p<0.01). Gender, maternal education, income, history of low birth weight, GFR, proteinuria, albumin-corrected calcium, PTH, and FGF 23 levels were not associated with 250HD deficiency.

Conclusions: Risk factors for 250HD deficiency in children with CKD are similar to those in normal children with age, race, BMI, sunlight exposure, milk intake, and use of nutritional vitamin D supplements being significant predictors.

Funding: NIDDK Support

TH-PO1074

Very High Resolution Ultrasound Reveals Peripheral Arterial Changes in Both Intima and Media in Children with Chronic Kidney Disease Frida Dansgard,1 Rukshana Shroff,2 Marietta Charakida,3 John E. Deanfield.1 Vascular Physiology, Univ College London, London, United Kingdom; 1Dept of Nephrology, Great Ormond Street Hospital for Children, London, United Kingdom.

Background: Children with chronic kidney disease (CKD) have multiple risk factors for vascular damage that will contribute to the very high cardiovascular morbidity and mortality seen in this group. We hypothesize that children with CKD develop changes in their arterial intima and media, associated with different risk factors and that varies between vascular beds.

Methods: Intimal (IT) and medial (MT) thickness of the carotid, radial and dorsal pedal arteries were measured using very high resolution ultrasound (VHRUS) (40-55MHz) in 22 children with CKD (14.6 ± 3.0 years) (n=9 pre-dialysis; CKD stages 4-5, n=7 dialysis, n=6 post transplant) and compared to radial and dorsal pedal arteries from 17 matched healthy controls. Results were compared with conventional carotid intima-media thickness (cIMT) and biochemical data in CKD patients.

Results: In CKD children, there was widespread medial thickening, most marked in dorsal pedal arteries (0.095±0.03 vs. 0.085±0.03 in controls, p=0.004). In children on dialysis, increased IT was also seen in radial arteries (0.060±0.01 vs. 0.056±0.01 in controls, p=0.02) and carotid arteries (p=0.07 vs. pre-dialysis and transplant).

Conclusions: VHRUS reveals changes of both intima and media, not only in the central, but also in peripheral arteries. These changes are more pronounced in children on dialysis, and associated with calcium levels. This suggests that, in CKD children, strategies to target both metabolic and atherosclerosis risk factors should be initiated from an early age.
**TH-PO1075**

Carotid Intima Media Thickness and Nailfold Capillary Density in Pediatric Hemodialysis Patients  
Alicia D. Edwards-Richards,1 Nao Sasaki,2 Chryso P. Katsoulis,1 Wacharee Seeberunwong,1 Vimal Master Sankar Raj,1 Marissa J. DeFreitas,1 Jayanthi Chandar,1 Michael Freundlich,1 Gaston E. Zilleruelo,1 Carolyn L. Abitbol.1  
1Pediatric Nephrology, Univ of Miami/ Holtz Children’s Hospital, Miami, FL; 2Pediatric Cardiology, Univ of Miami/ Holtz Children’s Hospital, Miami, FL.

**Background:** Pediatric patients with chronic kidney disease (CKD) on hemodialysis (HD) are at increased risk of cardiovascular disease (CVD) and cardiac death. Early detection of microvascular abnormalities may prompt timely therapeutic interventions to reduce these risks.

**Methods:** Nailfold capillary density (NCD), an early marker of microvascular disease, was assessed by capillaroscopy in 19 pediatric HD patients (aged 16.6±3.5 years) and 16 age-matched controls. Carotid intima media thickness (cIMT) and left ventricular mass index (LVMI) were measured by echocardiography and compared to healthy adolescent controls. Laboratory assessments included demographics of ethnicity and gender, dialysis vintage, mean pre-dialysis and post-dialysis blood pressures and cardiac biochemistry as pro-Brain natriuretic peptide (pro-BNP) and high sensitivity C-reactive protein (hsCRP).

**Results:** NCD was significantly lower in HD patients and correlated significantly with mean arterial pressures (Figure A & B). LVMI was greater than that of controls (36.5±19 versus 29.5±27 mmHg; p<0.01) and cIMT was significantly less (0.37±0.05 versus 0.41±0.07 mm; p=0.03). All other biochemical markers of CVD injury were elevated above normal limits but did not correlate with NCD or echocardiographic measures.

**Conclusions:** In the present cross-sectional pilot study, pediatric HD patients had significantly lower NCD measurements than age-matched controls. NCD appears to be a valuable tool to detect early subclinical CVD risk in young hemodialysis patients. Further studies are very much warranted.

**TH-PO1076**

Peritoneal Membrane Transformation: Results from the International Pediatric Peritoneal Biopsy Study  
Bradley A. Warady,1 Betti Schaefer,2 Stephan Macher-Goeppinger,2 Maria Bartosova,2 Benjamin L. Laskin,3 Stefan Holland-Cunz,2 Franz S. Schaefer,2 Klaus P. Schmitt.2  
1Pediatric Nephrology, Univ of Miami/ Holtz Children’s Hospital, Miami, FL; 2Pediatric Cardiology, Univ of Miami/ Holtz Children’s Hospital, Miami, FL.

**Background:** The peritoneal membrane has not yet been studied systematically in healthy children and adults, and age dependent differences are unknown. In adults, acidic PD fluids with abundant glucose degradation products (GDP) induce major alterations of the peritoneum. The impact of exposure to these same fluids or to “biocompatible PD fluids” in children is unknown.

**Methods:** Standardized peritoneal specimens were obtained from 56 healthy children (0.1-16.6 yrs), 9 healthy adults (15-62 yrs), 56 children at time of PD catheter insertion (0.1-19.6 yrs) and 51 children on PD (0.3-20.1 yrs) from 26 centres in 14 countries. 46 patients had low GDP fluids.

**Results:** In controls, the mesothelial cell layer was mostly intact, but in young children calcification negative, indicating immaturity. Submesothelial compact zone was absent in 95% of samples, and submesothelial fat was missing in children under 2 yrs of age. Total submesothelial zone thickness was 269(207-370) μm. Capillaries were located in 3 layers (male: mean 545±79 μm before dialysis, 605±76 μm after dialysis; female: mean 523±76 μm before dialysis, 593±62 μm after dialysis). Accordingly, IVCD significantly decreased following a CCPD interval (male: mean 12.1±3.4 mm before dialysis, 10.2±3.0 mm after dialysis; female: mean 11.1±1.8 mm before dialysis, 8.8±2.2 mm after dialysis).

**Conclusions:** Bioelectric impedance analysis is an easy and reproducible method in children undergoing PD to determine body fluid volume on a daily basis. In contrast, determination of the IVCV is more laborious and combined with a greater observer variance. Although both methods simplify the assessment of fluid balance in children, the uncritical use of nomograms leads to false high dry weights with subsequent overhydration.

**Funding:** Clinical Revenue Support

**TH-PO1077**

The Bioelectric Impedance Analysis Using a Body Composition Monitor Allows Adequate Determination of Body Fluid Volume in Children and Adolescents following Peritoneal Dialysis  
Rainer Büscher.1 Univ Hospital Essen, Dept of Pediatrics II, Essen, Germany.

**Background:** The adequacy of body fluid volume in children requiring dialysis is difficult to assess and a gold standard for the best method of measurement is missing. Chronic overhydration or hypovolemia are serious side effects of an inadequate dialysis treatment and a major risk for cardiovascular sequelae. This study was performed to determine whether body composition monitoring (BCM) or sonographic measurement of the inferior vena cava diameter (IVCD) is a valid means to study overhydration in children following peritoneal dialysis (PD).

**Methods:** Fourteen children (7 male) undergoing PD (CCPD n=11, CAPD n=3), mean age 14.5±3.1 years (male) and 12.2±1.2 years (female), age at onset of dialysis 11.7±5.8 (male) and 11.1±3.4 years (female) were included. Using a BCM device (Fresenius, Bad Homburg, Germany) we determined resistance (R) as well as sonographic IVCV (mm) in supine position before and following a CCPD interval. In addition, SDS-blood pressure was monitored using a 24-h ambulatory blood pressure monitor (ABPM). Data are presented as mean±SD.

**Results:** Resistance as a marker of fluid reduction increased significantly following a CCPD interval (male: mean 545±79 Ω before dialysis, 605±76 Ω after dialysis; female: mean 523±76 Ω before dialysis, 593±62 Ω after dialysis). Accordingly, IVCV significantly decreased following a CCPD interval (male: mean 12.1±3.4 mm before dialysis, 10.2±3.0 mm after dialysis; female: mean 11.1±1.8 mm before dialysis, 8.8±2.2 mm after dialysis).

**Conclusions:** Bioelectric impedance analysis is an easy and reproducible method in children undergoing PD to determine body fluid volume on a daily basis. In contrast, determination of the IVCV is more laborious and combined with a greater observer variance. Although both methods simplify the assessment of fluid balance in children, the uncritical use of nomograms leads to false high dry weights with subsequent overhydration.

**Funding:** Clinical Revenue Support

**Table 1. Percent patient-months with kV≥1.8 by facility characteristics**

<table>
<thead>
<tr>
<th>Category</th>
<th># PD pediatric pts</th>
<th># Urban</th>
<th># Rural</th>
<th># facility Type</th>
<th># free-Standing</th>
<th># hospital-Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>0.14</td>
<td>0.02</td>
<td>0.16</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
</tr>
<tr>
<td>Facilities Medium % with kV≥1.8</td>
<td>0.15</td>
<td>0.02</td>
<td>0.16</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
</tr>
<tr>
<td>Children</td>
<td>68 (37, 79)</td>
<td>19 (17, 71)</td>
<td>68 (37, 79)</td>
<td>19 (17, 71)</td>
<td>19 (17, 71)</td>
<td>19 (17, 71)</td>
</tr>
<tr>
<td>Hospital-Satellite</td>
<td>5 (2, 9)</td>
<td>0.15</td>
<td>0.02</td>
<td>0.16</td>
<td>0.18</td>
<td>0.18</td>
</tr>
<tr>
<td>Rural</td>
<td>14 (7, 19)</td>
<td>5 (2, 9)</td>
<td>0.15</td>
<td>0.02</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>Free-Standing</td>
<td>12 (6, 18)</td>
<td>5 (2, 9)</td>
<td>0.15</td>
<td>0.02</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>Hospital-Hospital</td>
<td>1 (0.5, 2)</td>
<td>12 (6, 18)</td>
<td>1 (0.5, 2)</td>
<td>5 (2, 9)</td>
<td>0.15</td>
<td>0.18</td>
</tr>
</tbody>
</table>
| Facilities with >10 pediatric PD patients (21%, 630 patient-months) did not have a single kV≥1.8 reported. Among patient-months with kV≥1.8, 76% had a kV≥1.8 but this was 48% when patient-months without reported kV≥1.8 were included. On facility-level analysis, the median 50th patient-months with weekly kV≥1.8 was 63% (interquartile range 40% [16%–78%]). Facilities with >10 pediatric PD patients had a higher percentage with kV≥1.8 (median=56%; IQR: 17%-79%), compared to facilities with <10 patients (median=49%; IQR: 7%-71%). Better achievement was observed in urban hospitals, facility satellite facilities, and independent facilities [Table 1].

**Conclusions:** Many pediatric PD patients do not report kV≥1.8. When including patient-months without reported kV≥1.8, over 50% of patient-months did not meet the target. Facilities with more pediatric PD patients, rural facilities, hospital or freestanding facilities, and chain-associated facilities were less likely to meet the kV≥1.8 target.

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

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

Underline represents presenting author/disclosure.
Performance of Quality Measures for Pediatric Hemodialysis Patients

Sylvia Paz B. Ramirez,1 Alissa Kapke,2 Jeffrey Pearson,3 Jordan Janhke,1 Bradley A. Warady.1 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2The Children’s Mercy Hospital, Kansas City, MO.

Background: Published studies suggest improvement in mortality among pediatric patients receiving maintenance dialysis over time but mortality remains high; improved quality of dialysis care in this fragile patient group may further improve survival. Several pediatric ESRD quality measures received endorsement from the National Quality Forum (NQF) in August 2011 and in June 2012 were proposed for inclusion the CMS ESRD 2015 QIP. This study aims to examine the change in performance of these measures between 2011 and 2012.

Methods: Monthly hemoglobin (Hb) and dialysis adequacy measurements, and the achievement of spKt/V ≥ 1.2 were evaluated using Medicare claims data from 2011-2012. Monthly claims were aggregated by quarter for reporting purposes.

Results: Performance for the adequacy measures remained stable from Q1 through Q4. In Q8, the spKt/V ≥ 1.2 increased nearly 5% over all other quarters to 85%, while the %smoothly KiV not measured decreased by 5% to 11.5%. The %patients whose monthly Hgb was not reported remained over 25% through 2011 and decreased to 19% after August 2011. In April 2012, Medicare claims reporting instructions changed to require facilities to enter a Hgb value or 99.99 if Hgb was not reported, which appeared to be associated with a marked increase in reporting of Hgb levels (approximately 98% reporting). Figure 1. Quarterly performance of pediatric ESRD quality measures.

Conclusions: The pediatric ESRD quality measures analyzed in this study show some improvement in clinical performance over a two year period when several important steps were undertaken to implement the quality measures. Future analyses are needed to evaluate whether improvement in clinical performance measures is associated with improved health outcomes.

Inpatient Citrate Based Hemodialysis in Pediatric Patients

Rita D. Sheth, Cheryl P. Sanchez, Drew C. Cutler, Shobha Sahney. Pediatric Nephrology, Loma Linda Univ, Loma Linda, CA.

Background: Heparin use in inpatient hemodialysis is limited in critically ill or perioperative patients. Citrate based dialysate allows heparin avoidance.

Methods: Pediatric inpatient hemodialysis treatments (HDRx) were performed at a single institution over 1 year with a citrate based dialysis solution. Ica were monitored perioperative patients. Citrate based dialysate allows heparin avoidance.

Results: In patients ≥ 2.2 increased nearly 5% over all other quarters to 85%, while the %smoothly KiV not measured decreased by 5% to 11.5%. The %patients whose monthly Hgb was not reported remained over 25% through 2011 and decreased to 19% after August 2011. In April 2012, Medicare claims reporting instructions changed to require facilities to enter a Hgb value or 99.99 if Hgb was not reported, which appeared to be associated with a marked increase in reporting of Hgb levels (approximately 98% reporting). Figure 1. Quarterly performance of pediatric ESRD quality measures.

Conclusions: The pediatric ESRD quality measures analyzed in this study show some improvement in clinical performance over a two year period when several important steps were undertaken to implement the quality measures. Future analyses are needed to evaluate whether improvement in clinical performance measures is associated with improved health outcomes.

Long-Term Hemodialysis Therapy in Neonates and Infants with End Stage Renal Disease

Shirley Pollack,1,2 Israel Eisenstein,1,2 Daniella Magen,1,2 Mahdi Tarabei,1 Israel Zelikovic,1,2 Pediatric Nephrology, Rambam Medical Center; 2Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel.

Background: Peritoneal dialysis (PD) is the preferred mode of renal replacement therapy (RRT) in infants with end stage renal disease (ESRD). Hemodialysis (HD) is seldom used in neonates and infants because of the major complications of this procedure in the very young.

Methods: We analyzed demographic, clinical, laboratory and imaging data in all infants younger than 12 months with ESRD who received HD therapy in our Pediatric Dialysis Unit between 1997-2013. In 11/2006-patient were hemodialyzed.(HDx5 HDx8)

Results: Eighteen infants (M:F 6/12; Arabs/Jews 4/4) with ESRD (median age, 5 months; median wt, 3.8 kg) received HD through a tunneled central venous catheter (CVC) for a total of 16,292 days. Seventeen (94%) were neonates (< 1 month of age); group 1 and 11 (61%) were infants (1-12 months; group 2) who received HD for a cumulative 7141 days (44% of total) and 9151 days (56%), respectively. In 6 of the patients, the initial mode of RRT was PD for 1-3 months. Five (28%) of the patients had serious complications. Thirty eight CVC were inserted (34 angiographically). There were 5 episodes of CVC infection- a rate of 0.3/1000 CVC days. Median catheter survival time was 428 days. Five (28%) of the infants (2 in group 1) underwent renal transplantation and 6-10 year graft survival was 80%. Seven (38%) of the patients died. Most infants had good oral intake and only 4 (22%) required gastric tube. Thirteen (72%) of the infants displayed normal growth. Eight (44%) of the patients (5 in group 1) had delayed psychomotor development. Of these infants, 5 (3 with comorbidities) had abnormal brain imaging, 4 had seizures, and 3 had sensorineural deafness.

Conclusions: Long-term HD in neonates and infants with ESRD, performed in the appropriate setting, is technically feasible, can be implemented without major complications, carries a very low rate of CVC infection and malfunction, and results in good nutrition, growth and survival. Future efforts should aim to improve neurodevelopmental outcome and lower mortality rate, especially in treated neonates.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

Peers4PATH: Testing Peer Support as a Mechanism to Improve Transplant Outcomes among Adolescents with Solid Organ Transplants

Sandra Amalraj,1,2 Nina Foster,1 Amy Yang,2 Justine Shults,1 Susan L. Furth.1,2 1Pediatrics, Children’s Hosp of Phila, Phila, PA; 2Biostatistics and Epidemiology, Univ of Pa, Phila, PA.

Background: Medication nonadherence contributes to inferior allograft outcomes among adolescents with solid organ transplants (SOT). Factors intrinsic to adolescence such as wanting to feel “normal” like peers may impact medication taking behavior. Peers4PATH
is an NIDDK-sponsored randomized clinical trial to examine peer mentoring as a means to improve medication taking behavior and health-related quality of life (HRQOL) among adolescents. Methods: SOT recipients 14-23 years old at a single center are randomized to receive a gender- and race-matched peer mentor vs. usual care. Mentors meet in-person with mentees at 1, 6 and 12 months and communicate with mentees by phone, email or FaceBook at less frequent intervals. In 2017/2018 24 patients (median age 17, range 13-23) were enrolled. Primary outcomes are 1) change in percent medication adherence (by pharmacy refill data and 2) change in HRQOL (PedsQL 3.0 Transplant Module) over one year. Target enrollment is 60 subjects. This interim analysis examines initial feasibility and acceptability. Results: Since April 2017, 30 subjects have enrolled: 17 kidney, 7 liver, and 6 heart transplant recipients. 14 subjects have completed six months of the study (5 intervention, 9 control). Thus far, mentees report that: “my mentor understands me”, “is there for me” and “makes me feel important.” Mentees (vs. controls) also report greater interim improvements in HRQOL related to problems with medication taking.

Conclusions: Peers4PATH is one of the first clinical trials to examine peer support as a means to improve medication adherence and HRQOL among adolescents with SOT. In its early phase, this study has shown feasibility and good acceptability by subjects. Further data are needed to assess the efficacy of the intervention. Funding: NIDDK Support

TH-PO1084


Background: Health literacy in caregivers and patients is associated with poor outcomes in multiple medical conditions. Little is known about health literacy in pediatric kidney transplant recipients and their parents. As poor adherence is linked to poor graft function and graft loss in solid organ transplant recipients, we sought to determine the association between lower health literacy and markers of poor adherence.

Methods: In this cross-sectional study, we assessed the health literacy of 24 participants using validated measures; S-TOFHLA (Short Test of Functional Health Literacy in Adults), and REALM (Rapid Estimate of Adult Literacy in Medicine)-Teen & Transplantation. We compared the health literacy levels of adolescent patients and their parents based on S-TOFHLA and REALM scores. Adherence was measured both by self-report using MAM (Modified Adherence Module) and by calculating variability of immunosuppressant levels over a period of 6 months, by retrospective chart review. We used >2.5 standard deviation (SD) and >30% co-efficient of variation (CV) of immunosuppressant levels as markers of poor adherence, as shown in previous studies.

Results: Among 17 caregivers and 7 transplant recipients with median age 16.9 (IQR 15.7-19.7) yrs, all participants had adequate functional health literacy with S-TOFHLA scores >23. Five out of 24 participants (20%) had >78°8 grade equivalent level of health literacy (REALM score 45-60) although they had higher levels of education. All participants had a MAM score of >20%, which indicated good adherence by self-report. Lower health literacy levels (REALM scores ≤61) was associated with >2.5 SD of immunosuppressant level in 47% and >30% CV in 57 participants. Comparing 5 adolescent patients and their parents, lower health literacy levels of either of them, is associated with significant variability in immunosuppressant levels (SD=2.5 and CV%=30).

Conclusions: Lower health literacy of both caregivers and adolescent kidney transplant recipients are associated with poorer adherence. Improving health literacy and using targeting interventions in this population may improve transplant outcomes.

Funding: Pharmaceutical Company Support - Fellowship support from an unrestricted educational grant from Amgen.

TH-PO1085

Transfer from Pediatric Nephrology to Adult Nephrology Goes along with Deterioration of Transplant Function Christina Taylan, Michaela Gessner, Gesa Schalk, Rasmus J.C. Ehren, Lutz Thorsten Weber. Pediatric Nephrology, Univ Hospital of Cologne, Cologne. Germany.

Background: The transfer to adult nephrology implies a decisive turning point in the medical life of a patient in most cases.

Methods: We present data of 24 renal transplant recipients (21 ±4 years of age) who had been transferred to adult nephrologists between 2010 and 2012 (follow-up 24 – 3 months). Median follow-up after renal transplantation (RTx) was 31 (6-113) months. The following parameters directly before transfer and the most recent follow-up were analyzed: retention values, number of rejections, blood pressure, change of medication, personal contentment with the actual situation, obtained through telephone survey.

Results: In 20/24 patients plasma creatinine levels had increased 0,65 (0,24 - 4,32) mg/dl. Five patients had to be hemodialyzed intermittently following the transfer, four of which were admitted back to the dialysis program. One patient died 1,5 years after the transfer from a PTLD. 7/24 patients had to be treated for acute rejection after transfer versus 4/24 before. Medication changes were rather due to rejection to follow changes in blood pressure medication. 19/24 patients were content, but reported a temporary sense of insecurity after the transfer.

Conclusions: Deterioration of renal function and increased risk of acute rejection after transfer underline the need for optimization of the transition process. The potential reasons for the described problems after transfer are manifold and comprise lower consultation frequency, higher expected self-reliance, limited team support, larger patient numbers etc. A refinanced standardized program for young adult chronic kidney patients might help the patients to reveal deficits in coping with their condition and prepare better for the transition to adult patient care.

TH-PO1086

Adherence to Cysteamine Therapy and Renal Outcomes in Cystinosis Larry A. Greenbaum1, Ben Cadieux1. 1Pediatric Nephrology, Emory Univ, Atlanta, GA. 2Raptor Pharmaceuticals, Novato, CA.

Background: Early initiation and adherence to cysteamine therapy are essential in delaying progression to ESRD in cystinosis. Immediate-release cysteamine (IR-C) requires chronic, lifelong QOL dosing. Objective measures of long-term adherence are challenging to quantify. Adherent patients are believed to significantly delay the onset of ESRD (beyond 10 yrs) observed prior to cysteamine.

Methods: We examined 12 years (7/1997 to 6/30/09) of Florida Medicaid claims to characterize IR-C adherence among cystinosis patients (ICD-9 270 and ≥1 IR-C claim).

Results: Among more than 7 million Florida Medicaid enrollees, we identified 12 (8 male) ages 1 to 22 years with cystinosis. Of these, 9 pts were born after FDA approval of IR-C: median age of diagnosis was 18 mos (range 11-42 mos). The majority (8/9) initiated IR-C within 3 mos of dx (delayed 14 mos in 1 pt). Duration of IR-C follow-up ranged from 11 mos to more than 1 yrs in 3 pts (total of 729 mos). Monthly refills for IR-C were skipped 26 times (41% of eligible months; ranged from 0 to 60%); Number of refill gaps averaged 1.3 yrs (no gaps in 1 pt; <4 gaps in 4 patients; 12-25 gaps in 4 pts). Two pts appeared to have discontinued IR-C (gaps of 33 and 117 mos from last refill to last non-IR-C claim). Two pts reached ESRD at 9 and 11 years (skipped refill rates of 41 and 93%, respectively). Two pts reached CKD stage IV, each at 13 years (skipped refill rates of 22% and 53%, and each with an extended gap of 12 and 17 months, respectively).

Conclusions: Retrospective claims analysis provides a means of assessing adherence to cysteamine in patients with cystinosis. Adherence with IR-C in this small group of Florida Medicaid recipients with cystinosis is poor, and is associated with adverse renal outcomes. Future analysis will correlate adherence with health outcomes, and analyze changes in adherence following the recent introduction of delayed release cysteamine (q12h dosing formulation). Ongoing studies of adherence in this population are warranted.

Funding: Pharmaceutical Company Support - Raptor Pharmaceuticals

TH-PO1087

Trends in Hospitalizations, Emergency Room Visits and Economic Burden of Pediatric Nephrolithiasis Kirsten A. Kusumij, Brian Becknell, Andrew L. Schwadeeert. Pediatric Nephrology, Nationwide Children’s Hospital, Columbus, OH.

Background: Nephrolithiasis poses a significant health burden with an approximately 10% lifetime risk and over 2 billion dollars in annual hospital charges for adults. The goal of this study was to examine national trends in hospitalization, emergency room utilization, secondary diagnoses, and charges associated with pediatric nephrolithiasis.

Methods: Nationally weighted data from the Kids’ Inpatient Database of the Healthcare Costs and Utilization Project (HCUP) were evaluated from 1997-2009 for the total number of discharges, age, gender, length of stay, and hospital charges associated with nephrolithiasis. Secondary diagnoses were available on the basis of clinical classification software codes from 2003-2009. Data were also collected from the HCUP National Emergency Room Sample from 2006-2010 to yield the total number of pediatric Emergency Department (ED) visits associated with nephrolithiasis.

Results: The average number of pediatric discharges over the past 12 years with a primary diagnosis of nephrolithiasis increased by 30%. Mean hospital charges increased by 155% over this time frame, with aggregate hospital charges of $24,911,605 in 2009. 60% of patients were female, 47.5% were 15-17 years old, and length of stay was constant over this time period (2.3-2.7 days). Likewise, the number of pediatric ED visits increased by 15% from 359,771 in 2006 to 407,430 in 2010. The most common associated secondary diagnoses associated with nephrolithiasis between 2003-2009 were: urinary tract infections (626/4437, 14%); asthma (314/4437, 7%); epilepsy (180/4437, 4%); paralysis (178/4437, 4%). In 2009, secondary diagnoses of mood disorders and attention-deficit, conduct, and disruptive behavior disorders each occurred in 4% of children with nephrolithiasis.

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

Underline represents presenting author/disclosure.

346A
Conclusions: Hospitalizations and inpatient health care charges associated with pediatric kidney stone disease continue to rise. Pediatric nephrolithiasis is associated with comorbid diagnoses of asthma, ADHD, disruptive behaviors and mood disorders. This raises the possibility that some of these conditions and/or medications used in their management may contribute to increased kidney stone frequency.

TH-PO1088

Urinary Stone Risk Factors in Pediatric Patients in Eastern North Carolina

Axita C. Patel,1 Basema I. Dibas,1 Guillermo Hidalgo,1 Leonard Curtis Hymes,1 Hsiao L. Lai,1 Pediatrics, Div of Pediatric Nephrology, East Carolina Univ, Greenville, NC; 2Undergraduate Honors College, East Carolina Univ, Greenville, NC.

Background: The incidence of pediatric stone disease is rising. We hypothesized that the current trend of BMI elevation may be linked to increased urinary stone risk. Using Litholink 24-hour urinary analysis we identified stone risk distribution within pediatric patients in eastern North Carolina.

Methods: 143 consecutive Litholink collections from 100 patients obtained over a 2-year period from a single pediatric nephrology practice were analyzed with respect to BMI, gender and race. Indications for Litholink were history of kidney stone or treatment for urinary stone disease. Findings are similar to those in adults, with the exception of race where Black subjects had a 2-fold increased stone risk compared to White subjects.

Results: The average age was 11 ± 4.2 years, 50% female, 56% White, 13% Black, and 23% Hispanic. 108 collections met volume adequacy criteria and were included in analysis. Prevalence of 3, 4, or 5 plus urinary risk factors were 32.4%, 15.7%, and 9.3%, BMI did not correlate with number of stone risk factors although male patients with BMI >85th percentile did have higher prevalence of uric acid supersaturation (17.6 ± 5.5%) compared to lean counterparts. Predominant risks were high urinary sodium excretion (69.4%) and low urinary volume (45.6%) and supersaturation of calcium phosphate (31.5%). Low urinary citrate was found in 38% of females and 22.2% of males, with especially high rate in Hispanic females (62.1%). Hispanic patients in general had lower supersaturation rates of calcium oxalate and calcium phosphate.

Conclusions: A high incidence of multiple urinary risks was observed, however we did not find the expected correlation of BMI with high urinary stone risk. The results of this study emphasize raising urinary volume and lowering dietary sodium intake for all patients with stone risk. Hispanic patients appeared to have some protection against stone formation with lower urine saturation levels, but this was balanced by low urinary citrate levels. In female patients, especially Hispanic females, addressing low urinary citrate is a good strategy.

TH-PO1089

The Agony and the Ecstasy of a Career in Pediatric Nephrology

William A. Primack,1 Larry A. Greenbaum,2 Holly S. Ruch-Ross,2 Suzanne Kirkwood,3 Carrie Radabaugh,1 Kevin E.C. Meyers.1 UNC Kidney Center; Univ of North Carolina School of Medicine, Chapel Hill, NC; Emory Children’s Center, Emory School of Medicine, Atlanta, GA; 3Academic Academy of Pediatrics, Evanston, IL; 4Nephrology, Children’s Hospital of Philadelphia and Univ of Pennsylvania, Philadelphia, PA; 5Self Employed, Chicago, IL.

Background: There is a shortage of pediatric nephrologists in the U.S., and close to 20% of trained pediatric nephrologists no longer practice pediatric nephrology (PN). Defining the perceived strengths and weaknesses of a career in PN may help to address this critical manpower shortage.

Methods: The AAP in collaboration with the ASPN sent an 88 item electronic survey to members. Questionnaire was sent to 1918 members; 149 respondents returned the survey; 33% response rate.

Results: 500 responses were received (response rate 65.8%). 445 respondents provided data for this question.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Conclusions: Intellectual stimulation, the opportunity to teach, and the clinical areas of transplantation and critical care nephrology are the perceived strengths of a career in PN. However, critical lifestyle issues such as work-life balance, compensation and hours worked are potent detractors. Efforts to address these issues may help to alleviate the shortage of pediatric nephrologists.

TH-PO1090

First-in-Man Study with BAY 85-3934 – A New Oral Selective HIF-PH Inhibitor for the Treatment of Renal Anemia

Andreas Eichler,1 Silvia Lentini,1 Andreas Kaiser,1 Ingo Flamme,2 Dagmar Kubitza,2 Georg Wensing,1 1Clinical Sciences, Bayer Pharma AG, Wuppertal, Germany; 2Global Biostatistics, Bayer Pharma AG, Berlin, Germany; 3GTR-CH Acute Care Research, Bayer Pharma AG, Wuppertal, Germany.

Background: Renal anemia is mostly caused by insufficient erythropoietin production (EPO) synthesis in CKD patients. BAY 85-3934, a selective hypoxia-inducible factor (HIF)-PH inhibitor, has shown to increase EPO dose-dependently in animal models thereby stimulating erythropoiesis.

Methods: This first-in-man study was a randomized, single-blind, placebo-controlled, group-comparison dose escalation study in healthy male subjects (18-45 years). Single oral doses of 5, 15, 25, 35, 50, 125, and 300 mg of BAY 85-3934 PH inhibitor solution were administered to 12 subjects each (9 active, 3 placebo) to investigate safety, tolerability, pharmacokinetics and pharmacodynamics (EPO, reticulocytes, hemoglobin, and packed cell volume (PCV)).

Results: 59 (45 active, 14 placebo) subjects participated in the study. All 5 dosages were well tolerated. 14 subjects experienced 23 treatment-emergent adverse events (AE). 14 AEs were considered drug-related and all of mild intensity. The most common AEs were throat irritation (n=5) and headache (n=3). Frequency and quality of AEs were not related to dose. BAY 85-3934 was rapidly absorbed. Mean Cmax and AUC of BAY 85-3934 increased dose-proportionally. Mean terminal half-lifes (t1/2) ranged from 4.6 to 10.4 hours. The dose-dependent EPO increase resulted in a reticulocyte rise after 37.5 and 50 mg BAY 85-3934, whereas changes in hemoglobin and PCV were not measurable. Peak EPO values of 14.8 U/L (placebo; geo. mean) and of 39.8 U/L (50 mg) were observed about 12 hours post dose and reached baseline after approx. 24 hours. Vital signs, ECG and clinical laboratory parameters were not influenced.

Conclusions: The HIF-PH inhibitor BAY 85-3934 was well tolerated in healthy male subjects and EPO increased EPO dose-dependently, with a time course resembling the physiological diurnal variation of EPO. Therefore, it promises to be a valuable new treatment option for patients with renal anemia.

TH-PO1091

Effect of Different Doses of GQ-16, a Novel Partial Peroxisome Proliferator Activated Receptor Gamma Ligand, on Metabolic Parameters in Mice with Obesity and Insulin Resistance Induced by High Fat Diet

Alexandre Martini, Michela Soares Coelho, Francisco R. Neves. Pharmacetical Sciences Laboratory of Molecular Pharmacology, Univ of Brasilia, Brasilia, DF, Brazil.

Background: Thiazolidinediones (TZDs) were used for the treatment of type 2 diabetes (T2D), and they act by activation of peroxisome proliferator-activated receptor gamma (PPARγ). Despite their clinical efficiency, their use is limited by side effects such as weight gain and edema. This has prompted the search for novel PPARγ agonists with reduced side effects. We have previously described a novel partial PPARγ ligand (GQ-16) with similar anti-diabetic efficiency as ROSI, yet in the absence of weight gain, in obese and insulin-resistant mice treated with GQ-16.

Methods: Mice were fed a normal-fat diet (NFD, 10% kcal fat) or HFD (60% kcal fat) since weaning. At the age of 16 wk, mice were randomly assigned into six groups and received GQ-16 (5, 10 or 20mg/kg/d), ROSI (4mg/kg) or vehicle by gavage daily for 2 weeks (groups: NFD, HFD, HFD+ROSI, HFD+GQ15, HFD+GQ10 and HFD+GQ20).

Body weight (BW), BW gain, food, water and energy intake, metabolic efficiency, and fasting blood glucose were measured daily or weekly. Serum aspartate (AST) and alanine (ALT) transaminase levels were evaluated in adulthood. White adipose tissue (WAT) fat pad was excised and weighed for adiposity determination.

Results: BW, BW gain, WAT fat mass content, blood glucose and food intake were greater in the HFD group compared to the NFD group (BW: 67±4.2 g; F: 6.0±2.6 g) since weaning. At the age of 16 wk, mice were randomly assigned into six groups and received GQ-16 (5, 10 or 20mg/kg/d), ROSI (4mg/kg) or vehicle by gavage daily for 2 weeks (groups: NFD, HFD, HFD+ROSI, HFD+GQ15, HFD+GQ10 and HFD+GQ20). The dose-dependent EPO increase resulted in a reticulocyte rise after 37.5 and 50 mg BAY 85-3934, whereas changes in hemoglobin and PCV were not measurable. Peak EPO values of 14.8 U/L (placebo; geo. mean) and of 39.8 U/L (50 mg) were observed about 12 hours post dose and reached baseline after approx. 24 hours. Vital signs, ECG and clinical laboratory parameters were not influenced.

Conclusions: The HIF-PH inhibitor BAY 85-3934 was well tolerated in healthy male subjects and EPO increased EPO dose-dependently, with a time course resembling the physiological diurnal variation of EPO. Therefore, it promises to be a valuable new treatment option for patients with renal anemia.

TH-PO1092

Therapeutic Monitoring of Serum Mibozirine (MZ) Concentration Is Effective for Preventing Adverse Events and Successive Engraftment in Renal Transplant Recipients

Kazuki Shimoishi,1 Sachiko Jingami,1 Eiko Fukunaga,1 Hideyuki Saito.2 1Clinical Sciences Laboratory of Molecular Pharmacology, Univ of Brasilia, Brasilia, DF, Brazil; 2Global Biostatistics, Bayer Pharma AG, Berlin, Germany.

Background: MZ is an oral immunosuppressive agent for the prevention of rejection in renal transplantation. MZ exhibits a low incidence of cytomegalovirus (CMV) infection and severe adverse events, such as myelosuppression, hyperuricemia and hepatotoxicity, making it useful in long-term immunosuppression therapy. MZ is excreted predominantly in the urine (∼80%), and its therapeutic window is considered to be set at 1.0 - 3.0 μg/mL.

Conclusions: Intellectual stimulation, the opportunity to teach, and the clinical areas of transplantation and critical care nephrology are the perceived strengths of a career in PN. However, critical lifestyle issues such as work-life balance, compensation and hours worked are potent detractors. Efforts to address these issues may help to alleviate the shortage of pediatric nephrologists.

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

347A
of trough serum concentration. However, the effectiveness of therapeutic monitoring of serum MZ has not been evaluated in practice. This study was to investigate retrospectively the relationship between serum MZ levels and adverse events in patients with renal transplantation.

**Methods:** Serum MZ concentration was determined in 12 male and 6 female recipients with renal transplantation, in those MZ was administered once a day at an average dosage of 145 mg. The toxicity grade was evaluated by CTCAE version 4.0 criteria.

**Results:** The mean trough serum concentration of MZ in the whole recipients was 2.5 ± 1.7 μg/mL. The significant relationship was found between the trough MZ level and serum creatinine (r = 0.83), eGFR (r = 0.65) and hemoglobin (r = 0.63), whereas there was no significant correlation between the MZ levels and the data of white blood cell, platelet, bilirubin, AST, ALT. The average trough level (3.7 ± 0.3 μg/mL) of MZ in the recipients with Grade ≥ 2 anemia was significantly higher than the level (2.3 ± 0.6 μg/mL) in those with Grade 1/0 anemia. There was no recipient that experienced reversion or severe adverse events except for anemia. Two recipients with Grade 3 anemia was recovered by reducing the dosage or discontinue of MZ considering serum MZ levels.

**Conclusions:** In conclusion, therapeutic monitoring of the serum MZ level is suggested to be effective for maintaining the adequate serum levels to prevent both adverse events and reversion, as a clinical tool for personalized therapy in renal transplantation.

**TH-PO1093**

**Analysis of 424 NEPharm Database Consultations on Drug Dose Adjustment in Kidney Patients**

**Bhupinder Palmo and Michael Kielstein. Internal Medicine 1, Nephrology, Univ Hospital, Ulm, Germany.**

**Background:** Half of all drugs and their metabolites are excreted renally and approximately 30% of all adverse effects have a renal cause or a renal consequence [Arch Intern Med. 2005;165:790]. However, 70% of all drugs lack any recommendation for dose adjustment in the case of renal dysfunction [Clin Pharmacol Ther. 2000;67:196].

**Methods:** We have been building up the NEPharm database since 1978 and have extracted over 12,000 PubMed citations [Clin J Am Soc Nephrol. 2010;5:314]. Based on NEPharm, we have developed tables for dose recommendations [http://www.uni-ulm.de/nephrologie/fkd.html] and regularly receive consultant queries on drug doses which were evaluated here. The dose we recommend is generally targeting the peak level, for pharmacodynamic reasons. This was compared with the dose resulting from the proportionality rule according to Dettli [Ann Oncal. 2010;21:1395] where the individual dose (D) is obtained from the normal dose, the renally eliminated fraction (fren) and the filtration rate (GFR).

**Results:** In the period between 2010 and 2013, there was a total of 424 queries, 286 concerned cystostatic and anti-cancer drugs (68 %), 26 concerned anti-infective agents (6 %), 47 concerned other drugs (11 %) and 65 concerned the dosage table (15 %). Overall, queries came from 76 hospitals and from 150 physicians, of which 20 hospitals (26 %) and 30 physicians (19 %) also posed repeat queries. The number of queries increased by 8.6 times, from 8 in 2007 to 72 in 2012. Of the 359 queries regarding dose recommendations, 280 queries were for patients requiring hemodialysis (78 %), 9 queries for patients with peritoneal dialysis (2.3 %), 60 queries for patients with chronic renal failure (17 %) and a mean GFR of 45 ± 19 ml/min. Compared with 100 % of the standard dose, our dose recommendation is 92 ± 16 %; by contrast, according to Dettli, it is only 69 ± 19 % (p < 0.001).

**Conclusions:** Based on pharmacodynamic considerations, we made individual dose recommendations which were higher than the proportionnal dose adjustment according to Dettli. Because of the increasing and repeated queries, it can be assumed, however, that the recommendations given were helpful.

**TH-PO1094**

**Single and Multiple Dose Pharmacokinetics of Ethambutol and Rifampin in a Patient Undergoing Extended Daily Dialysis and ECMO**

**Ann-Kathrin Strunk, Julius Schmidt, Olaf Boenisch, Eva Schönenberger, Jan T. Kielstein. Dept of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany.**

**Background:** ARDS in tuberculosis is associated with an almost 100 % mortality, if antibiotic therapy is late or ineffective. New therapies, like administration of cefazolin was started. Single and multiple dose PK were obtained. We report single and multiple dose pharmacokinetics of ethambutol - EMB (renally cleared 80 %) and rifampin RIF under combined ED and ECMO.

**Methods:** A 42 year-old male (62 kg) i.v. drug user was admitted with progressive dyspnea and fever. Respiratory failure lead to intubation and ventilation. As adequate pao2 could not be achieved the patient was transferred to our center for ECMO support. Due to acute kidney injury extended daily dialysis (1.3 m² polysulfone dialyser, blood and dialysate flow of 230 ml/min, 10 hrs per day) was initiated. A bronchovascular lavage yielded mycobacterium tuberculosis. Treatment with RIF (600 mg/d), EMB (1000 mg/d), pyrazinamid and moxifloxacin was started. Single and multiple dose PK were obtained. Diaylzer clearance were calculated. Amount of both drugs in the collected spent dialysate as well as pre- and post the ECMO oxygenator were measured.

**Results:** EMB trough levels at 1000 mg/d were 1.5 mg/l, subtherapeutic (2-5 mg/l), promoting the doubling of the dose to 2000 mg/d. This lead to therapeutic levels of EMB (2.8-3.1 mg/l). Dialysier clearance of EMB was 91 ml/min, i.e. higher than previously reported.

**About 25% of EMB could be recovered in the spent collected Dialysate. There were no detectable effects of the ECMO membrane on the removal of both drugs.**

**Conclusions:** Therapeutic drug monitoring is recommended for patients with mycobacterium tuberculosis infection undergoing renal replacement therapy as adherence to outdated dosing recommendations yields subtherapeutic plasma levels.

**Funding:** Clinical Revenue Support

**TH-PO1095**

**Optimized Dosing of Cefazolin in Patients on Nocturnal Home Hemodialysis**

**Marisa Battistella, 1 Robert M. Richardson, 2, 3 Christopher T. Chan. 1-3 Univ Health Network, Toronto, Canada; 1Univ of Toronto, Toronto, Canada.**

**Background:** The uptake of Nocturnal Home Hemodialysis (NHD) use is increasing; however the dosing of antimicrobials with this modality has not been described. We hypothesize that intensive hemodialysis will augment dialytic clearance of cefazolin. Consequently, the dosing of cezaolin may need to be titrated appropriately. Subtherapeutic dosing may lead to treatment failure and microbiological resistance, while high concentrations of cefazolin may cause seizures. Our objective was to determine the pharmacokinetics of cefazolin during NHD and propose an appropriate dosing regimen.

**Methods:** We conducted a prospective, single arm pharmacokinetic study of cefazolin in 15 patients on NHD. Both blood and dialysate flow rates were set at 300ml/min. Patients received an intravenous dose of 2 grams of cefazolin over 30 minutes after their NHD. The following day patients were dialyzed at the NHD unit for 6 hrs and blood samples were drawn pre HD, 60, 180, and 360 (end of HD). Patients then received a second dose of 2 grams of cefazolin after HD and blood samples were drawn at the end of the 30 minute infusion, 30 and 60 minutes post infusion; dialysate samples were also drawn pre- HD, at 3 hours and then at the end of HD. Cefazolin levels were measured by HPLC.

**Results:** The mean age of the study population was 46±7.8 years; 9 males and 6 females were enrolled in the study. The mean percentage cefazolin removal by hrs of HD was 70±10% and clearance of cefazolin was 1.7±0.57 L/h while on dialysis; off HD, the clearance was 0.26±0.09 L/hr. Mean % of cefazolin on HD was 3.8±1.33, while off HD, mean %t1/2 was 23.2±4.5h. The distribution of volume was 9.0±2.9L.

**Conclusions:** Although 70% of the drug was removed during a 6 hour NHD session, serum drug concentrations remained above the target interval for microbiological eradication. Our study validates that 1 g of cefazolin dosed at the end of each dialysis is an appropriate approach to antimicrobial dosing in NHD. Monte Carlo simulation can now be utilized to design empirical dosing regimens that ensure the greatest probability of achieving the pharmacodynamic targets associated with maximal antimicrobial response.

**Funding:** Private Foundation Support

**TH-PO1096**

**Gentamicin Dosing Protocol for Empirical Therapy in Hemodialysis Patients**

**Lavren M. Vercaigne, 1, 2 Robert E. Ariano, 3, 1, 3 Sheryl Zelenitsky. 1, 3 1Faculty of Pharmacy, Univ of Manitoba, Winnipeg, Canada; 2Manitoba Renal Program, Winnipeg Regional Health Authority, Winnipeg, Canada; 3St. Boniface General Hospital, Winnipeg, Canada.**

**Background:** Gentamicin is an important antibiotic for empirical treatment of Gram-negative infections in hemodialysis (HD) patients.

**Methods:** Monte Carlo simulation methods were used similar to those described previously (Clin Infect Dis 2012;55:527) using pharmacokinetics estimated from a population-pharmacokinetic model developed in the HD population (Clin Pharmacokinet 2004;43:505). The dosing regimen used by the Manitoba Renal Program (1.5 mg/kg load followed by 1.0 mg/kg post-dialysis) was tested as the baseline in subjects with normal body weights (40-80 kg). A dosing strategy to achieve similar gentamicin concentration profiles and exposures in patients with heavier body weights was determined (Table 1). Table 1.

<table>
<thead>
<tr>
<th>BODY WEIGHT (kg)</th>
<th>DOSSING DOSE (after next dialysis session)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>1.25 mg</td>
</tr>
<tr>
<td>51-60</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>61-70</td>
<td>1.75 mg</td>
</tr>
<tr>
<td>71-90</td>
<td>2.0 mg</td>
</tr>
<tr>
<td>91-120</td>
<td>2.25 mg</td>
</tr>
<tr>
<td>&gt;120</td>
<td>2.5 mg</td>
</tr>
</tbody>
</table>

**Results:** The proposed dosing protocol provided very similar predicted peaks and troughs in patients ranging from 40-140 kg. Figure 1 shows first dose results for 500 simulated patients in the lower and upper weight categories. Figure 1.
TH-PO1097

Clearance of Drugs for Multiple Myeloma Therapy during In Vitro High Cut-Off Hemodialysis

Methods: During in vitro hemodialysis with human blood (blood/dialysate ultrafiltration flow rate 250, 500 and 5 mL/min, resp.) comparing a highly permeable HCO (Theralite™, 2.1 m²) to a high-flux dialyzer (HFHD; 2.1 m²), ultrafiltered volume was obtained. The Filtration Fraction (FF) was monitored (RF/QB).

Conclusions: The proposed dosing protocol provides similar predicted peak and trough gentamicin values in patients with body weights ranging from 40-140 kg. This protocol is suitable for empirical dosing of gentamicin over the first two HD sessions.

TH-PO1098

A Meta-Analysis of Extracorporeal Ultrafiltration versus Intravenous Loop Diuretics in Patients with Acute Decompensated Heart Failure (ADHF)

Methods: We searched MEDLINE and EMBASE (through March 2013) and prior meta-analyses for RCTs comparing ultrafiltration/hemodialysis versus intravenous loop diuretic regimens. Random-effect model meta-analyses were used to examine several endpoints, including mean difference in fluid removal and weight loss, hospital length of stay, worsening of renal function, and cardiovascular events.

Results: We identified 7 RCTs (578 patients). Fluid loss was significantly greater among patients receiving ultrafiltration compared to diuretics (-19.8 mL; 95% confidence interval [CI] -30.99, -8.97; P=0.0004). Weight loss was also significantly greater among patients using ultrafiltration (-2.45 kg; 95% CI -4.01, -0.90; P=0.002). There was a non-significant trend toward a decrease in hospital length of stay (-2.4 days; 95% CI -5.12, 0.31; P=0.08), but there was no effect on more meaningful endpoints such as all-cause mortality (pooled risk ratio 1.05; 95% CI 0.68, 1.61; P=0.86), hospital readmission (P=0.86), and worsening of kidney function (P=0.39).

Background: The efficacy of ultrafiltration in patients with ADHF has been evaluated in several randomized controlled trials (RCTs) with conflicting results. We conducted a meta-analysis to assess the efficacy and safety of ultrafiltration compared to intravenous diuretics in hospitalized patients with ADHF.

Conclusions: While extracorporeal ultrafiltration resulted in greater fluid and weight loss among hospitalized patients with ADHF compared to loop diuretics, other potential short- and long-term benefits of this invasive therapy could not be demonstrated.

TH-PO1099

Membrane Therapeutic Plasma Exchange (mTPE) Performed by Nephrologists: Early Technical and Clinical Experience

Methods: Data was prospectively collected on all pts receiving mTPE since program inception in January of 2013. Procedures used the Asahi Plasmaflo™ OP filter with the NxStage® System One™ machine. The mTPE was performed by dialysis technicians in cooperation with nursing staff. Albumin, Fresh Frozen Plasma (FFP) or a combination were used as replacement fluid (RF). Central venous access with targeted blood flow (QB) rate of 200 mL/min was obtained. The Filtration Fraction (FF) was monitored (RF/QB).

Results: A total of 200 mTPE procedures were performed in 41 pts over a five month period. The patients were 50±14 years old with a F:M ratio of 1.6:1. The pts had neurologic (71%), cardiac (65%), and renal (44%) conditions. The mean procedure time was 154±34 min. The mean mean procedure time was 154±34 min. The mean fluid loss was similar among all groups (mean difference 3 kg; 95% CI -4.4, -0.8; P=0.008). Weight loss was also significantly greater among patients using ultrafiltration -2.4 kg; 95% CI -4.01, -0.90; P=0.002). There was a non-significant trend toward a decrease in hospital length of stay -2.4 days; 95% CI -5.12, 0.31; P=0.08), but there was no effect on more meaningful endpoints such as all-cause mortality (pooled risk ratio 1.05; 95% CI 0.68, 1.61; P=0.86), hospital readmission (P=0.86), and worsening of kidney function (P=0.39).

Results: A total of 200 mTPE procedures were performed in 41 pts over a five month period. The patients were 50±14 years old with a F:M ratio of 1.6:1. The pts had neurologic (44%), nephrologists including renal transplant (32%) and hematology (17%) indications for therapy. RF was albumin in 57%, FFP in 38% and a combination of the two in the remaining treatments. Mean achieved QB was 179 mL/min. An average of 3746±909 mL of plasma was exchanged over 117±46 minutes (exchange rate of 35±10 mL/min). The average FF was 25%. Filter clotting was observed in 6% of treatments without the use of anticoagulation. This rate was similar (7%) in the small number of treatments that used anticoagulation (2 in 28 treatments). Parenthesia and cramping associated with FFP infusion was rare (1%). There were no central line-associated blood stream infections.

Conclusions: Nephrologists can safely and efficiently perform mTPE as an alternative to centrifuge-based therapeutic plasma exchange (cTPE). Advantages over cTPE include lack of anticoagulation and faster exchange rates, which could allow for shorter treatment time.

TH-PO1101

The Effect of N-Acetylcysteine on Methotrexate-Induced Nephrotoxicity: In Vitro Study in Renal Tubular Cells

Methods: We searched MEDLINE and EMBASE (through March 2013) and prior meta-analyses for RCTs comparing ultrafiltration/hemodialysis versus intravenous loop diuretic regimens. Random-effect model meta-analyses were used to examine several endpoints, including mean difference in fluid removal and weight loss, hospital length of stay, worsening of renal function, and cardiovascular events.

Results: We identified 7 RCTs (578 patients). Fluid loss was significantly greater among patients receiving ultrafiltration compared to diuretics (-19.8 mL; 95% confidence interval [CI] -30.99, -8.97; P=0.0004). Weight loss was also significantly greater among patients using ultrafiltration (-2.45 kg; 95% CI -4.01, -0.90; P=0.002). There was a non-significant trend toward a decrease in hospital length of stay (-2.4 days; 95% CI -5.12, 0.31; P=0.08), but there was no effect on more meaningful endpoints such as all-cause mortality (pooled risk ratio 1.05; 95% CI 0.68, 1.61; P=0.86), hospital readmission (P=0.86), and worsening of kidney function (P=0.39).

Conclusions: While extracorporeal ultrafiltration resulted in greater fluid and weight loss among hospitalized patients with ADHF compared to loop diuretics, other potential short- and long-term benefits of this invasive therapy could not be demonstrated.
Methods: Renal tubular cells (MDCK) and B-Lymphoma cells were exposed to MTX (10μM) alone and with NAC (2.5 mM). Reactive oxygen species (ROS) generation was measured by 2′,7′-dichlorofluorescin diacetate (DCFDA) and flow cytometer. Percentage apoptosis was also measured using flow cytometer. Calorimetric measurement of GSH production was assayed by glutathione assay kit (Cayman Chemicals) as per manufacturer’s instructions.

Results: Results are summarized in table below.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ROS generation in MDCK cells at 6 hrs</th>
<th>GSH generation in MDCK cells at 6 hrs</th>
<th>Uptake of NAC in MDCK cells at 4 hrs</th>
<th>Apoptosis in B cell lymphoma cells at 24 hrs</th>
<th>NAC or MTX alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX 10 μM</td>
<td>Increases</td>
<td>Increases</td>
<td>Increases</td>
<td>No significant change</td>
<td>66.5%</td>
</tr>
<tr>
<td>MTX 10 μM</td>
<td>Significant increases then MTX alone</td>
<td>Significant increases then MTX alone</td>
<td>Significant increases then MTX alone</td>
<td>No significant change</td>
<td>66.5%</td>
</tr>
<tr>
<td>NAC 2 mM</td>
<td>Increases</td>
<td>Increases</td>
<td>Increases</td>
<td>No significant change</td>
<td>66.5%</td>
</tr>
</tbody>
</table>

Conclusions: NAC may prevent MTX induced renal tubular cytotoxicity by reducing ROS and increasing GSH production. Using NAC for kidney protection might not interfere with the anti-tumor activity of MTX. Further preclinical and clinical studies should be conducted to check this effect.

TH-PO1102

Safety, Tolerability and Efficacy of Febuxostat in Patients with Hyperuricemia and Severe Renal Impairment: A 24-Week Prospective, Open-Label, Non-Controlled Study

Yuu Shibagaki, 1 Iwao Ohno, 1 Tatsuo Hosoya, 2 Kenjiro Kimura. 1

1Div of Nephrology and Hypertension, St. Marianna Univ Hospital, Kawasaki, Japan; 2Div of Nephrology and Hypertension, Jikei Univ School of Medicine, Tokyo, Japan.

Background: Hyperuricemia (HU) is a very common comorbid condition in patients with chronic kidney disease (CKD). The novel xanthine oxidase inhibitor, febuxostat, has been shown to be efficacious and well tolerated in patients with HU. However, safety, tolerability and efficacy of febuxostat are not well determined in patients with HU and severe renal impairment.

Methods: We conducted a 24-week prospective, non-controlled study to investigate the safety, tolerability and efficacy of febuxostat in patients with HU and moderate to severe CKD (stage 3b to 5). 71 prevalent adult outpatients (55 males with average age of 66.3 years, 18, 33, and 19 in stage 3b, 4, and 5, respectively) at two tertiary care hospitals who met the inclusion criteria [serum urate > 8 mg/dl, estimated GFR (eGFR) < 45 ml/min/1.73m2, non-use of urate lowering drug in the previous month] were recruited from November 2011 to April 2012. All the participants received febuxostat. Starting dose of febuxostat was 10 mg qd, increased to 20 mg, 40mg qd in week 4, and week 8, respectively. We observed during the study period the adverse events and adherence as a primary outcome and levels of serum urate as a secondary outcome.

Results: Baseline serum urate level (mg/dl) were 9.9, 10.6, and 8.8, in stage 3b, 4, and 5, respectively. 14 out of 71 participants (19.7%) were dropped out of the study. 8 adverse events (constipation, chest pain, edema, gout attack, palpitation, numbness, uric acid kidney stone) occurred in patients (8.5%). Out of 8 adverse events, 1 occurred in CKD stage 3b (5.6%), 5 in stage 4 (9.1%), and 2 in stage 5 (10.5%). Most adverse events were mild without permanent sequelae. Average serum urate in each stage of CKD reached below target of 6 mg/dl by 8 weeks in stage 5, and by 12 weeks in stage 3b and 4. More than 70% of participants reached this target by 24 weeks.

Conclusions: Treatment of hyperuricemia with febuxostat was safe, tolerable and efficacious in patients with CKD stage 3b to 5.

TH-PO1103

Carboxysteraselast (CES1) Single Nucleotide Polymorphism (SNP) Significantly Reduces Mycophenolic Acid (MPA) Associated Leucopenia in Renal Transplant Recipients (RTR) Natalie L. Borman, 1 Anthony Marinaki, 1 Gopalakrishnan Venkat-Raman. 1

1Wessex Renal and Transplantation Unit, Portsmouth; 2Guy’s and St Thomas, London.

Background: Mycophenolic acid precursors(MPAP) are widely used in transplantation. Adverse drug reactions are dose dependent and improve with reduction/cessation, but with increased rejection risk and poorer long-term graft survival. Genetic variability accounts for 20-90% of the individual variation in response to immunosuppression. Given these challenges, interest is growing in the use of pharmacogenetics to individualise drug regimens Aim: To identify and investigate associations of SNP’s with clinical response to MPAP in RTR.

Methods: 287 RTR were studied for primary outcome measures of biopsy proven acute rejection(BPAR) leucopenia(wcc<3) anaemia(Hb<10) gastro-intestinal side effects(GISE) and infection in all patients post transplant. Exosome sequencing was carried out using Illumina Human exosome Beadchip. Associations were sought between SNP’s and primary outcome measures. Extensive clinical data was collected in these patients.

Results: All participants received CN1(61.4% Cyc, 38.5% Tac) and MPAP(91.3% MMF 8.7% MPS), 60.9% male, 93.4% Caucasian, mean age at RTx 47 years (range 17-79). Primary outcome event rates were 10.8% and 34.5%. Results were analysed for associations between SNP’s and candidate genes and primary outcomes. Fisher’s exact test was used for allele frequency, dominant and recessive model analysis. Logistical regression was used to correct for confounders. 20 statistically significant results(P<0.05) were found in 13 SNP’s across 3 genes(UGT, SLCO1B1, CES1). Associations were seen with GISE and GISE, BPAR, anaemia, leucopenia and MPAP reduction. Example results are shown below, full results to be presented at conference.

Conclusions: This SNP in CES1 is significantly associated with leucopenia in MPA treated RTR. Non wild phenotype significantly reduced risk of leucopenia and time to leucopenia. This SNP would appear to have important clinical implications in this cohort.

TH-PO1104

Influences of Single Nucleotide Polymorphisms (SNP) on Mycophenolic Acid Tolerance and Side Effects in Renal Transplant Recipients (RTR) Natalie L. Borman, 1 Anthony Marinaki, 1 Gopalakrishnan Venkat-Raman. 1

1Wessex Renal and Transplantation Unit, Portsmouth; 2Guy’s and St Thomas, London.

Background: Mycophenolic Acid precursors(MPAP) are widely used in transplantation. Adverse drug reactions are dose dependent and improve with reduction/cessation, but with increased rejection risk and poorer long-term graft survival. Genetic variability accounts for 20-90% of the individual variation in response to immunosuppression. Given these challenges, interest is growing in the use of pharmacogenetics to individualise drug regimens Aim: To identify and investigate associations of SNP’s with clinical response to MPAP in RTR.

Methods: 287 RTR were studied for primary outcome measures of biopsy proven acute rejection(BPAR) leucopenia(wcc<3) anaemia(Hb<10) gastro-intestinal side effects(GISE) and infection in all patients post transplant. Exosome sequencing was carried out using Illumina Human exosome Beadchip. Associations were sought between SNP’s and primary outcome measures. Extensive clinical data was collected in these patients.

Results: All participants received CN1(61.4% Cyc, 38.5% Tac) and MPAP(91.3% MMF 8.7% MPS), 60.9% male, 93.4% Caucasian, mean age at transplant 47 years (range 17-79). Primary outcome event rates were 10.8% and 34.5%. Results were analysed for associations between SNP’s and candidate genes and primary outcomes. Fisher’s exact test was used for allele frequency, dominant and recessive model analysis. Logistical regression was used to correct for confounders. 20 statistically significant results(P<0.05) were found in 13 SNP’s across 3 genes(UGT, SLCO1B1, CES1). Associations were seen with GISE and GISE, BPAR, anaemia, leucopenia and MPAP reduction. Example results are shown below, full results to be presented at conference.

Conclusions: This SNP has shown several SNPs in genes known to be associated with MPA metabolism/excretion have a significant and important impact on clinical outcome after renal transplantation.

TH-PO1105

Effect of Erythropoietin on Hepatic Expression and Function of Cytochrome P450 Drug Metabolizing Enzymes in an Adenine-Fed Model of Chronic Kidney Disease David A. Feere, 1 Thomas Velenosi, 1 Anzel Hempen, 1 Brad Urquhart, 1,2 Schulpich School of Medicine and Dentistry, Dept of Physiology and Pharmacology, Western Univ, London, Canada; 1Lawson Health Research Institute, London, Canada; 1Medicine (Clinical Pharmacology/Nephrology), Western Univ, London, Canada.

Background: Chronic kidney disease (CKD) causes decreased hepatic drug metabolism secondary to a decrease in expression of drug metabolizing enzymes (DMEs). As kidney function declines, it loses the ability to produce erythropoietin (EPO) leading to anemia. Consequently, CKD patients are treated with recombinant EPO and the effect of this on hepatic drug metabolism is unknown.

Methods: Male Wistar rats were placed on an adenine (n=16) or chow diet (n=16) for 4 weeks prior to receiving 150μg/kg IP injections of EPO or vehicle saline every other day for 2 weeks. Hepatic DME expression was determined by real-time PCR. Rat liver microsomes were isolated to assess enzymatic activity of cytochrome P450 DMEs. Testosterone was used as a probe substrate for CYP activity and resulting metabolites were quantified by ultra-performance liquid chromatography with PDA detection.

Results: CYP3A2 expression was significantly decreased in EPO treated rats relative to controls (P<0.01). Significant reduction in CYP3A2 expression was also seen in CKD and CKD EPO treated rats relative to both control and control EPO injected animals (P<0.05). CYP2C11 expression was significantly decreased, relative to control, in CKD and CKD EPO but not in EPO control animals (P<0.001). Maximal enzyme velocity of CYP3A was significantly decreased, relative to control, in CKD and CKD EPO groups (95% CI 0.5-0.9, vs control 1.3, P<0.001) and CKD EPO groups relative to control (67%, 49% and 39% of control, respectively). CYP2C11 mediated metabolism of testosterone was significantly decreased (P<0.001) in the CKD and CKD EPO groups relative to control EPO (13% and 8% vs. 100% and 95% of control, respectively).

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

350A
Conclusions: EPO administration causes a significant decrease in CYP3A2 mRNA expression and enzymatic activity. Our data suggest that EPO and CKD both decrease hepatic drug metabolism and that EPO administration to manage anemia in CKD could affect drug metabolism and clearance of CYP3A substrates.

TH-PO1106
Expression and Function of Hepatic Drug Metabolizing Enzymes and Transport Proteins in End-Stage Renal Disease (ESRD)  
David A. Feere,1 Thomas Velenosi,1 Linda J. Asher,2 Andrew A. House,2 Thomas D. Nolin,3 Thomas Velenosi,1 David A. Feere,1 Michael J. Knauer,1 Michael A. Crowder,3 Linda J. Asher,1 Andrew A. House,2 1Physiology & Pharmacology, Western Univ, Canada; 2Schulich School of Medicine and Dentistry, Dept of Physiology and Pharmacology, Western Univ, London, Canada; 3Lawson Health Research Institute, London, Canada; 4Medicine (Clinical Pharmacology/Nephrology), Western Univ, London, Canada.

Background: Pharmacokinetics of several drugs are altered in end-stage renal disease (ESRD). Non-renal drug clearance pathways such as altered expression/activity of drug metabolizing enzymes and transporters have been implicated in rodent models of kidney disease however human data is controversial. In this study we assessed expression and function of hepatic drug metabolizing enzymes and drug transport proteins in liver samples from human patients with ESRD.

Methods: Liver samples were collected from ten recently deceased patients with ESRD and eleven recently deceased controls. Relative gene expression of drug metabolizing enzymes, transport proteins and nuclear receptors were determined by real-time PCR.

Results: Results show that select drug metabolizing enzymes and transport proteins are down-regulated in ESRD. Current studies are evaluating protein expression and enzymatic activity of hepatic microsomes from ESRD patients using specific P450 probe substrates. Our results suggest that drug transporter activity may be especially impacted in ESRD and likely explains the decrease in non-renal drug clearance observed in patients with ESRD.

Figure 1

Conclusions: We show a significant reduction in MDZ CI and Vd without changes in half-life suggesting decreased Vd and not hepatic intrinsic CI after MDZ PK in CKD. In addition, we show that the PK of MDZ is significantly different between HD and PD patients indicating that dialysis modality plays an underappreciated role in the PK of some drugs. In contrast, FEX pharmacokinetics are similarly altered in CKD, HD and PD patients. Collectively, our data indicate that dose adjustment for drugs that are not predominantly renally cleared warrants consideration in CKD.

TH-PO1108
Hepatic Drug Metabolizing Enzymes Are Downregulated by the Uremic Toxin Indoxyl Sulfate  
Thomas Velenosi,1 David A. Feere,1 Andrew Kai Cheong Wong,1 Brad Urquhart,12 1Physiology and Pharmacology, Western Univ, London, Canada; 2Medicine (Clinical Pharmacology/Nephrology), Western Univ, London, Canada.

Background: Patients with chronic kidney disease (CKD) require many medications to treat their CKD and associated co-morbidities. The majority of prescribed medications are metabolized by the drug metabolizing enzymes CYP3A and CYP2C. CYP3A and CYP2C expression is decreased in CKD; however the factors causing this downregulation are unclear. As kidney function declines, organic waste products accumulate in the blood resulting in uremia. It has been suggested that these waste products affect drug metabolizing enzyme function and expression. The objective of this study was to screen various uremic toxins to determine which toxin(s) affect hepatic drug metabolizing enzyme downregulation in CKD.

Methods: Hepatocyte cultures were prepared from human livers obtained from organ donors with a history of liver disease. Human liver cultures were treated with indoxyl sulfate. Relative expression of CYP3A and CYP2C was determined by qPCR.

Results: CYP3A mRNA expression was decreased when cultured with a cocktail of selected uremic toxins (P<0.05). Indoxyl sulfate (300 μM) was the only uremic toxin in the cocktail that significantly decreased CYP3A expression by 49% (P<0.05). Cell viability was unaffected at indoxyl sulfate concentrations routinely observed in CKD patients. Indoxyl sulfate treated rats had approximately 3-fold greater plasma indoxyl sulfate level than controls. Hepatic CYP3A2 and CYP2C11 mRNA levels were decreased 49% and 34%, respectively compared to controls. Results for the rat study are represented as n = 3 and are currently ongoing.

Conclusions: CYP3A and CYP2C expression are decreased in ESRD livers compare to control. Hepatic OATP1B3 expression was significantly increased in ESRD livers relative to controls (P<0.05). Significantly increased in ESRD livers compared to control. Hepatic OATP1B3 expression was significantly increased in ESRD livers relative to controls (P<0.05).

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

TH-PO1109
Tacrolimus Dose Requirement Based on the CYP3A5 Genotype in Renal Transplant Patients  
Jinghua Chen, Zhejiang Univ.

Background: To determine CYP3A5*1 and CYP3A5*3 genotype could be the predictive index of tacrolimus dose requirement.

Methods: We tested archival peripheral blood of 69 kidney recipients for CYP3A5 genotyping with PCR-SSP. We measured the dose-normalized blood concentrations of tacrolimus at 1 and 2 months after the renal transplantation.

Results: The frequency of CYP3A5*1 and CYP3A5*3 was 22/69 and 41/69. CYP3A5*1 was associated with significant lower tacrolimus dose adjusted concentration at 1 and 2 months after transplantation. Hepatic and renal function showed no significant effect on tacrolimus dose adjusted concentration at 1 and 2 months after transplantation. Gender did not show a significant impact on tacrolimus dose. Carriers of CYP3A5*1 allele had lower predicted measures for tacrolimus dose adjusted concentration and higher predicted measures for volume of distribution.

Conclusions: These results indicate that CYP3A5*1 carriers need higher tacrolimus dose than CYP3A5*3 homozygote to achieve the target blood concentration. CYP3A5*1 genotyping is a new approach for detecting tacrolimus dose requirement in kidney recipients.

TH-PO1110
Influence of Kidney Function on Overanticoagulation Related Hemorrhage Risk in Warfarin Users  
Nina A. Limdi,1 Sarah Booth,2 Thomas D. Nolin,1 Marisa B. Marques,1 Michael R. Crowley,1 Michael Allon,1 Timothy Mark Beasley,1 1Univ of Alabama at Birmingham; Tufts Univ; Univ of Pittsburgh.

Background: Patients with chronic kidney disease (CKD) require lower warfarin dose, have poor anticoagulation control and a higher hemorrhage risk than those without CKD. Herein we evaluate if CKD patients have a differentially higher risk of hemorrhage associated with the episodes of over-anticoagulation (INR>4); and slower over-anticoagulation reversal rate.

Methods: We evaluated the influence of kidney function on over-anticoagulation and hemorrhage in 1270 warfarin users. Reversal of over-anticoagulation was evaluated in a subset of 79 patients. Warfarin and metabolite concentrations, clotting factors (II, VII, IX and X), and prothrombin induced in vitamin K antagonism (PIVKA-II) and INR levels were assessed at presentation with high INR and after reversal. The influence of the CKD-INR interaction on hemorrhage risk was assessed by Cox proportional hazards regression. The influence of CKD on anticoagulation reversal (rate of INR decline) was assessed using linear regression and path analysis. Multivariable analysis accounted for clinical (age, sex, vitamin K dose) and genetic factors (CYP2C9, VKORC1, CYP4F2, GGCG) known to affect warfarin response.

Results: CKD patients experienced more frequent episodes of over-anticoagulation (p<0.0001) and a higher risk of hemorrhage (p=0.0001). The risk of hemorrhage was similar among patients with eGFR=60 and those with eGFR<45 mL/min/1.73 m2, and was modified by the INR at the time of the event (p=0.79). In contrast, the risk of hemorrhage was higher if the INR was >4 vs. <4 for patients with eGFR 30-44 (HR 2.7; 95%CI 1.1-
TH-PO1111
Anti-Depressant Dose and Adverse Outcomes in Chronic Kidney Disease

Varun Dev,1 Stephanie Dixon,1,2,3 Jamie L. Fleet,4 Sonja Gandhi,1,2 Amit X. Garg,1,2,5 Ziv Harel,4 Arsh Jaff,1,2 Salimah Z. Shariﬁ,1,4 1Schulich School of Medicine, Western University, London, Canada; 2Div of Nephrology, Western University, London, Canada; 3Dept of Epidemiology and Biostatistics, Western University, London, Canada; 4Institute for Evaluative Sciences, Canada; 5Leslie Dan Faculty of Pharmacy, Univ of Toronto, Toronto, Canada; 6Keenan Research Centre, Li Ka Shing Knowledge Institute, Toronto, Canada; 7Div of Nephrology, Univ of Toronto, Toronto, Canada.

Background: A lower dose of certain anti-depressants is recommended in patients with chronic kidney disease (CKD) to prevent drug accumulation from reduced elimination. In routine care this recommendation is often ignored.

Methods: We conducted a retrospective population-based cohort study to describe the 30-day risk of delirium and mortality in older adults from Ontario, Canada who initiated a higher vs. lower dose of three anti-depressants (paroxetine, mirtazapine or venlafaxine). We deﬁned delirium using the proxy of hospitalization with an urgent head computed tomography (CT) scan. We also determined if CKD status modiﬁed the risk of delirium and examined 30-day all-cause mortality.

Results: We identiﬁed older adults (mean age 75 years) who started a new study anti-depressant at a higher dose (n=36,651; 31%) or a lower dose (n = 81,160; 69%) between 2002 and 2011. Initiating a higher vs. lower anti-depressant dose was associated with a higher risk of hospitalization with head CT (incidence 1.09% vs. 1.27%; adjusted relative risk 0.90; 95% CI 0.80 to 1.02). This relative risk was not modiﬁed by the presence of CKD (interaction P value = 0.16). Initiating a higher vs. lower anti-depressant dose was associated with a lower risk of all-cause mortality (incidence 0.76% vs. 0.97%; adjusted relative risk 0.82; 95% CI 0.71 to 0.95). This relative risk was not modiﬁed by the presence of CKD (interaction P value = 0.68).

Conclusions: We did not observe an increase in adverse outcomes when anti-depressant was initiated at a higher dose in patients with CKD. Contrary to our hypothesis, the 30-day risk of mortality was lower in patients initiating a higher dose.

TH-PO1112
Exposure-Response Relationship for Atrasentan in Patients with Diabetic Nephropathy

Naël M. Mostafá,1 Chih-Wei Lin,2 Aksana Kaefer,2 Blai Coll,2 Dennis L. Andress,1 John J. Brennan,1 Cheri E. Klein,1 Walid Awwi,1 AbbVie,1 North Chicago, IL.

Background: The pharmacokinetics (PK) and efﬁcacy of atrasentan (ATR) in patients (pts) with diabetic nephropathy (DN) was studied in Phase 2 clinical trials (2 in Western and Japanese pts. 1 in Japanese pts). The objective of this analysis was to characterize the exposure-response relationship with mean predicted EC50 of 0.58 ng/mL and mean predicted Emax of 0.58 ng/mL. ATR PK and ER relationship were similar between Western and Japanese pts.

Funding: AbbVie, AbbVie Pharmaceutical Company Support - AbbVie.

TH-PO1113
Identiﬁcation of SULF-2 by Transcriptome-Wide Sequencing as a Candidate Nephrosis Factor in Childhood Nephrotic Syndrome

Richard F. Ransoms,1,2,3 4 Milan Popovic,1,4,5 Audrey Carol Papp,1,2 Amy Webb,2,6 Sarasawathi Sundararajan,2 Shippa Agrawal,7 Juan Luis Fernandez Martinez,9 Rainer Benndorf,1,4,5 Andrzej Kloczkowski,2,10 Wolfgang Saeed,5,6,7 William E. Smoyer,1,4,8 9 1Center for Clinical and Translational Research; 2Battelle Centre for Mathematical Medicine; 3The Research Institute at Nationwide Children’s Hospital; 4Pediatrics; 5Biomedical Informatics; 6Pharmacology; 7Program in Pharmacogenomics, Spain; 8The Ohio State Univ; 9Dept of Mathematics, Univ of Oviedo, Spain; 10The Midwest Pediatric Nephrology Consortium.

Background: Glucocorticoids (GC) induce remission of nephrotic syndrome (NS) in most children, though ~20% present with or develop GC resistance. This study was designed to identify candidate genes (nephrosis factors) that are associated with GC by comparing gene expression in circulating leukocytes between children with steroid-sensitive (SSNS) and steroid-resistant nephrotic syndrome (SRNS).

Methods: cDNA libraries were produced from mRNA from leukocytes collected at presentation (S1) and after the ~8 weeks of GC therapy (S2) from children with SSNS and SRNS. Deep sequencing yielded whole transcriptome sequencing data over a wide range of transcript expression. The collected complex data sets were then analyzed by statistical, ‘Extreme Learning Machine’ (ELM), and ‘Particle Swarm Optimization’ (PSO) approaches to obtain candidate nephrosis factors.

Results: Transcriptome-wide deep sequencing identiﬁed numerous known GC-regulated genes. Expression analysis of the ELM and PSO algorithms identiﬁed the gene “extracellular endoglucosamine-6-sulfatase 2” (SULF2) to be associated with clinical responsiveness to GC in these children. The biological relevance of these ﬁndings to NS was then conﬁrmed by demonstration that the plasma SULF2 enzyme activity ratio (S2/ S1) was greater in children with SSNS vs. SRNS.

Conclusions: SULF2 is a secreted enzyme necessary for full activity of a variety of growth factors, and known to be crucial for podocyte homeostasis. Our ﬁndings suggest that SULF2 may act as a “positive” nephrosis factor, where a deﬁciency in circulating SULF2 activity may result in the development of NS.

Funding: Other NIH Support - Supported in part by NIGMS U01 GM092655

TH-PO1114
Transcriptome Proﬁle from Leukocytes of Children with Steroid Sensitive and Resistant Nephrotic Syndrome

Sheptra Agrawal,1 Amy Webb,2 Richard F. Ransoms,1 Audrey Carol Papp,1 Milan Popovic,1 Rainer Benndorf,1,4 Wolfgang Saeed,5 William E. Smoyer,1,4,7 1Center for Clinical & Translational Research, The Research Institute at Nationwide Childrens Hospital; 2Biomedical Informatics; 3Pharmacology; 4Pediatrics; 5Pharmacogenomics, The Ohio State Univ; 6The Midwest Pediatric Nephrology Consortium.

Background: RNA-sequencing is emerging as a powerful tool for transcriptome analysis and identiﬁcation of disease biomarkers. The present study aims to generate the transcriptome landscape from children with steroid sensitive and resistant nephrotic syndrome (SSNS and SRNS) and to explore its potential in identifying biomarkers for SRNS. This is important because ~20% of NS cases present with or develop resistance to steroid therapy, due to largely unknown reasons.

Methods: RNA-sequencing was performed with SOLID™ technology from SSNS and SRNS leukocytes collected at disease presentation and after ~8 weeks of steroid therapy. After alignment with Lifescope, transcript expression was measured with Cufflinks. Single nucleotide polymorphism analysis (SNP) was performed using the Mann-Whitney U test and used to obtain candidate genes for expression differences associated with SRNS. Alternative transcripts were identiﬁed by splicing junction alignment, SNPs detected by Samtools and AEI calculated. Databases and genes for steroid sensitivity/resistance in leukocytes and of relevance to NS are being integrated into the transcriptome data.

Results: Of 23,080 gene transcripts (including non-coding) studied, 4018 showed >1.4 fold ratio change between SSNS and SRNS. These included PTGS2 and C7T4NP3 (type of Neurexin), potentially relevant to NS, and numerous differences among these groups along the varied parameters (i.e. expression, AEI, splice variants) and provides the potential to identify novel biomarkers for SRNS.

Funding: Other NIH Support - Supported in part by NIGMS U01 GM092655

TH-PO1115
Intravitral Multiphoton Microscopic Imaging of the Effect of Chronic Kidney Disease on Hepatocellular Transport

Brian S. Decker,1 Jennifer Ryan,2 Ken Dunn,1 Indiana Univ School of Medicine.

Background: Animal studies have shown that the uric solutes of chronic kidney disease (CKD) attenuate CYP450 enzyme and hepatocyte transporter activity. These animal studies utilized incubated hepatocytes with uric serum and measured the extent of mRNA transcription of the specific CYP450 enzyme or drug transport protein. Though the cultured cells provide a reproducible system, they cannot duplicate the cellular interactions

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
that occur in living organisms. A more powerful research tool is intravital multiphoton microscopy (IVM) which provides direct visualization of drug transport and anatomic features in living organisms. A more powerful research tool is intravital multiphoton microscopy.

**Methods:** Chronic kidney disease was induced in six Sprague-Dawley rats using a two-thirds nephrectomy. Three Sprague-Dawley rats received sham surgeries and served as controls. On day 42 post surgery, the CKD and control rats were prepared for intravital multiphoton microscopy.

**Results:** In adult mice, RFP labeled almost all of principal cells (Aqp2+ and Calbindin-D28k+, and vast majority of intercalated cells (CAII+, V-ATPase B1B2+, AE1+, and aquaporin-2 (Aqp2)) throughout the whole kidney. However, RFP was detected in none of cells in the cortex were RFP+.

**Conclusions:** RFP faithfully recapitulates the temporal and spatial expression pattern and served as controls. On day 42 post surgery, the CKD and control rats were prepared for intravital multiphoton microscopy.

**TH-P01I18**

**Activated Omentum Slows Progression of Chronic Kidney Disease**

Ignacio García-Gomez,1 Nishit Pancholi,2 Jilpa Patel,3 Krishnamurthy P. Gudehithlu,1 Perianna Sethupathi,2,3 Peter D. Hart,2,4 George Dunca,1,2,3 Jose A.L. Arruda,1,2,3 Ashish K. Singh,1,2,3 "Dir of Nephrology, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL; 2Hektoen Institute of Medicine, Chicago, IL; 3Section of Nephrology, Univ of Illinois Medical Center at Chicago, Chicago, IL; 4Internal Medicine, Rush Univ Medical College, Chicago, IL.

**Background:** We examined whether attaching the omentum (a source of mesenchymal stem cells) to a subtotally nephrectomized kidney could slow the progression of chronic kidney disease.

**Methods:** Two groups of rats were studied, an experimental group which underwent 5/6 nephrectomy (removing left kidney and 2/3 of the remaining kidney), and a control group that underwent 5/6 nephrectomy as well as complete omentectomy. Polyclonal gel particles were added intravenously and the activated omentum attached to the omentum and facilitated its attachment to the injured kidney. Control omentectomy rats did not receive polydextran particles.

**Results:** After 12 weeks the experimental rats having omentum attached to the remnant kidney had 30% lower plasma creatinine and 50% lower urine nitrogen levels, 30% less glomerulosclerosis, 30% less tubulointerstitial injury, and reduced extracellular matrix and thickening of basement membranes. A fusion zone formed between the injured kidney and the omentum abounded in mesenchymal stem cells positive for sca-1, W1 and CD 34, suggestive of an active and healing tissue. Kidney extracts showed a four-fold increase in VEGF levels at 1-4 weeks as well as significant increases of HGF and IGF-1 levels, increased number of proliferating cells especially at the injured edge, 2-fold increase of W1-t cells in the glomeruli and 5-fold increase in the gene expression for W1-t.

**Conclusions:** These results suggest that the activated omentum attached to the injured kidney slowed the progression of chronic kidney disease. The effect appears to be brought about by the presence of stem cells and their secretory products in the vicinity of the injured kidney.

** Funding:** Private Foundation Support

**TH-P01I19**

**Stem Cells in the Repair of the Damaged Mesangium: An Ultrastructural Study**

Jiamin Teng, Elba Turbat-Herrera, Guillermo A. Herrera. *Pathology, LSU Health, Shreveport, LA.*

**Background:** In previous studies our group has shown the role of stem cells in repair of the damaged mesangium in a model of light chain-mediated mesangial injury. Mechanistically, the stem cells selectively home to the damaged mesangial areas and proceed to repair them.

**Methods:** Rat kidneys (n=10) were procured and maintained physiologically intact using a perfusion model previously described by us. Using this ex-vivo renal perfusion model, the renal artery was perfused with purified glomerulopathic light chains (GLC) obtained from the urine of patients with renal biopsy-proven AL-amyoilodiosis and light chain deposition disease. 10μ/ml of purified light chains were used to perfuse the renal artery. The perfused GLC reached the mesangium and were allowed to interact with peritubular capillaries and surrounding matrix for 24 hours. Subsequently, mesenchymal stem cells were perfused through the renal artery. Tissue for light microscopic, immunofluorescence, and ultrastructural evaluation was obtained at different time frames up to 96 hours post stem cell perfusion.

**Results:** Using transmission electron microscopy, stem cells were observed in glomerular capillaries and in the neighborhood of damaged mesangial areas where there was either amyloid or increased extracellular matrix. Furthermore, the light chains engaged in phagocytosis of amyloid and altered mesangial constituents, as they cleaned the damaged areas. With time, stem cells which normally have a very small amount of cytoplasm essentially devoid of organelles, were transformed into primitive mesangial cells as they acquired cytoplasm with contractile elements.

**Conclusions:** This study provides objective evidence of the crucial action of stem cells in the repair of the damaged mesangium. Stem cells are attracted to the damaged areas, clear the damaged mesangium, and differentiate into mesangial cells eventually laying down new mesangial matrix.

**Funding:** Private Foundation Support

**TH-P0120**

**Repair and Regeneration of the Diabetic Kidney**

Tarig Jayed, Kuntal Mohare, Himanshu Vashistha, Leonard G. Meggs. *Nephrology, Ochsner Clinic Foundation, New Orleans, LA.*

**Background:** The adult kidney retains intrinsic regenerative potential, but the identity of adult stem cells remains in question. Src homology transforming protein 1 (p66) controls mitochondrial metabolism and cellular responses to oxidative stress, aging and apoptosis. Our working hypothesis is kidney mesenchymal stem cells (MSC) genetically deficient in p66 (p66-/-MSC) will be resistant to senescent and apoptosis phenotype(s) associated with diabetes, participating in organ maintenance and repair through self renewal, autocrine/paracrine mechanisms and regenerative properties.

**Conclusions:**

- **TH-P0116**
  - Renal Tissue Engineering Based on Decellularized Matrix Scaffolds
  - Barbara Ronzindri,1 Marina Figituzzi,2 Evangelia Papadimitriou,1 Marina Morigi,1 Fabio Belli,1 Giuseppe Brennig,1 Giuseppe Remuzzi,2 Andrea Remuzzi,2,3,4 IRCCS - Mario Negri Institute, Bergamo, Italy; 1Univ of Bergamo, Dalmine, Italy; 2Papa Giovanni XXIII Hospital, Bergamo, Italy.
  - **Background:** Chronic kidney disease is a leading cause of mortality and morbidity. New strategies to replace function of severely damaged kidneys are needed due to limited regenerative capacity and organ donor shortages. The concept of using decellularized animal kidneys for engineering a functional organ is a potential future treatment option. The aim of the present study was to produce a three-dimensional whole kidney scaffolds by a decellularization process and to recellularize the scaffolds with mouse embryonic stem (mES) cells under physiological perfusion condition.
  - **Methods:** We obtained whole organ scaffolds with intact 3D geometry and vasculature by decellularization of rat and porcine kidneys, as shown by histologic examination. TEM and SEM analysis confirmed the preservation of kidney architecture. Micro-CT scan established integrity, patency and connection of the vascular network. Immunohistochemistry demonstrated preservation of native expression patterns of extracellular matrix proteins, with collagen IV, laminin and fibronectin.
  - **Results:** We repopulated acellular rat kidneys with mES cells seeding the cells through the renal artery and perfusion of cell medium for up to 3 days. Seeded cells were completely retained into the organ and uniformly distributed in arterial tree and in glomerular capillaries, without major signs of apoptosis. mES cells lined the luminal surface of arterial vessels and express endothelial markers. Occasionally mES cells reached peritubular capillaries and tubular compartment.
  - **Conclusions:** Our findings indicate that rat and porcine kidneys can be successfully decellularized, creating a vascular matrix that can be used to scaffold tissue engineering. Decellularized kidneys retain their basic components and show intact vasculature. We also demonstrated the ability of the decellularized matrix to support the engraftment of mES cells in a continuous perfusion system. This is an important step toward development of a tissue engineered kidney.

- **TH-P0117**
  - Aqp2 Is the Missing Progenitor Cell Marker of Renal Principal and Intercalated Cells
  - Lihe Chen,1 Zhou Xiao,1,2 Qiaoling Zhou,2 Wenzheng Zhang,1 "Univ of TX Medical School at Houston; 2Central South Univ.
  - **Background:** While the renal principal and intercalated cells regulate the electrolyte/ fluid and acid-base balance, respectively, the progenitors of these cells remain mysterious, because a specific lineage-tracing marker is still not available.
  - **Methods:** We developed an Aqp2-lineage tracing mouse model. These mice harbor a targeted mutation of the Gt(ROSA)26Sor locus with a loxP-framed fluorescent protein (Rosa-RFP). They carry an Aqp2Cre transgene that permits Cre expression under the control of Aqp2 regulatory elements. A series of double immunofluorescence staining experiments were performed.
  - **Results:** In adult mice, RFP labeled almost all of principal cells (Aqp2+ and Calbindin-D28k+) and intercalated cells (CAII+, V-ATPase B1B2+, AE1+, and Pendrin+). 4 and 2-day post surgery. The CKD and control rats were prepared for intravital multiphoton microscopy.
  - **Conclusions:** 1) RFP faithfully recapitulates the temporal and spatial expression pattern of the endogenous Aqp2; 2) Expression of Aqp2 is detectable at E14.5; 3) Aqp2-lineage cells give rise to Aqp2+ principal cells and intercalated cells (V-ATPase B1B2+ and CAII+) at E16.5; 4) Most of α-IC (AE1+) and JIC-PC (Pendrin+) are derived from Aqp2-lineage cells around day 7 after birth; 5) Aqp2 is the missing progenitor cell marker of renal principal and intercalated cells; and 6) The double transgenic mice (Rosa-RFP/Aqp2Cre+) is a valuable model to study cell differentiation under normal and pathological conditions. 

**Funding:** NIDDK Support
Methods: Akita (Ins2ΔC57B6) diabetic mice were crossed with p66h(+/−) (KO) mouse to generate p66h(−/−) Akita mice. Kidney MSC were isolated and expanded in culture. By immunocytochemistry 90% of MSC expressed stem cell antigen-1 (Sca-1) but did not express hematopoietic markers c-kit, CD31,CD34, CD45, CD106.

Results: p66−/−MSC show no increase in ROS metabolism, when maintained at high ambient glucose (HG), whereas wild type (WT) MSC show robust ROS signal. Growth curve of p66h(−/−) MSC at HG, were markedly attenuated by day 6. By contrast, p66h(+/−)MSC remained in active growth phase up to 12 days. Consistent with this analysis, WT MSC show upregulation of senescent associated proteins (p21, p53 and p16INK4a), DNA damage and apoptosis; all of which were suppressed p66h(−/−)MSC. We identified Sca-1+CD34−lin MSC and p66h(+/−) cells in kidneys of p66h(−/−) Akita, but these cells were rarely encountered in WT and Akita. Senescent phenotypes associated with diabetes (glomerulosclerosis; interstitial fibrosis; tubular atrophy), were barely detectable in p66h(−/−) Akita, with near normalization of urine albumin excretion (UAE), whereas in Akita, kidney lesions and UAE were substantially increased.

Conclusions: Kidney MSC genetically enhanced by p66 null mutation offer a potential strategy to repair and regenerate the diabetic kidney.

Funding: Private Foundation Support

TH-PO1121

Bone Marrow-Derived Mesenchymal Stem Cells Transplantation Repairs Glomerular Podocytes in Mouse with Pumoyumcine Aminonucleoside-Induced Nephrosis. Jian-Xin Wan, Nephrology, The First Affiliated Hospital of Fujian Medical Univ, Fuzhou, Fujian, China.

Background: To investigate the effects of bone marrow derived stem cells (BMSCs) on nephropathy of glomeruli in pumoyun amino nucleoside (PAN) nephritic mice models.

Methods: Isolating bone mesenchymal stem cells from the bone of mice. The model of mice was established by PAN. Then the mice were randomly divided into three groups: Control group, PAN group and BMSCs group. The 24-hour urinary protein was obtained from each group after modeling, and urinary protein excretion was determined. The mice were killed for the blood samples and kidney specimens after the tenth day of modeling. The blood sample were collected for measuring Scr and Bun. The one part of kidney specimens was taken for observing the pathological changes by HE staining and electronmicroscope, and the other part is for detecting the expression of the protein and mRNA of Nephrin, CD2AP, synaptopodin, TRPC6 by the methods of real-time quantitative PCR, western-blot and immunohistochemistry.

Results: After tail vein injection of PAN (0.5 mg/g) into the BALB/C mice, foot process fusion phenomenon was detected by electron microscopy, and the 24-hour urinary protein excretion increased significantly than control mice on day 3, day 7 and day10 (P<0.05). The fusion of foot processes in glomerulus was ameliorated after the transplantation of BMSCs, and the 24-hour urinary protein decreased (P<0.05). The expression of nephrin, CD2AP, synaptopodin in the glomerular slit diaphragm (SD) were up-regulated than PAN nephropyathy model mice (P<0.05) while TRPC6 was down-regulated (P<0.05).

Conclusions: Administration of PAN induced foot process fusion and proteinuria, thus successfully established minimal change nephropathy models. BMSCs transplantation could reduce foot process fusion and urine protein, and protect the podocyte damage caused by PAN.

TH-PO1122


Background: Models in our and most investigations of seeding cells into acellular whole organ scaffolds for tissue regeneration have used rodent kidneys. For human applications, however, there is a paucity of research decellularizing swine kidneys, which are the most common source of organs needed further time to remove residual detergents. Fluid limited to approx 40 mm

Results: After tail vein injection of PAN (0.5 mg/g) into the BALB/C mice, foot process fusion phenomenon was detected by electron microscopy, and the 24-hour urinary protein excretion increased significantly than control mice on day 3, day 7 and day10 (P<0.05). The fusion of foot processes in glomerulus was ameliorated after the transplantation of BMSCs, and the 24-hour urinary protein decreased (P<0.05). The expression of nephrin, CD2AP, synaptopodin in the glomerular slit diaphragm (SD) were up-regulated than PAN nephropyathy model mice (P<0.05) while TRPC6 was down-regulated (P<0.05).

Conclusions: Administration of PAN induced foot process fusion and proteinuria, thus successfully established minimal change nephropathy models. BMSCs transplantation could reduce foot process fusion and urine protein, and protect the podocyte damage caused by PAN.

TH-PO1124

Development of Renal Regeneration with Human Renal-iPS Cells Using Epigenetic Memory Osamu Takeaka, Keichi Hisihikawa. Dept of Advanced Nephrology and Regenerative Medicine, Graduate School of Medicine, Univ of Tokyo, Tokyo, Japan.

Background: We have investigated about the renal regeneration with human Renal-iPS cells using epigenetic memory. Recently, it has been suggested that iPS cells derived from specific tissue is easy to differentiate into the original cells. We have already established original three R-iPS cells derived from tubular cells, mesangial cells, and proximal tubular cells. On DNA-methylation analysis in epigenetics, the undifferentiated marker and undifferentiation character such as nephrin and p-cadherin which was mitigated in the presence of AFSC. Activation of this pathway involved both AT1 and AT2 receptors and blockade of one or the other resulted in a dampering of the response. In vivo, injection of AFSC in Alport mice resulted in a significant downregulation of ILK protein levels at 10 weeks post treatment. More specifically, in glomeruli injected with AFSC lower expression of ILK was detected when compared to a non-treated sibling, indicating that AFSC regulates ILK expression in glomerular cells including the podocyte. Treated kidneys also had less presence of b-catenin at protein level.

Conclusions: AT1 and AT2 receptors play a significant role in mediating Ang II induced podocyte injury. Taken together our data suggest that AFSC contribute to podocyte preservation by preventing the activation of Ang II receptors, which trigger injurious mechanisms that result in podocyte depletion.

Funding: Other U.S. Government Support, Private Foundation Support
Developmental Expression of Stem Cell Factor Receptor c-kit Is Lost in Adult Renal Cortex, but Detected Following Renal Injury in Glomerular Cells

Kotlikoff, 2 Christian Hugo, 1 Bernd Hohenstein. 1

Background: Stem cell factor receptor c-kit is a central marker of hematopoietic stem cells (HSC) and we previously showed that HSC are recruited to the kidney upon injury. c-kit was described as a marker of resident stem cells in the heart. c-kit expression has been studied in prenatal mice and can be detected in the renal medulla (collecting duct). Less is known about the localization and fate of c-kit expressing cells after birth and during renal injury. We now used c-kit eGFP transgenic mice to investigate expression patterns of c-kit positive cells in the kidney after endothelial injury.

Methods: We studied c-kit eGFP transgenic mice during late renal development in healthy adult mice and after selective endothelial injury. Mice were sacrificed 4-6 days post-partum, and control and injured 10 week old mice were examined 1, 3 and 5 days after selective endothelial injury using anti c-kit antibodies. Flow cytometry and immunohistochemistry were performed.

Results: Around day 5, a large set of cortical renal cells demonstrated c-kit expression. Many c-kit+ cells could be found in the medulla, which was described before in renal development. Tubules as well as cells of Bowman’s capsule and many glomerular cells expressed c-kit, while adult mice lack c-kit+ cells in the cortex and glomeruli (except collecting duct cells). Following renal injury, c-kit positivity could be detected in tubules and glomeruli, localized in endothelial and podocytic positions. In addition, c-kit+ cells were also detected outside tubules along peritubular capillaries.

Conclusions: Many renal cells express c-kit during development, while adult mice virtually lack c-kit+ cortical cells. After injury, c-kit+ cells increased, which is consistent with our previous data on c-kit+ HSC using FACS analysis. Whether these c-kit+ cells immigrate from outside or consist of c-kit expressing resident renal cells needs to be clarified.

Endothelial Progenitor Cells Recruited to the Kidney Do Not Originate from Bone Marrow

Jan Sradnick, 1 Anika Luedemann, 1 Vladimir T. Todorov, 1 Michael Kotlikoff, 1 Christian Hugo, 1 Bernd Hohenstein. 1

Background: The present study demonstrates that EPC recruited to the kidney are not BM derived endothelial progenitor cells (EPC) participating in repair upon renal injury. Most of this data are based on in vitro studies. We have previously shown that mainly endothelial outgrowth cells (EOC, ECFC) can be detected in the kidney after selective endothelial injury. To investigate the origin of such cells in vivo, we induced chimeric mice via BM transplantation to trace these cells.

Methods: BM cells were isolated from 8-10 week old ubiquitous tdTomato expressing reporter mice. Recipients were C57Bl6 mice of the same age. Endothelial injury was induced 6-8 weeks later in 20 of the 25 chimera. 5 mice were used as controls. Kidney, spleen, blood and BM were harvested on days 1, 3, 5 and 7 (n=5 per group) and analyzed using multicolor FACS-analysis and histology. EPC/ECFC (CD34, Flk-1, CD31, CD105, CD106, CD45, CD45, CD133, CD115, CD14), hematopoietic stem cells (c-kit+, Sca-1+ and Lin-), macrophages (F4/80+CD11b+ CD11c-GR1-) and dendritic cells (CD11c+CD11b+ GR1-) were studied. B-cells (CD19+ cells) were measured using FACS-analysis.

Results: Injured kidneys the percentage of macrophages (d3: 0.5% vs control: 0.1%), dendritic cells (4.4% vs 1.5%) and T-cells (CD4 0.7% vs 0.2%; CD8 0.3% vs 0.05%) significantly increased on d3 (p<0.05). B-cells were unchanged. EPC were increased on d3 (1.7% vs 0.4% p<0.001) and HSC on d1 (0.6% vs 0.2% p<0.05). Compared to controls, significantly more tdTomato positive cells were recruited to injured kidneys (d1: 4.3±3.2% vs 2.0%. Almost all macrophages (94.9±6.4%), dendritic cells (96.6±1.5%), neutrophils (99.7±0.8) and B-cells (92.9±0.7) were tdTomato positive, while only the minority of T-cells (34.3±2.12%; CD4 42.0±11.0) and HSC (14.7±11.0) were tdTomato positive. Basically none of the ECFC (0.3%±0.7) recruited to the kidney were tdTomato positive.

Conclusions: The present study demonstrates that EPC recruited to the kidney are not of BM origin, while HSC might partially emanate from BM. Further studies will have to define the niche for these stem cells in or outside the kidney.

Sequential Activation of mTOR Network Components Determines Progression of Vascular Calcification

Theres Schaub, 1 Bjorn Hegner, 1 Claudia Lange, 1 Tobias B. Huber, 1 Duska Dragan. 1 Charité Universitätsmedizin Berlin, 1 Univ Medical Center Hamburg, 2 Univ Medical Center Freiburg.

Background: Conversion of mesenchymal stromal cells (MSC) towards osteoblast like phenotype is instrumental for the development of uremic calcifying vasculopathy. mTOR kinase contained in mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) translates extracellular signals into cell differentiation responses such as osteoblastic transformation occurring during uremic vasculopathy. A key enzyme of osteoblast differentiation, rose to a peak after 15 days paralleled by deposition of calcified extracellular matrix starting at day 6. Rapa treatment blocked mTORC1 activity while increasing mTORC2 activity resulting in inhibition of senescence and apoptosis and induction of autophagy. Rapa attenuated induced and delayed osteoblast differentiation with calcium phosphate. Abrogation of mTORC2 by lentiviral shRNA transfer reversed protective effect of rapa by induction of apoptosis and increased extracellular calcium content.

Conclusions: Our findings reveal induction of mTORC1 and deregulation of mTORC2 signaling as possible mechanisms which delay development of different cell fate programs operative during osteoblastic MSC transformation. Modulation of mTOR signaling with rapa may evoke induction of alternative cell fate sequences and confer protection from accelerated osteoblastic transformation occurring during uremic vasculopathy.

Stem Cells and Regeneration: Developmental Biology and Inherited Kidney Diseases


Poster/Thursday

TH-PO1127

Cellular Characterization of Nephron Regeneration after Acute Kidney Injury in the Zebrafish

Kristen K. McCampbell, Rebecca A. Wingert.Dept. of Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: Acute kidney injury (AKI) is a devastating and often lethal condition in which a given nephron cell population is damaged by ischemia or toxin exposure.

Methods: The zebrafish is an attractive and viable system to study the molecular pathways responsible for nephron regeneration, as its nephrons are simple, yet they maintain the biologic complexity inherent to that of higher organisms including kidney. Previous studies have demonstrated that gentamicin-based chemical injury in zebrafish mimics human AKI, but detailed analysis of the cellular events associated with damage was not reported. We generated a novel toolkit of cellular and molecular protocols to perform this analysis in the zebrafish.

Results: Next, we extensively characterized the cellular changes resulting from gentamicin injury in the adult zebrafish using our platform of histology and immunohistochemistry techniques. This work has established the timing of renal cell death after injury, identified proliferative compartments within the kidney, and led to the assessment of gene expression changes associated with the regenerative response of proliferating cells.

Conclusions: Taken together, these data have provided a greater understanding of the full cycle of regenerative events. Insights from this work can be applied in future studies toward the design of chemical genes screens in the adult and/or embryonic zebrafish to identify renal regeneration pathways and provide novel insights into the signals that orchestrate kidney epithelial regeneration.

Funding: Other NIH Support - NIH Director’s New Innovator

Amniotic Fluid Kidney Progenitors as a Tool to Study the Glomerular Filtration Barrier In Vitro

Stefano Da Sacco, Astigk Petrosyan, Sargis Bedraykan, Kevin V. Lemley, Roger E. De Filippo, Laura Perin. Children’s Hospital Los Angeles, Los Angeles, CA.

Background: The glomerular filtration barrier (GFB), essential for blood ultrafiltration, is formed by three major compartments: the podocyte, the glomerular basement membrane (GBM) and the fenestrated endothelial cell. While podocytes are the only cell in the glomerulus to produce collagen IV, endothelial cells play an important role in the formation of the GBM. However, the possibility to recapitulate the formation of a human GFB in vitro to study diseases and possible treatments, is still lacking. We have previously shown that human amniotic fluid progenitor cells (hAKPC) can differentiate into mature podocytes producing collagen IV alpha3-4-5 chains in vitro. In this study, we have evaluated the ability of hAKPC and glomerular endothelial cells to form in vitro a functional filtration barrier in vitro.

Methods: hAKPC were differentiated in VRADD media for 20 days. Immunofluorescence, qPCR, SEM and TEM were performed to confirm formation of a human GFB in vitro.

Results: hAKPC were differentiated in VRADD media for 20 days. Immunofluorescence, qPCR, SEM and TEM were performed to confirm formation of a human GFB in vitro.

Conclusions: The present study demonstrates that hAKPC are capa...
C-kit+ Cells Restore Podocyte Function in a Model of Acute Glomerulonephritis
Erika B. Rangel,1 Samirah Abreu Gomes,1 Rosemere Kanasashi-Takeuchi,2 Phillip Ruiz,2 Jochen Reiser,2 Joshua M. Hare.1
1Univ of Miami; 2Rush Univ.

Background: C-kit-kidney derived cells exhibit the properties of stem cells and regenerate epithelial tubular cells following ischemia-reperfusion injury. We hypothesize that c-kit+ cells have the capacity to improve podocyte function in a model of acute glomerulonephritis induced by puromycin aminonucleoside (PAN).

Methods: A single dose of PAN (15 mg/100g) was administered intraperitoneally into rats. After 5 days, animals were injected with saline or c-kit cells. Metabolic parameters (serum creatinine, blood urea nitrogen [BUN] and urinary ratio of albumin/creatinine), and histologic and gene expression analyses were performed at 10 and 21 days. A single dose of PAN (15 mg/100g) was administered intraperitoneally into rats. After 5 days, animals were injected with saline or c-kit+ cells. Metabolic parameters (serum creatinine, blood urea nitrogen [BUN], urinary ratio of albumin/creatinine), histologic and gene expression analyses were performed at 10 and 21 days.

Results: C-kit treated animals exhibited lower values of BUN after 10 days compared to the saline group (92 mg/dL vs 58.2 mg/dL, P<0.001). At 21 days, kidney weight was lower in c-kit-treated animals (0.54 g/100 g BW, P=0.024). Urinary ratio of albumin/creatinine was lower in c-kit treated animals (0.77±0.46 g/mg) compared to the saline group (1.15±0.77 g/mg). A few c-kit+ cells were engrafted into the tubule-interstitial compartment. Expression of CD2AP and α-actin 4 (involved in podocyte cytoskeleton) and mTOR (mammalian target of rapamycin) were up-regulated after 21 days in the c-kit treated group. Of importance, Raptor/Rictor ratio was lower in c-kit treated animals compared to the saline group (1.17 vs 1.78, P = 0.029). Rictor expression was comparable between c-kit treated animals and normal kidneys, but was higher than the expression observed in the saline treated group (P<0.05). Autophagy was less efficient in the saline group compared to the c-kit treated group when the number of autophagosomes/autophagolysosomes was analyzed (4.3±0.6 up-regulating the mTOR-Rictor pathway and modulating the autophagic pathway. Taken together, these results suggest that c-kit+ stem cells have the potential to differentiate into renal tubular lineage cells through tubular formation. Human ES cells possess many characteristics distinct from those of mouse ES cells, and the investigation of human ES cells is indispensable to clarify the kidney differentiation process in humans. In the present study, we utilized KSP as a marker to investigate the ability of human ES cells to differentiate into tubular lineage cells.

Methods: We performed monolayer multistep culturing of the human ES cell line Khes-1 on collagen substrate. As a first step, human ES cells were induced to differentiate into mesodermal lineage cells using a GSK-3β inhibitor. As a second step, further differentiation was induced under the low serum and several growth factors. Then the KSP-positive cells were sorted by flow cytometry at day 10.

Results: Quantitative RT-PCR analysis showed that significant amounts of intermediate mesoderm markers were expressed in human ES cells cultured with a GSK-3β inhibitor. Western blotting, immunocytochemistry, and flow cytometry showed that human ES cells cultured with a GSK-3β inhibitor were positive for KSP at day 10. On the other hand, human ES cells cultured without a GSK-3β inhibitor showed less protein expression of KSP, indicating that GSK-3β inhibition is essential to produce KSP-positive cells in this differentiation technique. Furthermore, the KSP-positive cells were able to form tubular-like structures when grown in a 3D culture in Matrigel.

Conclusions: We showed that human ES cells have the potential to differentiate into KSP-positive cells. Although the characteristics of KSP-positive cells should be investigated, the present technique is a promising step to obtaining renal tubular lineage cells from human ES cells.

TH-PO1113
Early Endothelial Outgrowth Cells (eEoCs) in Murine Diabetic Nephropathy

Background: Early Endothelial Outgrowth Cells (eEoCs), a major subpopulation of EPCs (Endothelial Progenitor Cells) have reliably been shown to protect mice from acute ischemic renal failure. These effects can significantly be improved by BMP-5. Chronic diabetic nephropathy is characterized by renal fibrosis during later stages of the disease, a process which partly results from mesenchymal transition of mature endothelial cells (EnMt). Aim of the current study was to analyze consequences of eEoC treatment of diabetic nephropathy.

Methods: Male C57/B16 mice were repeatedly injected with STZ. Animals received either untreated or BMP-5 pre-treated syngeneic murine eEoCs at 2 and 7 days after the last STZ administration. Renal function, proteinuria, renal fibrosis and EnMt were analyzed 8 weeks later.

Results: STZ treatment induced significant and persistent increases of blood glucose levels, the animals additionally displayed renal dysfunction and proteinuria at 8 weeks after the last STZ administration. Renal function and proteinuria significantly improved after injection of untreated and BMP-5 pre-treated eEoCs. Reduction of proteinuria was more pronounced with BMP-5 treated eEoCs. Renal fibrosis was diminished by eEoCs as well. All experimental groups were characterized by increased expression of aSMA by CD31+ endothelial cells, indicating mesenchymal transition of the endothelium. BMP-5 treated eEoCs diminished aSMA expression in a statistically significant manner.

Conclusions: Early Endothelial Outgrowth Cells protect mice from diabetic nephropathy. In this situation BMP-5 augments antiproteinuric and antimesenchymal cell effects.

TH-PO1134
Pretransplant Dialysis Duration Is a Risk Factor for Death after Kidney Transplantation also in the Current Era
Ilkka Helanterä,1 Kaija Salmela,2 Laura Kylönen,1 Petri Koskinen,1 Carola Gronhagen-Riska,1,5 Patrik Finne.1,5
1Dept of Medicine, Div of Nephrology, Helsinki Univ Central Hospital, Helsinki, Finland; 2Dept of Transplant Surgery, Helsinki Univ Central Hospital, Helsinki, Finland; 3Finnish Registry for Kidney Diseases, Helsinki, Finland.

Background: Although longer pretransplant dialysis has been associated with poor kidney transplant outcome, no data about this association exist from the current era or Europe. We studied the association of pretransplant dialysis duration with outcomes after kidney transplantation across different time periods.

Methods: All recipients of kidney transplantation between 1964 and 2010 in Finland were included (N=5205) in this observational follow-up study of an inception cohort. Pre- and posttransplant data, and outcome data were collected from the Finnish Registry for Kidney Diseases. The association of the duration of pretransplant dialysis with patient and graft survival after transplantation was analyzed with multivariable Cox
regression and competing risk analyses. The association of pretransplant dialysis duration with the risk of specific causes of death (cardiovascular, infectious, or other causes) was analyzed using competing risk analysis.

Results: Longer duration of pretransplant dialysis was an independent risk factor for patient death after transplantation (Risk ratio 1.14 per one year increase) in the whole study population, but not for graft loss. Risk of death was increased in patients with more than 12 months of pretransplant dialysis. Longer duration of dialysis was an independent predictor of death due to cardiovascular diseases (RR 1.13 per one year increase), but not for other causes. After further adjustment in patients transplanted in 2000-2010, longer duration of dialysis remained an independent risk factor (RR 1.23 per one year increase). After stratification according to the era of transplantation, the risk of death associated with dialysis duration did not decrease over time.

Conclusions: Dialysis duration remains an independent predictor of patient death after kidney transplantation also in the current era, because of increased risk of death due to cardiovascular diseases.

Funding: Government Support - Non-U.S.

TH-PO1135

Associations of Pre-Transplant Narcotics Use with Death and Graft Loss after Kidney Transplantation Krista L. Loten1, David A. Axelrod2, Daniel C. Brennan1, Vikas R. Dharidharka3, Mark Schnitzler1. 1Saint Louis Univ; 2Dartmouth Univ; 3Washington Univ.

Background: Limited data are available on the implications of narcotics use for outcomes after kidney transplantation (KT).

Methods: We examined a novel database wherein OPTN identifiers for KT recipients were linked to pharmacy fill records from a large U.S. pharmaceutical claims clearinghouse (2005 to 2010). For this study, we selected adult KT recipients with 1yr of captured pre-transplant pharmaceutical fill records (N=29,882). Pharmacy fills for narcotics in the year prior to KT were normalized to Morphine Equivalents (ME), and expressed as average mg/kg/d exposures. Associations of ME with post-transplant graft and patient survival (adjusted hazards ratio, aHR) were quantified by multivariate Cox regression including recipient, donor and transplant clinical factors in the OPTN registry.

Results: 28.9% of the sample filled narcotics in the year before KT. Among narcotic users, the 25th, 50th and 75th percentiles of ME were: 0.01, 0.02, and 0.06 mg/kg/d, respectively. 3-yr survival of deceased donor (DD) recipients declined with higher quartiles of ME exposure, from 88.9% among non-users to 87.6% (Q2), 85.3% (Q3), 83.2% (Q4) (P=0.0001). After multivariable adjustment, the risks of post-transplant death and graft loss in DD recipients with the highest quartile ME exposure were 1.6-times and 1.4-times that of non-users, respectively (Table). Patterns were similar among live donor KT recipients, with the upper quartile of pre-transplant narcotic exposure predicting 2.4 times the risk of death (P<0.0001) and 1.8 times the risk of all-cause graft loss (P<0.0001) (Table).

ADJUSTED ASSOCIATIONS OF PRE-TRANSPLANT NARCOTIC USE with 3yr PATIENT & GRAFT SURVIVAL after DEceased DONOR KT

<table>
<thead>
<tr>
<th>Death</th>
<th>Death-Censored Graft Failure</th>
<th>All-Cause Graft Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-User</td>
<td>aHR (95% CI)*</td>
<td>aHR (95% CI)*</td>
</tr>
<tr>
<td>Quartile 1 ME</td>
<td>1.02 (0.91-1.28)</td>
<td>0.72 (0.44-1.17)</td>
</tr>
<tr>
<td>Quartile 2 ME</td>
<td>1.21 (1.01-1.48)*</td>
<td>1.10 (0.75-1.65)</td>
</tr>
<tr>
<td>Quartile 3 ME</td>
<td>1.34 (1.13-1.58)*</td>
<td>1.87 (1.06-3.37)*</td>
</tr>
<tr>
<td>Quartile 4 ME</td>
<td>1.55 (1.32-1.84)*</td>
<td>1.12 (0.79-1.60)</td>
</tr>
</tbody>
</table>

ADJUSTED ASSOCIATIONS OF PRE-TRANSPLANT NARCOTIC USE with 3yr PATIENT & GRAFT SURVIVAL after Live DONOR KT

<table>
<thead>
<tr>
<th>Death</th>
<th>Death-Censored Graft Failure</th>
<th>All-Cause Graft Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-User</td>
<td>aHR (95% CI)*</td>
<td>aHR (95% CI)*</td>
</tr>
<tr>
<td>Quartile 1 ME</td>
<td>1.34 (0.88-2.01)</td>
<td>0.46 (0.23-1.19)</td>
</tr>
<tr>
<td>Quartile 2 ME</td>
<td>1.07 (0.71-1.60)</td>
<td>1.12 (0.48-2.62)</td>
</tr>
<tr>
<td>Quartile 3 ME</td>
<td>1.55 (1.03-2.31)*</td>
<td>1.10 (0.52-2.44)</td>
</tr>
<tr>
<td>Quartile 4 ME</td>
<td>2.43 (1.79-3.28)</td>
<td>2.10 (1.06-4.18)*</td>
</tr>
</tbody>
</table>

*Based on Cox’s regression, adjusted for recipient, donor and transplant factors in the SRTR transplant survival equations. P<0.05, KT, kidney transplantation; ME, morphine equivalents

Conclusions: While these associations may in part reflect underlying conditions that require pain management, KT recipients who use chronic narcotics should be identified as a high risk group.

TH-PO1136

Pre-Transplant Geriatric Nutritional Risk Index (GNRI) and Outcomes after Kidney Transplantation Mikkiko Yoshikawa, Kentaro Nakai, Yuriko Yonekura, Hideki Fuji, Shinichi Nishi. Div of Nephrology and Kidney Center, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan.

Background: Malnutrition is a prevalent condition in chronic dialysis patients and seems to be a risk factor for mortality. The association between pre-transplant nutritional assessments and post-transplant outcome is unclear. Geriatric nutritional risk index (GNRI: 1.489×albumin (g/dL)+41.7×body weight/ideal body weight) is a simple nutritional assessment tool for chronic dialysis patients. We hypothesized that pre-transplantlower GNRI might be associated with the worse post-transplant renal outcomes.

Methods: We studied a retrospective cohort of 79 patients who received first kidney transplantation at our center from April 2003 to March 2011 and surveyed their clinical courses for 12 months after transplantation. Chi-squared test, t-test (Mann-Whitney test), Pearson correlation coefficient, and multivariate logistic regression model were used to analyze the data.

Results: The GNRI was significantly correlated with eGFR changes at 12 months. (r= -0.281, p=0.012) Patients were divided into two groups; “High-GNRI group” (≥99) and “Low-GNRI group” (<99). Low-GNRI group did not predict delayed graft function and acute rejection, but were independently associated with eGFR deterioration (HR=3.00, [95% confidence interval: 1.168-7.96]), and every graft failure in Low-GNRI group developed within 5 years. There was no significant relationship between the episodes of post-transplant complications such as infection and cardiovascular events.

Conclusions: Lower pre-transplant GNRI is an independent risk factor for the deteriorating post-transplant graft function.

TH-PO1137

Left Ventricular Systolic and Diastolic Dysfunction and Mitral Regurgitation Are Key Determinants of Pulmonary Hypertension in Chronic Kidney Disease Patients Aditi Puri, Randall K. Dettwiler, Abhijit V. Kshirsagar, Hubert James Ford, Alan L. Hydrotest. Univ of North Carolina Chapel Hill.

Background: Pulmonary hypertension (PH) is common in patients with chronic kidney disease (CKD), and is associated with reduced survival in patients who undergo renal transplant. The exact mechanism of PH in CKD patients is unclear. Potential contributing factors include high cardiac output due to anemia and the presence of a graft or fistula; chronic inflammation or other adverse effects of hemodialysis (HD); and a high left atrial (LA) pressure due to mitral regurgitation (MR) or left ventricular (LV) systolic or diastolic dysfunction.

Methods: To gain insight into mechanisms underlying PH in CKD patients, we examined clinical, laboratory, and echocardiographic characteristics of 349 patients who were referred for cardiac evaluation prior to kidney transplant at UNC. A diagnosis of PH was based on measurement of tricuspid regurgitant jet velocity (TRV) by Doppler echocardiography, and defined as TRV ≥2.8 m/s.

Results: The average age of our patients was 56.10 years. Most (75%) had end-stage renal disease (ESRD); 60% were on HD. The prevalence of PH was 17%, LV systolic dysfunction (ejection fraction ≤40%) (odds ratio 4.12, 95% confidence interval 1.73-9.81), moderate or severe LA dilation (OR 3.53, 95% CI 1.89-6.56), ≥ grade 2 LV diastolic dysfunction (OR 3.95, 95% CI 1.68-5.67), and moderate or severe MR (OR 9.85, 95% CI 2.78-34.9) were significant predictors of PH. Age, race, gender, body mass index, ESRD, HD, hemocrit, C-reactive protein, and LV hypertrophy were not associated with PH. Diastolic dysfunction and MR remained significant independent predictors in a multivariable model.

Conclusions: There was a high prevalence of PH in our cohort of patients with CKD undergoing kidney transplant evaluation. LV systolic and diastolic dysfunction, LA dilation, and MR were predictors of PH. These findings suggest that LV systolic and diastolic dysfunction and MR may play important roles in development of PH in CKD patients. PH may be associated with poor outcomes in part because it is a marker of advanced left heart disease.

Funding: Other NIH Support - Clinical and translational research center sponsored by NIH

TH-PO1138

Preoperative Recipient Parathyroid Function Affects Intratubular Calcification in Transplanted Kidney Grafts Junichiro J. Kazaama1, Emiko Kono1, Michihiro Hosojima1, Suguru Yamamoto1, Kazuhide Saito2, Ichie Nairui1. 1Clinical Nephrology and Rheumatology, Nigata Univ, Nigata, Japan; 2Urology, Niigata Univ, Niigata, Japan.

Background: Intratubular calcification is occasionally found in transplanted kidney grafts. Its clinical significance remains unknown.

Methods: Among adult CKD patients who received kidney transplantation in Niigata University Medical and Dental Hospital between 2006 and 2012, those in whom the absence of intratubular calcification had been confirmed in the biopsied kidney graft tissue obtained immediately after the operation were retrospectively studied. The second biopsy of kidney graft was performed 4 weeks after the first biopsy.

Results: Of the 116 patients (M70 F46, 43.4 ± 12.7yo, dialysis vintage 82.0 ± 97.3M) analyzed, intratubular calcification was found in 23 (19.8%) in the second biopsy specimen.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Diseases, Northwestern Univ; Hematology, Northwestern Univ, Chicago, IL.

**TH-PO1139**

### Utility of Thrombophilia Screening in Children Awaiting Kidney Transplantation

**Margaret E. Bock,1 Amy Bobrowski,1 Rukhmi Bhat,2**

**Kidney Diseases, Northwestern Univ; Hematology, Northwestern Univ, Chicago, IL.**

**Background:** Vascular thrombosis is one of the more common causes of early allograft loss in children after kidney transplantation (KTx). The utility of screening for acquired & inherited thrombophilia is controversial. We posited that universal pre-transplant screening for thrombophilia was of low predictive value for post-operative outcomes.

**Methods:** We reviewed 84 children, aged 1-18 years, who underwent comprehensive thrombophilia evaluations prior to KTx & were then followed longitudinally.

**Results:** Pre-operative screening demonstrated thrombophilia in over 90% of patients (76/84). Low protein C, S & anti-thrombin 3 (AT) were found in 22.5%, 10.7%, and 22.5% patients, respectively. Homocysteine was elevated in 25.8% patients, respectively. Antiphospholipid antibodies (aPL, lupus anticoagulant) were positive in 14.5% patients. Hypercalcemia developed in patients with high PTH, but not in those with low PTH.

**Conclusions:** Intratubular calcification is a potential harm for a transplanted kidney graft. Both hyperactivated and suppressed preoperative parathyroid hormone levels are associated with increased risk of the incidence of intratubular calcification.

---

**TH-PO1140**

### Impact of Preemptive Referral for Kidney Transplant Evaluation on Waitlisting and Transplantation

**Mohua Basu, Brenda P. Lovasik, Justin D. Schrager, Stephen O. Pastan, Rachel E. Patzer.**

**Emory Univ School of Medicine.**

**Background:** Little is known about how preemptive referral, or referral for kidney transplant (KTx) evaluation prior to initiating dialysis, is associated with access to waitlisting and KTx in ESRD (end-stage renal disease) patients.

**Methods:** KTx center-level data for 4,914 patients with no previous transplant referred to a Southeastern transplant center for KTx evaluation from 2005-2010 were linked with United States Renal Data System baseline and follow-up data through September 2011. Patient addresses were geocoded and linked with 2009 Census poverty data. Cox models were used to examine the association between preemptive referral and access to 1) waitlisting and 2) KTx.

**Results:** Of 4,914 referred patients, 934 (19.0%) were preemptively referred. Among referred patients, 1,977 (40.2%) were waitlisted (62.8% of preemptively referred patients and 34.9% of patients referred after dialysis start), and 725 (14.8%) patients received KTx (35.0% preemptively referred and 10.0% referred after dialysis start). In analyses adjusted for demographic factors (age, sex, race, distance to KTx center), clinical factors (ESRD etiology, body mass index, tobacco use, cardiovascular disease, cancer, pre-ESRD nephropathy care, erythropoietin use, hemoglobin and albumin levels), and SES factors (insurance and poverty), preemptively referred patients had a significantly higher rate of waitlisting (HR=1.70; 95% CI: 1.52-1.89) and KTx (HR=2.01; CI=1.69-2.40) compared to patients referred after initiating dialysis (Figure). Preemptive referral was associated with improved access to both deceased (HR=1.87; 95% CI: 1.50-2.33) and living donor KTx (HR=3.63; 95% CI: 2.73-4.81).

**Conclusions:** Preemptive referral for KTx evaluation is associated with improved access to waitlisting and both deceased and living donor KTx. Interventions to increase early referral may improve access to KTx.
Knowledge and attitudes toward Kidney Transplantation among Non-Physician Dialysis Providers: An Opportunity to Improve Kidney Transplantation Education and Access

Fidel Barreras,1 Elizabeth Evans,1 Akcela Oaris,2 Milagros D. Samaniego-Picota,3 Fu L. Luan.3 1Renal Medicine Associates, Albuquerque, NM; 2Internal Medicine, Presbyterian Health System, Albuquerque, NM; 3Internal Medicine, Univ of Michigan, Ann Arbor, MI.

Background: Non-physician dialysis staff (NPDS) are the primary sources of education for patients with end stage renal disease (ESRD). However, many feel uncomfortable answering questions related to kidney transplantation (KT) and thus hinder early referral.

Methods: This survey was designed to evaluate NPDS knowledge and attitudes toward KT referrals. Survey was validated before implementation.

Results: We surveyed 259 providers nationwide. Amongst, 75% worked for for-profit dialysis organizations, 19.3% locally owned, and 5% were university affiliated; 51% dialysis nurses, 18.5% nurse practitioners, and 11.4% technicians. The average dialysis working years was 12.5. Only 58.1% stated that KT was the best replacement therapy option for ESRD patients, whereas 15.4% opted daily home hemodialysis, 11.8% peritoneal dialysis, 8.1% in-center nocturnal (3/week), and 8.1% intermittent hemodialysis. One third of participants thought kidneys from young living donors last 5-10 years. About 359A

Access to Transplantation in the Elderly: Defining the Unmet Need

Elizabeth Hendren,1 Elke Schaeffer,2 Jagbir Gill,3 John S. Gill.1 1Univ of British Columbia; 2Charité Univ Medicine.

Background: To what extent the low use of transplantation in the elderly is justified because of a high burden of comorbid disease and limited life expectancy is unclear. The objectives of this USRDS analysis were:

1) To determine the proportion of incident ESRD patients ≥65 years that are transplant eligible (TE) and examine their access to transplantation (defined as wait-listing or transplantation).

2) To determine if the Medicare and Medicaid Services (CMS) requirement to report discussion of transplant treatment options at dialysis initiation (implemented in May 2005) was associated with an increase in access to transplantation.

Methods: We defined transplant eligibility using the following conservative criteria: 1) ESRD Survival ≥5 years, 2) no relative contraindications to transplantation, 3) no comorbid conditions and 4) no inability to ambulate or transfer.

Results: Overall 8.5% of elderly incident ESRD patients met our TE criteria, and 15.9% of these patients were ever wait-listed or transplanted. Among 65-9 year-olds, 14% were transplant eligible and 30% of these patients gained access to transplantation. Among patients ≥70 years, 7% were TE but only 9% gained access to transplantation.

In a separate analysis, the proportion of TE elderly patients who gained access to transplantation within one year of first ESRD transplantation treatment increased by 100% in the two years after the implementation of the CMS requirement.

Conclusions: We conclude that 85% of TE elderly ESRD patients never gain access to transplantation. However, simple interventions such as required reporting of transplant discussions at dialysis initiation may increase access to transplantation among elderly patients.

Funding: Clinical Revenue Support

Incorporating Uncertainties and Contingencies in a Paired Donation Program

Mathieu Bray,1 Wen Wang,1 Peter X.K. Song,2 Alan B. Leichtman,1 Michael A. Rees,2 John Kalbfleisch.1 1Univ of Michigan, Ann Arbor, MI; 2Univ of Toledo, Toledo, OH.

Background: A kidney paired donation (KPD) pool consists of transplant candidates and their incompatible donors along with altruistic donors (ADs). In a match run, exchanges are arranged among pairs in the pool and chains created from ADs. A problem of importance is how best to arrange exchanges and chains to optimize the number of transplants performed. This study examines allocation schemes in a realistic model of a KPD system, incorporating into the scheme probabilities (PR) that chosen transplants may not be complete, as well as allowing for contingency plans (CON) when the optimal solution fails.

Methods: The simulations use data from the Alliance for Paired Donation and the University of Michigan KPD program. Simulations compared optimization schemes in 200
repetitions over 8 months, with 30 pairs and 1 IAD added each month. A virtual crossmatch was used to identify potential donations; PRs were specified from the literature. At each match a set of optimal cycles and chains were determined for each scheme, with and without PR and with and without CON, and the number of realized transplants was then obtained. Cycles of size 2 and 3 were considered and simulations were done for chains of length 2 to 6. Two schemes for contingencies (CON1 and CON2) were complex with present algorithms for the CON options.

Results: Table 1 compares the allocation schemes in terms of ratios of average number of transplants to a standard where chains are of length 2, without PRs or CONs. Approaches that aim to maximize the number of transplants without allowing for PRs are suboptimal and deliver diminishing returns for longer chain lengths. Average, 17-18% more transplants are realized based on chains of size 3 or 4 that account for PRs and CONs.

<table>
<thead>
<tr>
<th>Chain Length</th>
<th>No PR</th>
<th>No CON</th>
<th>PR</th>
<th>No CON</th>
<th>PR CON1</th>
<th>PR CON2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.06</td>
<td>1.11</td>
<td>1.17</td>
<td>1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.06</td>
<td>1.11</td>
<td>1.17</td>
<td>1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.06</td>
<td>1.11</td>
<td>1.17</td>
<td>1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.06</td>
<td>1.11</td>
<td>1.17</td>
<td>1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.06</td>
<td>1.11</td>
<td>1.17</td>
<td>1.18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: It is advantageous to consider clinically relevant uncertainties and incorporate them into kidney allocation.

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

TH-PO1146 Feasibility and Benefit of Kidney Paired Donation between Pools of Ethnic Difference Kyung Sun Park, Da Jeong Kim. Div of Nephrology, Internal Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine.

Background: Kidney paired donation (KPD) is an established method to overcome ABO incompatibility and positive cross-match in living kidney transplantation. We hypothesized that the opportunities and quality of matching in KPD may be enhanced by using KPD pools of ethnic difference.

Methods: To identify the feasibility and effectiveness of international KPD, we analyzed ABO blood type and HLA-AB, DR data of 2 donor-recipient pools (DRP) of USA (1 from Allied Paired Donation (APD), another from Methodist San Antonio (SA) and 1 DRP of Korea (KR). The calculated panel reactive antigen (cPRA) was defined as the proportion of donors who have same HLA as the recipient’s anti-HLA antibodies.

Results: In APD, SA and KR DRPs, 627, 298 and 369 donors, and 515, 237, 369 recipients were registered respectively. Blood type of donors (P<0.001) and of recipients (P<0.001) were significantly different between USA and KR DRPs. The distribution of HLA typing of donors (P<0.001 for A, P=0.001 for B and P=0.001 for DR) and of recipients (P<0.001 for A, P=0.001 for B and P=0.001 for DR) were also different significantly. Mean cPRA of APD recipients (75.3% with APD donors) decreased significantly when calculated with KR donors (69.4%, P<0.001) in comparison with SA donors (75.8%). In SA recipients (80.7% with SA donors), cPRA decrease was more evident with KR donors (75.0%, P<0.001) than with APD donors (80.2%).

Conclusions: Our data showed that the distributions of blood type and HLA type were different between USA and KR DRPs and cPRA of US patients decreased significantly in pools of different countries. Considering ethnic differences, the feasibility and efficacy of KPD could be improved by using international kidney exchange network.

TH-PO1147 Impact of Human Leukocyte Antigen-DR Mismatches on Poor Outcome of Living Unrelated Kidney Transplantation in Comparison with Living Related Kidney Transplantation Kyung Sun Park, Hye Ryoun Jang, Jung Eun Lee, Woosong Huh, Yoon-Goo Kim, Ha Young Oh, Dae Joong Kim. Div of Nephrology, Dept of Internal Medicine, Samsung Medical Center Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea.

Background: Living-unrelated donors (LURD) have been widely used for kidney transplantation (KT). We compared clinical outcomes of KT from LURD and from related donors in our hospital unit. Consent for longer chains were too complex with present algorithms for the CON options.

Methods: To identify the feasibility and effectiveness of international KPD, we analyzed ABO blood type and HLA-AB, DR data of 2 donor-recipient pools (DRP) of USA (1 from Allied Paired Donation (APD), another from Methodist San Antonio (SA) and 1 DRP of Korea (KR). The calculated panel reactive antigen (cPRA) was defined as the proportion of donors who have same HLA as the recipient’s anti-HLA antibodies.

Results: In APD, SA and KR DRPs, 627, 298 and 369 donors, and 515, 237, 369 recipients were registered respectively. Blood type of donors (P<0.001) and of recipients (P<0.001) were significantly different between USA and KR DRPs. The distribution of HLA typing of donors (P<0.001 for A, P=0.001 for B and P=0.001 for DR) and of recipients (P<0.001 for A, P=0.001 for B and P=0.001 for DR) were also different significantly. Mean cPRA of APD recipients (75.3% with APD donors) decreased significantly when calculated with KR donors (69.4%, P<0.001) in comparison with SA donors (75.8%). In SA recipients (80.7% with SA donors), cPRA decrease was more evident with KR donors (75.0%, P<0.001) than with APD donors (80.2%).

Conclusions: Our data showed that the distributions of blood type and HLA type were different between USA and KR DRPs and cPRA of US patients decreased significantly in pools of different countries. Considering ethnic differences, the feasibility and efficacy of KPD could be improved by using international kidney exchange network.


Background: In 1998, the Department of Health and Human Services’ Final Rule requested the elimination of geographic disparities in organ allocation. Despite this action, geographic disparity persists for kidney transplantation. We aim to develop an alternative kidney allocation strategy to reduce geographic disparity over time without greatly altering current kidney allocation.

Methods: Kidney transplant patient and standard criteria donor kidney allocation dynamics were obtained from 2000 to 2009 at Donor Service Area (DSA) precision from Organ Procurement and Transplantation Network data. Our kidney sharing strategy establishes regional and national sharing partnerships between DSAs to prioritize the offering of non-locally used kidneys. Using simulation optimization techniques, we determine the optimal sharing partners for each DSA to best reduce geographic disparity over time.

Results: After ten years of use, our alternative kidney sharing strategy reduces geographic disparity significantly for all blood types. This reduction occurred when only 40% of shared kidney organs were redirected following our alternative strategy. Compared to actual 2009 kidney allocation, the range in DSA waiting times to transplantation fell by 31%, 38%, 27% and 27% for blood types A, AB, B, and O kidney allocation, respectively. The range in DSA transplant rates also fell by 32%, 43%, 19%, and 26% for blood types A, AB, B, and O kidney allocation, respectively. Approximately 400 (9%) less waitlist mortalities took place each year over all blood types.

Conclusions: Alternative kidney allocation strategies are necessary to reduce geographic disparities in kidney transplantation. We provide a simple change to current kidney allocation policy that reduces geographic disparity over time without affecting current local kidney allocation levels.

TH-PO1149 An Evaluation of the ECD Classification in Canadian Kidney Transplant Recipients Ann Young, 1,2 Charmaine E. Lok, 1,2 Stephanie Dixon, 2 Greg A. Knoll, 3 Amit X. Garg, 1 Joseph Kim. 4Univ Health Network, Toronto, Canada; 5Institute for Clinical Evaluative Sciences, Canada.

Background: Although outcomes of kidney transplant recipients in Canada have been shown to be superior to their U.S. counterparts, a critical evaluation of the Expanded Criteria Donor (ECD) classification system has not been undertaken in a Canadian kidney transplant population.

Methods: This retrospective, population-based cohort study followed deceased kidney allograft recipients from Ontario, Canada from Jan/2005 to March/2011. Subjects were identified through a transplant database and linked to large administrative healthcare databases in Ontario (www.ICES.on.ca). ECD status was ascertained based on age, serum creatinine, history of hypertension, and death due to stroke. Outcomes were defined using reliable ICD codes compared to chart review. Multivariable survival analysis assessed total graft loss (i.e., graft loss or death), death-censored graft loss, graft loss with death as a competing event, and all-cause mortality.

Results: We studied 1,470 deceased donor kidney transplants, of which 286 were from ECD and 1136 from non-ECD. The median age was 64 vs. 46 years for ECD vs. non-ECD, respectively. There were significantly more donors in the ECD group with hypertension (65% vs. 24%) and death due to stroke (22% vs. 10%). Pre-terminal serum creatinine was not significantly different (71 vs. 74 μmol/L). Recipients of ECD kidneys were older (median: 62 vs. 54 years). The five-year cumulative incidence of total graft loss was 28.8% vs. 21.1% in ECD vs. non-ECD kidney transplants, respectively. There was an increased relative hazard for total graft loss (HR 1.42 [95% CI 1.04, 1.84]) and death-censored graft loss (1.63 [95% CI 1.05, 2.52]) in the ECD vs. non-ECD kidney transplants. Similar trends were observed for graft loss with death as a competing risk and total mortality.

Conclusions: The ECD classification identifies deceased donor kidneys at increased risk of graft failure among Canadian kidney transplant recipients. The performance of more granular measures of donor risk (e.g., KDRI) and its impact on allocation or organ utilization in Canadian patients requires further study.

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


Background: During the last two decades we have seen a substantial increase in the incidence of elderly patients who require replacement therapy. In these patients, renal transplantation (RT) should be considered a treatment option. There are a large number of kidneys from elderly patients that are not used. The cadaveric pre-emptive RT has a better survival (SV) graft and patient- in comparison to the patient on dialysis. The aim of our study was to analyze the evolution of elderly patients on end stage renal disease non-diagnosis (ESRDND) after receiving a preemptive RT.

Methods: Prospective observational study (years 2007-2012) analyzing pre-emptive RT from a cadaveric donor in our hospital unit. (ESRDN) aged 65 years with a glomerular
filtation rate (GFR) <15 ml/min at the time of inclusion. We established a control group of patients of the same age in hemodialysis (HD) of which 30% of the cases shared the same donor.

Results: We included 26 patients (ESRDND) patients (57.7% women) of mean age 74.2 ± 2.9 years, nephroclerosis (38.5%) as the main cause of nephropathy. RT received a first donor mean age was 73 ± 7.2 years. Cerebral hemorrhage was the most common cause of death (76.9%) and had a GFR of 90.4 ± 19 ml/min at the time of extraction. The cold ischemia time was 21.4 ± 5.3 hours. Immunosuppression was basiliximab induction, tacrolimus, mycophenolate mofetil and steroids (96.2%) in both groups. All baseline characteristics were identical for both groups. At the end of follow-up time 35.5 (5-67) months, death or graft was similar in both groups (42.2 ± 11.7 vs 43.7 ± 11.2 ml/min, p=0.72). Delayed graft function was higher in the group HD (4 vs 39.1%, p=0.03) and acute rejection was higher in the PRD group (23.1 ± 3.8%, p=0.04). The patient SV was similar in both groups (78 vs 83.5%, p=0.79), however the SV graft was higher in the group ESRD non-dialysis or censoring death (100 vs 77, p=003 and 92 vs. 64%, p=0.03).

Conclusions: In conclusion, our study suggests that pre-emptive kidney transplant is an interesting alternative for end-stage renal disease. However, it is necessary to perform studies with more patients and longer follow-up to establish a stronger conclusion.

TH-PO1151

Long Term Outcomes of Kidney Transplants and Risk of Infection Transmission from High-Infectious Risk Donors

Mili Jay Shah,1 Gaurav Gupta,1 Dona John,1 Martha Behnke,1 Marie P. Posser,1 Amit Sharma,1 Adrian Cotterell,1 Robert Fisher,2 Anne L. King,1 1Nephrology, Virginia Commonwealth Univ, Richmond, VA; 2Transplant Surgery, Virginia Commonwealth Univ, Richmond, VA.

Background: The use of kidneys from deceased donors considered at high infectious risk based upon CDC criteria (CDCHR) represents a strategy to increase the limited donor pool. Concern over transmission of viral infections is reported to result in a higher discard rate of these kidneys. Prospective studies on viral transmission rates are lacking. We report our experience with CDCHR kidneys.

Methods: All patients signed an informed consent to receive CDCHR kidneys. Nucleic acid testing (NAT) for HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) was performed on all CDCHR donors before kidney transplant (KTx). Per protocol, viral transmission testing using HBV surface antigen, HIV ELISA and HCV PCR was performed at least once during the first year and then annually post-KTx.

Results: There were 89 CDCHR KTx and 533 Non-high risk (NHR) KTx during the study period from June 2004 to Dec 2011. Although median waiting time was shorter for the CDCHR group (44.8 mths) as compared to the NHR group (20 mths), these results were not statistically significant. Nearly all patients underwent post-KTx screening for HIV (79.89%; 89%), HBV (83.89%; 93%) and HCV (82.89; 92%). Among patients tested, there was a 0% rate of viral transmission. When compared to the NHR group, CDCHR kidneys were more likely to be HCV positive (34% vs 11%; p<0.01) and receive a HCV positive graft (28% vs. 7%; p=0.01). Graft and patient survival at 1, 3 and 5 years were similar between the two groups.

Conclusions: In this till date largest single-center report with prospective screening we demonstrate that CDCHR donor kidneys can be used safely with achievement of excellent renal function and graft survival. This data can guide counseling of potential kidney transplant recipients about the benefits of CDCHR kidneys which might also include shorter waiting times.

TH-PO1152

CDC High Risk Designation for Deceased Kidney Donors Is a Misnomer


Background: Approximately 10% of deceased donor kidneys meet the CDC criteria as “high-risk” for infection (HIV, HCV, HBV) and disease transmission. While this designation may lead to lower organ utilization by some centers, the risk of not detecting infection with “high-risk” donors is currently unknown. Concern over transmission of viral infections is reported to result in a higher discard rate of these kidneys. Prospective studies on viral transmission rates are lacking. We report our experience with CDCHR kidneys.

Methods: All patients signed an informed consent to receive CDCHR kidneys. Nucleic acid testing (NAT) for HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) was performed on all CDCHR donors before kidney transplant (KTx). Per protocol, viral transmission testing using HBV surface antigen, HIV ELISA and HCV PCR was performed at least once during the first year and then annually post-KTx.

Results: There were 89 CDCHR KTx and 533 Non-high risk (NHR) KTx during the study period from June 2004 to Dec 2011. Although median waiting time was shorter for the CDCHR group (44.8 mths) as compared to the NHR group (20 mths), these results were not statistically significant. Nearly all patients underwent post-KTx screening for HIV (79.89%; 89%), HBV (83.89%; 93%) and HCV (82.89; 92%). Among patients tested, there was a 0% rate of viral transmission. When compared to the NHR group, CDCHR kidneys were more likely to be HCV positive (34% vs 11%; p<0.01) and receive a HCV positive graft (28% vs. 7%; p=0.01). Graft and patient survival at 1, 3 and 5 years were similar between the two groups.

Conclusions: In this till date largest single-center report with prospective screening we demonstrate that CDCHR donor kidneys can be used safely with achievement of excellent renal function and graft survival. This data can guide counseling of potential kidney transplant recipients about the benefits of CDCHR kidneys which might also include shorter waiting times.

TH-PO1153

The Discrepancy between Biological Age and Calendar Age: A Large Histology Study in Pre-Implantation Biopsies

Katienn De Vusser1, Nicky Pieters,2 Evelyne Lerut,1 Bjorn Meijers,1 Dirk R. Kuypers,1 Maarten Naesens,1 1Nephrology and Renal Kidney Transplantation, UZ Leuven, Leuven, Belgium; 2Pathology, UZ Leuven, Leuven, Belgium; 3Center for Environmental Science, U Hasselt, Hasselt, Belgium.

Background: Replicative senescence (biological aging), associated with telomere shortening, plays an important role in tissue aging. The relationship between calendar age, telomere length, markers of replicative senescence and renal histology is currently unknown.

Methods: DNA was extracted from a peripheral blood sample in 300 deceased kidney donors. Telomere length was measured by real-time PCR. All 300 kidneys were biopsied prior to implantation, and the histology was evaluated using the Banff classification. Kidney donor demographics and transplant outcome data were recorded prospectively. IHC was performed for p16, p53, KI-67 and Beta-galactosidase.

Results: Telomere length correlated with donor calendar age (p=0.0002). Older donor calendar age associated with IFTA grade and gs (both p<0.006), independent of the other donor characteristics. Telomere length predicted overall graft survival (p=0.02), but not death censored graft survival. Telomere length associated independently with intragraft arteriosclerosis (p=0.0001), independent of the other donor characteristics. Positive staining for p16 correlated (p=0.03) with longer telomere length, while intrarenal KI-67 expression with shorter telomere length. Thus, both molecules constitute the renal senescent phenotype.

TH-PO1155

CDC High Risk Designation for Deceased Kidney Donors Is a Misnomer


Background: Approximately 10% of deceased donor kidneys meet the CDC criteria as “high-risk” for infection (HIV, HCV, HBV) and disease transmission. While this designation may lead to lower organ utilization by some centers, the risk of not detecting infection with modern nucleic acid testing appears low.

Methods: Since 2004, 170 patients received kidneys that meet CDC high-risk criteria at Columbia University Medical Center. In addition to standard pre-transplant serologic screening for HIV, HCV, and HBV these patients are also screened by antibody and PCR testing at 6, 12 and 24 weeks post transplant. All patients received our standard of care immunosuppressive protocol.

Results: Recipients were predominantly male (69.4%), Hispanic or White (68.8%), receiving a first transplant (80%) after waiting 1.7±1.2yrs and 27.7% experienced delayed graft function (DGF). Donors were 37±11.5yrs (10% extended criteria donors) and predominantly male (72.7%). Donor organs had 29±16.0hrs of cold ischemia, with a terminal creatinine of 2±1.7mg/dL. Among these donors, 57.1% had a history of IVDU, 25.9% had high risk sexual behavior, 11.8% were incarcerated, 7.1% were men who had sex with men, and 4.7% had received triple blood transfusions resulting in hemodilution. The majority (77.8%) were imported from other OPOs suggesting that other centers declined to use these organs. After a median of 2-4yrs of follow up, 86.5% of allografts were functioning (figure 2) with the most recent creatinine of 1.62±0.87mg/dL and no evidence of infectious seroconversion.

Conclusions: Our single center experience of 170 high-risk criteria organs demonstrates the relative safety of this important pool of deceased donor organs when screened by current methods. These organs should probably be labeled as “identified risk”; “high-risk” appears to be a misnomer.

TH-PO1156

Transplantation in Clinical and Translational Research

Poster/Thursday


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

Underline represents presenting author/disclosure.

361A
PERITUBULAR CAPILLARY (PTC) NUMBER IN PRE-IMPLANTATION BIOPSY OF LIVING DONORS IS ASSOCIATED WITH CARDIOVASCULAR RISK FACTORS AND LATER GRAFT FUNCTION

Hendren,1 James Dong,1 Michael Mengel,2 John S. Gill.1

Overweight BMI were associated with percent decrease in kidney function after donation but may still prove useful in the screening of higher-risk donors with other co-morbidities or early CTD. The absence of a significant association between glomerular diameter and volume as determined by Weibel-Gomez method at time of transplantation (time zero) with change in kidney function (% decrease in eGFR 1 year after live donation function decline. Furthermore, we show that donor sex, but also CVD risk factors are associated with altered PTC density in the M0 Bxs. Our findings indicate that CVD risk factors may affect PTC no. which can contribute to the progression of early CTD.

CONCLUSIONS: Our analysis suggests that renal transplantation is not cost-effective in all patients compared with dialysis from third-party-payers perspective and utilitarian grounds.

Funding: Other NIH Support - NH/NIH K12CA156709-01

TH-PO1154

Glomerular Size on Time Zero Kidney Allograft Biopsies and Change in Kidney Function after Live Kidney Donation

Howard Hao Yan1, Elizabeth Hendren,1 James Dong,1 Michael Mengel,2 John S. Gill.1

Div of Nephrology, Univ of British Columbia, Vancouver, Canada; 2Alberta Transplant Applied Genomics Centre, Univ of Alberta, Edmonton, Canada.

BACKGROUND: Identification of predictors of kidney function after live kidney donation may help expand the living donor pool or identify donors for long-term clinical follow-up.

METHODS: In this study, we determined the association of demographic factors (donor age at transplantation, gender, race, body mass index), pre-donation kidney function (eGFR), and kidney allograft biopsy findings (glomerular diameter and volume as determined by Weibel-Gomez method) at time of transplantation (time zero) with change in kidney function (% decrease in eGFR 1 year after live donation) among n=60 live kidney donors in our centre from 2000-2009.

RESULTS: Mean±SD pre- and post-donation eGFR were 93±14 and 61±15 ml/min/1.73m2, respectively. Mean±SD percent change in eGFR after donation was 34±12%, with 91% having ≥30% decrement in eGFR. Mean glomerular diameter was 163±17 μm, while mean glomerular volume was 2.8±1.0±10 μm³. No donors had glomerulonephry as defined as volume ≥6.8±10 μm³). In regression analyses, contrary to previous reports, glomerular diameter was not associated with donor age, gender, race or BMI. Donor age and overweight BMI were associated with percent decrease in kidney function after donation (3% decrement in pre-donation eGFR for each decade older, p=0.018; 6% decrease in overweight compared to normal BMI, p=0.04), but there was no significant association with pre-donation eGFR, glomerular diameter or volume, donor race or gender.

CONCLUSIONS: We conclude that eGFR percent decrement post-donation is highly variable, and associated with donor age and overweight BMI at transplantation. eGFR decline in donors with increased BMI is independent of glomerular size. The absence of an association between glomerular diameter and volume with change in kidney function in this study may be due to conservative donor selection. These parameters may still prove useful in the screening of higher-risk donors with other co-morbidities or more marginal levels of pre-donation kidney function.

TH-PO1156

Is Deceased Donor Kidney Transplantation Cost-Effective across All End Stage Kidney Disease Patients?


BACKGROUND: Allocation of deceased donor kidneys is primarily based on waiting time in the US. The current system causes unnecessarily high re-transplantation and death with functioning graft resulting from survival mismatch between donor and recipient.

METHODS: The United States Renal Data System (USRDS) linked Medicare database was analyzed to obtain real life outcomes, health care utilization related cost of wait-listed end stage kidney disease (ESRD) patients between 2000 and 2008. A probabilistic model was developed to simulate the natural history of a group of potential kidney transplant candidates (n = 100,000), stratified based on their underlying co-morbidities (low risk recipient – RL, defined as age <60 and no co-morbidities and high risk recipient – RH defined as age >60, diabetes, prior history of cardiovascular events including CABG, PTCA/stent, stroke, and peripheral arterial stent and bypass) and deceased donor categorized based on the Kidney Donor Risk Index-KDRI (low risk donor – DL, KDRI<1.6 and high risk donor – DH, KDRI ≥1.6).

RESULTS: Under current waiting time for deceased donor transplantation, a potential recipient-donor pair achieves an average incremental cost-effectiveness ratio (ICER) of less than $50,000/LYG, except RH-DH group. In overall model, of all renal transplant recipients, 37.7% had worse survival and 38.8% cost more compared to matched-wait-listed dialysis patients.

CONCLUSIONS: Our analysis suggests that renal transplantation is not cost-effective in all patients compared with dialysis from third-party-payers perspective and utilitarian grounds.

Funding: Other NIH Support - NIH/NIH K12CA156709-01

TH-PO1157

OUTCOMES OF KIDNEY TRANSPLANTATION FROM OLDER VS YOUNGER LIVING DONORS: EXPANDING THE DONOR POOL

Imanishi V. Patel,1 Panjik R. Shah,1 Aruna V. Vanikar,1 Vivek Balkrishna Kute1, Monal R. Gumber,1 Hargovind L. Trivedi.1

Nephrology and Transplantation, JKBCITS, Ahmedabad, Gujarat, India; 1Pathology, India, Ahmedabad, Gujarat, India.

BACKGROUND: The disparity between donor kidney availability and demand has increased utilization of kidneys from older living donors (OLD). We compared outcome of OLD kidney transplants (group-1) with younger live donor (YLD) (<60 years) kidney transplants (group-2).

METHODS: Outcome of renal transplants performed between 2007 to 2012 was compared in terms of demographics, survival and graft function.

RESULTS: Out of 1457 transplants, 147(10.1%) belonged to group-1 and 1310 (89.9%) belonged to group-2. Mean donor/recipient age was 62.7/36.6 years in group-1 and 43.5/33.8 years in group-2 and HLA-match was 3.12 and 2.46 respectively. Post-transplant immunosuppression consisted of calcineurin inhibitor based regimen in both groups. Patient survival at 1, 3 and 5 years was 95.7%, 89.4% and 82.6% in group-1 and 93.8%, 89.1% and 83.1% in group-2 (P=0.785). Death-censored graft survival at 1, 3 and 5 years was 95.9%, 88.4% and 76.1% in group-1 and 98.5%, 96.1% and 92.9% in group-2 (P=0.166). Biopsy proven acute rejections were and in 21% and 16.8% (P=0.206) and chronic rejections 5.03% and 3.4% respectively (P=0.542).

CONCLUSIONS: Patient survival and immune injuries were comparable for recipients of YLD kidneys and OLD kidneys. This study suggests that in organ availability crisis, OLD kidneys can be utilized without compromising the recipient 5-year patient or graft survival. This facilitates in decreasing the transplantation waiting lists.

TH-PO1158

ETHNICITY DOES NOT DETERMINE LONG-OUTCOME after Donor Nephrectomy


BACKGROUND: Living donor transplantation is the treatment of choice for ESRD. Although long term data suggests that survival and chronic kidney disease risk in living donors (LD) is similar to general populations, data is limited regarding ethnic groups, particularly South Asian(SA) and Afro-Caribbean(AC) populations. We previously reported 5-year data on LD from different ethnic groups in our centre.

METHODS: We prospectively collected data on consecutive LD(2000-2012). We analyzed follow-up data for 24-hour Creatinine Clearance(CrCl) and protein excretion, and blood pressure control. We included LD with at least one year of follow-up. We used one-way and repeated measures ANOVA for analysis.

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

Underline represents presenting author/disclosure.
Results: We studied 555 LD. 424 completed 12-month,170 had 60-month and 52 had 96-month follow-up. 338(56.8%) were Caucasian (CA),111(19%) were SA, 53(8.9%) were AC. There were 51 LD with history of hypertension (HTN). 48 donors developed HTN during the follow up period. AC patients were at increased risk for developing HTN(0.21±0.2 vs 0.18±0.1 g/24h,p<0.05).

The mean CrCl (mL/min) at baseline, 60 and 96 months was 110.1 (H=115.2, NH=109.6, p=0.26) at time 0 and 90.4 (H=93.0, NH=90.0, p<0.001) with a mean weight of 75.6 Kg(H=78.6, NH=75.0, p=0.01). The mean CrCl remained stable over 3 years. In the multivariate model, however, donor age was negatively associated with donor pre-transplant GFR. On the other hand, while donor GFR at 1 year post donation is a significant univariate predictor of donor eGFR at 1 and 2 years (p<0.05), but not at 3 years. Donor iGFR less than 90 mL/min/1.73m² was associated with a significant increase in donor and recipient eGFR at 1 year post transplant.

There was significant ethnic group age difference (CA=48±12, SA=43±13 and AC=38±9 years, p<0.01). There was no difference in the degree of proteinuria at baseline and at five years (0.11±0.1 vs 0.12±0.1 g/24h), even in patients with pre-existing HTN (0.21±0.2 vs 0.18±0.1 g/24h, p=NS).

Conclusions: Donor nephrectomy in high risk ethnic groups is safe and not associated with poorer outcomes. Kidney function was preserved and proteinuria was minimal over time. AC population is at increased risk for developing HTN.

TH-PO1159
Impact of Donor Glomerular Filtration Rate on Post Transplant Donor and Recipient Renal Function
Anoela A. Shetty, Eric Soukup, Emilio D. Poggio.
Dept of Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH.

Background: A glomerular filtration rate (GFR) greater than 80 mL/min/1.73m² independent of age and gender is considered suitable by certain living kidney donor selection guidelines. We studied the association of pre-transplant donor GFR with donor and recipient renal function post transplant to the impact of this screening criteria.

Methods: Pre-transplant 125I-thallium GFR was measured and pertinent demographic data was captured in 570 living kidney donors as part of donor evaluation. Follow up donor and recipient estimated GFR (eGFR) was calculated using the MDRD equation at 1, 2 and 3 years post-transplant.

Results: Mean pre-transplant donor BSA adjusted GFR (iGFR) was 106±23 mL/min/1.73m² and unadjusted GFR (eGFR) was 116±21 mL/min. Mean age was 43.5±11.6 years with 41.4% males and 14.4% African Americans. Mean donor eGFR was 63.8±12.1 mL/min, 66.4±15.8 mL/min and 68.7±10.6 mL/min, and mean recipient eGFR was 58.4±21.9 mL/min, 56.6±24.5 mL/min and 55.1±23.5 mL/min at 1, 2 and 3 years of follow up.

Donor iGFR was a significant univariate predictor of donor GFR at 1 and 2 years (p <0.05), but not at 3 years. Donor iGFR less than 90 mL/min/1.73m² was associated with lower donor eGFR at 1 year (p=0.01) but not at 2 or 3 years. In multivariate analyses donor iGFR was a significant predictor of donor GFR at 1 year only (p=0.003), while donor age remained a significant predictor of donor eGFR at 1 year (p=0.006) and 2 years (p=0.03). Gender and race were not significant predictors.

On recipient outcomes analyses donor eGFR was not associated with recipient eGFR over 3 years. In the multivariate model, however, donor age was negatively associated with recipient eGFR at 1 and 2 years (p<0.001) but not at 3 years.

Conclusions: Recipient renal function up to 3 years post-transplant is independent of pre-transplant donor GFR. On the other hand, while donor GFR at 1 year post donation is lower for older donors with pre-transplant GFR less than 90 mL/min/1.73m², long term donor GFR appears to be independent of pre-donation GFR. Importantly, the compensatory effects of the remaining donor kidney GFR appears to be sustained or even increased over time.

TH-PO1160
Kidney Biopsy in Potential Donors with Non Visible Haematuria Is a Valuable Component of Donor Work-Up
Emma O’Lone, Abigail Lee, Ravindra Rajakarier, Raj C. Thuraisingham, Mark Blunden.
Nephrology, Barts and The London Hospitals, United Kingdom.

Background: BTS guidelines recommend renal biopsy if non-visible haematuria (NVH) is >1+ on dipstick. Glomerular pathology precludes donation with the possible exception of thin basement membrane (TBM) disease. The level of evidence for these guidelines is graded as “moderate”; little data exists to support them. All biopsies performed on potential living kidney donors with NVH were reviewed.

Methods: A single centre review of prospectively collected data of patients between Jan 2008 and June 2013. Patients with undiagnosed NVH underwent biopsy. Percutaneous biopsy was performed under direct ultrasound (US) guidance using an 18 or 16 gauge needle. Samples were examined by a consultant histopathologist by light microscopy (LM), immuno-histochemistry and electron microscopy (EM).

Results: 148 living donor transplants were performed in the 5 year period. 15 renal biopsies were done for undiagnosed NVH in 14 potential donors. Work-up included urine cytology, flexible cystoscopy, US and CT examination of urinary tract. Of those patients biopsied: Mean age 41.5 years and 33% male. Mean eGFR (by MDRD) of 94.5 mL/min and mean corrected EDTA clearance 93.7 mL/min. 11 (68.8%) biopsies had normal LM and immuno-histochemistry. Of these EM was normal in 6; TBM was diagnosed in 2 and minor paramesangial deposits seen in 2. 1 patient was found to have Zebra bodies on EM, Fabry’s disease was excluded and the patient had previous exposure to chloroquine so donation went ahead. 4 biopsies precluded donation; 2 showed significant scarring, 1 a granulomatous TN consistent with TB and repeat biopsy after treatment showed IgA nephropathy. Overall 11 patients were deemed suitable for donation and 4 biopsies (25%) precluded donation in patients. All biopsies were performed as a day case and no complications were seen.

Conclusions: Biopsy for investigating NVH in potential donors is a safe and helpful investigation. It led to rejection of 25% of potential donors, despite acceptable EDTA GFR results but re-assured the transplanting team in 75% of cases. The long term significance of TBM disease and minor paramesangial deposits is uncertain in this scenario.

TH-PO1161
Hypertension Is Not a Contraindication to Living Kidney Donation
Imperial College Kidney and Transplant Centre, Hammersmith Hospital, London, United Kingdom.

Background: The increasing numbers of patients with ESRF on waiting list for a kidney transplant has been the main driving force for expanding the donor pool. We undertook living donor transplantation from hypertensive donors after initial reports that short-term outcomes are safe. We report 5-year data in this group and compare these with the outcomes of non-hypertensive donors from our centre.

Methods: Data were prospectively collected on 555 consecutive live donors (LD) from 2000-2012. The hypertensive group consists of LD presenting with a pre-existing diagnosis of hypertension (HTN), well-controlled on at least one antihypertensive agent and without evidence of end-organ damage. We analysed 5-year follow-up data for 24 hr Creatinine Clearance (CrCl) and protein excretion as well as blood pressure (BP) control.

Results: 51 LD were hypertensive (H) and 504 non-hypertensive (NH). In the NH group 302 (59.9%) were Caucasian (C), 104 (20.6%) South Asian (SA), 49 (9.7%) Afrocaribbean (AC) and 49 (9.7%) of other ethnicity. There was a higher percentage of C in the H group (70.6%) but similar of SA and AC. Mean age was 45.5 years (H=54.6, NH=44.6, p=0.001) with a mean weight of 75.6 Kg (H=78.6, NH=75.0, p=0.01). The mean CrCl in the NH group was 110.1 (H=115.2, NH=109.6, p=0.26) at time 0 and 90.4 (H=93.0, NH=90.0, p=0.17) at 5 yrs.

We did not find evidence of developing proteinuria in with 24-hour protein excretion of 0.12 (H=0.17, NH=0.10, p=0.03) g/24hrs at 5 yrs. BP remained well-controlled in the H group at 5 yrs at 139/85 vs 135/81 in the NH group (p=0.25). 48 donors in the NH group developed HTN post donation.

Conclusions: Donor nephrectomy in well-controlled hypertensive donors with no evidence of end-organ damage is safe and does not result in poorer outcomes compared to non-hypertensive donors.

TH-PO1162
Screening for Adequate GFR in Obese Potential Kidney Donors
Medicine, Univ of Illinois at Chicago, Chicago, IL.

Background: As organs become scarce, more obese donors are being considered for kidney donation. Assessment of glomerular filtration rate (GFR) is critical in the evaluation of these potential donors. Accurate measurement of GFR using exogenous markers is expensive and time-consuming which complicate the medical evaluation of potential kidney donors. The objective of this study is to identify potential obese donors that need formal measurements of GFR.
Methods: This is a single-center, retrospective analysis of potential kidney donors between 2009-2012. Estimation of GFR was by 24 hour urine collection (CrCl) or by using the Modification of Diet in Renal Disease (MDRD) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. Measured GFR (mGFR) was either by camera-based technetium clearance or iohexol clearance. Sensitivity and specificity was calculated for mGFR > 80 and 90 mL/min/1.73m2 using estimated cutoffs 10mL/min/1.73m2 above the corresponding measured cutoff to increase specificity. Groups were divided by BMI (<35, >35).

Results: There were 250 potential kidney donors with a mGFR. The average age was 38.0±11.9 years with 60% female and a racial composition of 44% Black, 26% White, and 20% Hispanic. The sensitivity/speciﬁcity is shown in the Table. Pre-donation proteinuria was similar between the groups as was post-donation microalbuminuria (n=135) and prevalence of those with eGFR < 60mL/min/1.73m2 (n=151) with median follow up time of 6 months (3-12 months).

<table>
<thead>
<tr>
<th>n</th>
<th>BMI &lt;35 (n=176)</th>
<th>n</th>
<th>BMI &gt;35 (n=74)</th>
</tr>
</thead>
</table>
| Sensitivity | 0.97 | 0.95 | 0.96
| Specificity | 0.62 | 0.72 | 0.69

*72 individuals with a BMI < 35, 31 with a BMI > 35.

Conclusions: The MDRD equation with a cutoff of 10mL/min/1.73m2 higher than the required mGFR may identify both obese and non-obese potential kidney donors needing a mGFR. Results should be validated in an independent cohort before screening potential kidney donors.

Funding: NIDDK Support

TH-PO1163

The Change of Single Kidney Function in Kidney Donor after Uninephrectomy

Ji Hyeon Lee, Eun Nim Kim, Cheol Wook Park, Yong-Soo Kim, Chul Woo Yang, Eun Soon Choe, Transplant Research Center, Div of Nephrology, Dept of Internal Medicine, Seoul St Mary’s Hospital, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: It was not fully investigated that how reserved capacity of single kidney for healthy kidney donor changes after unilateral nephrectomy. The aim of this study was to assess the change of remaining single kidney function after kidney donation and to evaluate predictive pre-donation factor for reserved single kidney capacity in donors.

Methods: Total 74 kidney donors who underwent DCD and OTCA Scintillation-Camera renography before and after kidney donation were included in this study. By the renography, we measured single-kidney glomerular filtration rate (sk-GFR) of both kidney before donation and post-donation GFR of remaining kidney during 12 months. We investigated the factors that are associated with reserved capacity of remaining single kidney after donation.

Results: After uninephrectomy the mean of serum creatinine increased significantly (P=0.000, from 0.77 to 1.07 mg/dL) and the mean GFR measured by the renography declined (P=0.000, from 112.9 to 74.9 mL/min/1.73m²). Nevertheless the mean of serum creatinine and the GFR stabilized during 12 months follow-up period (mGFR at Post-donation, P=0.165 [6 month 74.9 ± 18.2 vs 12 month 81.4 ± 14.8 mL/min/1.73m²]). The sk-GFR of remaining kidney significantly increased by 33.6 % after uninephrectomy (sk-GFR, P < 0.01 [Pre-nephrectomy 57.9 vs Post-nephrectomy 77.5 mL/min/1.73m²]). By univariate linear regression, BMI, total mGFR, sk-GFR of remaining kidney and total kidney volume at pre-donation were included as independent predictors of change of sk-GFR. Among these, BMI (P=0.013) and sk-GFR of remaining kidney at pre-donation (P=0.019) were statistically related to reserved single kidney capacity in multivariate regression analysis.

Conclusions: After kidney donation, reserved single kidney capacity shows significant increase due to adaptive hyperferilation. Especially in donor with lower BMI and lower sk-GFR of remaining kidney at pre-donation shows more compensatory response.

TH-PO1164

Kidney Transplant Outcomes among prior Live Organ Donors

Vishnu S. Potluri, Meera Nair, Francis P. Wilson, Roy D. Bloom, Peter P. Reese. Renal Div, Univ of Pennsylvania, Philadelphia, PA.

Background: OPTN gives high priority in organ allocation to wait-listed candidates who are previous organ donors. However, information about waiting time for kidney transplant, organ quality and post-transplant outcomes among former live donors has not been reported.

Methods: We assembled a cohort of candidates listed for a kidney transplant from 1996 to 2010 using Scientific Registry of Transplant Recipients data. We used multivariable Cox regression to examine the association of prior kidney donor status to time to kidney transplantation. Among candidates who received a kidney transplant, we used a 1:1 propensity score approach to compare allograft quality as measured by the kidney donor risk index (KDRI) and post-transplant outcomes among prior organ donors to recipients with similar demographic and clinical characteristics.

Results: During the study period, there were 407,212 listings for a kidney transplant, of which 208 were prior organ donors. Among listed candidates, 82% (n=214) of donors received a deceased donor kidney transplant as compared to 34% (n=140,046) of non-donors. The median time to transplant for organ donors was 174 days (HR for transplant associated with prior organ donor status 4.8, p<0.001). Most prior donors received dialysis by the time of listing (68% vs 65%, p=.56). Compared to matched recipients, prior organ donors received higher quality allografts (Median KDRI 0.72 for donors vs 0.82 for non-donors), p<.001. Donors did not have better all-cause graft survival than non-donors (HR 1.3, p=.3), but had lower mortality (HR .32, p=.003).

Conclusions: OPTN policy has enabled transplant candidates who are previous organ donors to have a brief waiting time for kidney transplantation. However, >60% of donors had dialysis by wait-listing. Early nephrology referral and transplant evaluation may enable pre-emptive transplantation for donors.
Spit It Out to Check Your Kidneys: Saliva Urea Nitrogen Dipstick as a New Bedside Diagnostic Tool of Acute Kidney Injury

Viviane Calice da Silva,1-2 Marcos Alexandre Vieira,1 Jochen G. Raimann,3 Mary Carter,2 John Callegari,2 Nathan W. Levin,2 Peter Kotanko,3 Roberto Pecoits-Filho,2 Pró-rim Foundation, Brazil; 2School of Medicine, Pontifícia Universidade Católica do Paraná, Brazil; 3Renal Research Institute.

Background: Kidney dysfunction can be identified non-invasively using a dipstick that semi-quantitatively determines saliva urea nitrogen (SUN) levels. The SUN dipstick may be useful in areas with limited access to clinical chemistry facilities. Here, we evaluated the performance of SUN dipstick in patients with acute kidney injury (AKI) as per AKIN criteria.

Methods: Unstimulated saliva from hospitalized patients with pre-renal (PrR), renal (R) or post-renal (PoR) suspected AKI; blood urea nitrogen (BUN) was measured concurrently. After collected, saliva was transferred to the SUN dipstick (Integrated Biomedical Technology, IN) and SUN’s levels were read within one minute. The color of the test pad was compared to 6 standardized test pads indicating SUN concentrations: 15–24 (#1), 25–34 (#2), 35–54 (#4), 55–74 (#5), and 75-96 mg/dL. Spearman’s correlation test (Rs), areas under receiver operating characteristic curves (AUC ROC) and 95% confidence intervals evaluated the performances of SUN and BUN to diagnose AKIN 3. Youden’s index was used to compute thresholds to discriminate AKIN 3 from earlier AKI stages.

Results: 44 AKI patients (59.5±18 years, 58% female) (PrR: 67%; R: 24%; PoR: 9%) with AKIN stage I (33%), 2 (27%), and 3 (40%) were enrolled. SUN and BUN levels were correlated (R= 0.77; p<0.001) irrespective of AKIN stage and AKI etiology. The diagnostic performance of SUN (AUC ROC: 0.76 (95% CI 0.61-0.91)) and BUN (AUC ROC: 0.69 (95% CI 0.51-0.87)) was comparable. Optimal diagnostic threshold levels were 72 mg/dL for BUN and 25-34 mg/dL (test pad #3) for SUN.

Conclusions: Our study indicates that SUN dipsticks discriminated AKIN 3 from earlier AKI stages which carry a lower probability to require dialysis. This low-resource technology may help to improve the diagnosis of advanced AKI and aid triaging patients in areas with limited access to healthcare facilities and may improve outcomes.

Biomarker Panels Can Predict and Classify Acute Kidney Injury

Rajit K. Basu,1 Catherine D. Krawczeski,1 Lakhmir S. Chawla,2 Derek Wheeler,1 Stuart Goldstein,1 1Center for Acute Care Nephrology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Anesthesia and Critical Care, George Washington Univ, Washington, DC.

Background: The ability to classify AKI severity or category of AKI (functional change or kidney damage) using biomarkers, a key directive from the 10th Acute Dialysis Quality Initiative (ADQI) conference, has yet to be demonstrated.

Methods: We retrospectively studied 359 children following cardiopulmonary bypass (CPB) surgery (pts) to determine if a biomarker panel taken 12 hours after CPB could differentiate the following AKI ‘categories’: 1) severity of AKI or 2) AKI type: functional change or kidney damage. Severe AKI was defined as pSFLHE i-F (by creatinine) within the first seven days after CPB. AKI lasting only 1-2 days was deemed functional change. The functional change biomarker used was plasma Cystatin C (pCysC) while the kidney damage biomarker was urinary neutrophil gelatinase associated lipocalin normalized to creatinine (uNGAL/uCr). Sensitivity analyses identified cut-off values for both pCysC and uNGAL/uCr (*p<0.05).

Results: AKI occurred in 62 pts (17.3%). Pts with dual marker positivity were highly unlikely to develop severe AKI (likelihood ratio (+LR): 99.5) while pts with dual marker negativity were highly unlikely (-LR: 6.12). Pts with only (+)functional marker demonstrated a negligible increase in likelihood of severe AKI (+LR: 1.04). In pts with AKI, a (+) functional/(-)damage panel carried a higher likelihood of functional injury (reversible), than any other biomarker combination and were unlikely to have persistent severe AKI (+LR:0.76). Addition of a positive damage marker (both positive) predicted a persistent AKI.

B-Type Natriuretic Peptide Reduces Acute Kidney Injury: A Meta-Analysis

Sayyad F. Kyzazimadeh,1 Daniel M. Pearlman,2 Jeremiah R. Brown,1 Alex L. Yerukhimov.2 1The Dartmouth Institute for Health Policy and Clinical Practice at the Geisel School of Medicine, Lebanon, NH; 2Dartmouth College, Hanover, NH.

Background: B-type natriuretic peptide (BNP) has been shown to improve renal function in individual clinical trials. However no systematic review or meta-analysis has been performed to determine whether BNP prophylaxis prevents acute kidney injury (AKI) in multiple randomized clinical trials involving coronary artery bypass graft (CABG) or primary percutaneous intervention (PCI). We hypothesized prophylactic treatment with BNP reduces the risk of AKI in cardiac procedures.

Methods: We conducted a meta-analysis for published randomized clinical trials involving treatment of BNP in percutaneous interventions or cardiac surgery procedures and reporting renal function. Our search identified 71 records, of which 5 RCTs, including 839 patients, met our pre-specified eligibility criteria. One article was excluded because BNP was administered after AKI was established. We calculated a random effects summary estimate for all trials and stratified by procedure type.

Results: Overall, only 12.2% of patients receiving BNP developed AKI compared 22.0% in controls with an odds ratio of 0.49 (95% confidence interval: 0.31 to 0.77, P = 0.002 see figure). After stratifying this analysis by procedure type, risk of AKI remained significantly decreased for PCI (17.6% vs. 30.9%; OR, 0.48; 95% CI, 0.27 to 0.85; P = 0.011) but not CABG (7.6% vs. 14.0%; OR, 0.51; 95% CI, 0.24 to 1.07; P = 0.074). There was no observed heterogeneity (I-squared 0.0%; P = 0.50).

Conclusions: Perioperative administration of BNP reduces the risk of AKI for patients undergoing PCI but not CABG surgery.

Biomarker Profile in Biopsy-Proven Renal Diseases

Natalie M. Otto,1 Volker Schmitz,2 Stephan Wolfgang Hanschke,1 Joe F. Keenan,3 Ralf Schindler.1 1Nephrology and Intensive Care, Charité, Berlin, Germany; 2EKF Diagnostics Limited, Trinity Technology Campus, Dublin, Ireland.

Background: The major tool to assess renal disease is the kidney biopsy. Efforts have been made to identify non-invasive markers to predict the type of renal damage. We investigated a variety of serum biomarkers to predict the category of renal histology obtained by biopsy.

Methods: 140 consecutive patients underwent renal biopsy as clinically indicated. Serum and urinary samples were prospectively collected and analyzed for 46 biomarkers. Serum levels of biomarkers were adjusted for serum creatinine. Biopsy results were categorized in 8 disease entities and biomarker levels compared in each category.

Results: Biopsy results were: minimal change/FSGS (n=58), vasculitis (n=19), IgA-nephropathy (n=20), membranous nephropathy (n=19), diabetic nephropathy (n=11), hypertensive nephropathy (n=19), post-streptococcal nephritis (n=2), amyloidosis (n=4) and tubulointerstitial lesions (n=8). 10 healthy subjects without biopsy served as controls. There was a characteristic pattern of biomarker elevation for certain histological entities. For instance, IL-3 was elevated only in vasculitis and post-streptococcal nephritis (figure).

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

Underline represents presenting author/disclosure.
Several biomarker such as IL-6, IL-7, IL-8 were exclusively elevated in post-streptococcal nephritis. In contrast, tubulointerstitial disease was characterized by elevated levels of KIM-1 but marked decreased levels of biomarkers such as IL-23 or MMP-9. Hypertensive- and IgA-nephropathy did not show characteristic profiles of the investigated markers. Urinary biomarker results will also be presented.

Conclusions: In some types of renal disease serum levels of certain biomarkers are significantly different from controls. There appears to be a characteristic biomarker pattern for several disease entities that could help predict the renal disease by straightforward non-invasive analysis.

Funding: Government Support - Non-U.S.

FR-PO005

Urine Microscopy – A Golden Tool in Diagnosis of Acute Kidney Injury

Piniak Mukhopadhyay,1 Piayli Banerjee,2 Gautam Mukherjee.1 Nephrology, NRS Medical College & Hospital, Kolkata, West Bengal, India; Medicine, Bagann Rural Hospital, Howrah, West Bengal, India; Gynaecology & Obstetrics, North Bengal Medical College, Siliguri, West Bengal, India.

Background: Urine microscopy is very important diagnostic modality. The aim of the study was to review the role of urine microscopy and urine sediment examination in the differential diagnosis and outcome prediction of acute kidney injury (AKI).

Methods: All patients admitted with AKI (RIFLE criteria) were included and urine was tested for different cast, including granular cast (GC), renal tubular epithelial cell (RTEC). AKI cause (pre-renal/acute tubular necrosis, ATN) was evaluated by nephrologist two times before urine testing and at discharge. A scoring system (scoring 1 (RTEC & GC = 0), 2 (RTEC = 0 & GC = 1), 3 (RTEC = 1 & GC = 1), 4 (GC > 1) or RTEC > 1 & GC > 1) was created based on casts and RTEC and evaluated its accuracy for differentiating ATN from pre-renal AKI. Likelihood ratios. (LR) were calculated for a diagnosis of both ATN and prerenal AKI.

Results: The urinary sediment scoring system was highly predictive of the final diagnosis of ATN. The odds ratio (OR) for ATN incrementally increased with an increase in severity of the scoring system (all compared with score 0; score 1: OR 9.7, 95% CI 5.3 to 18.6; score 2: OR 7.4, 95% CI 16.6 to 32.9; 1. Patients with a high pretest probability of ATN (initial diagnosis of ATN), any granular casts or RTEC (score ≥ 2) resulted in very high Positive Predictive Value (100%) and low Negative Predictive Value (44%) for a final diagnosis of ATN. In patients with a low pretest probability of ATN (initial diagnosis of prerenal AKI), the lack of granular casts or RTEC on urinary sediment examination had a sensitivity of 0.73 and a specificity of 0.75 for a final diagnosis of ATN. The NPV of lack of granular casts or RTEC in patients with low pretest probability of disease was 91%.

Conclusions: Urine microscopy on the day of nephrology consultation is a valuable diagnostic tool for strengthening the probability of a diagnosis of ATN. Furthermore, an ATN scoring system is useful for improving the differential diagnosis of ATN versus prerenal AKI.

FR-PO006

Urinealysis (UA) Dipstick Proteinuria (DP) at ICU Admission Predicts Mortality in Sepsis

John Manlio, Javier A. Ncaya, Fabrizio Canepa, Ghassan Bandak, Jerry Yee, Lenar T. Yessayan. Dept of Medicine, Henry Ford Hospital, Detroit, MI.

Background: Sepsis is one of the most common causes of admission to the ICU, with a high degree of mortality, early predictors for mortality are helpful in clinical practice, to ensure prompt intervention. The purpose of our study is to assess the utility of UA DP as a predictor of clinical outcome in patients with sepsis.

Methods: 5,558 consecutive patients admitted to the ICU between October 2007 and April 2012 with severe sepsis (N=4,032) or septic shock (N=1,826) were screened for DP within 24 h of admission. Exclusion criteria: >100 RBC/hpf on microscopic UA, bacteriuria, urinary tract infection diagnosed by 24 h of admission; and within 3 months pre-admission, absence of UA testing, UA DP, or documented proteinuria by other means.

Results: 229 patients fulfilled study criteria. Bivariate analysis revealed that UA DP was associated with ICU mortality OR=3.9 (1.7-8.8, p=0.001) and hospital mortality OR=3.5 (1.7-7.3, p=0.001). Associations persisted in a Multivariate model that adjusted for ICU severity score (APACHE II), vasopressor use, age, and level of creatinine in the first 24 h post-hospitalization.

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

Underline represents presenting author/disclosure.

366A
FR-PO009
Evaluation of New Urine Biomarker TIMP-2 in Intensive Care Unit
Tetsuya Yamashita, Kent Doi, Maki Tsukamoto, Yoshitumi Hamamasaki, Massomi Nakaguki, Naoki Yahagi, Eisei Noiri. The Univ of Tokyo, Tokyo, Japan.

Background: Tissue inhibitor of metalloproteinases-2 (TIMP-2) was recently reported as a novel for predicting severe AKI in critical ill patients. We evaluated the performance of urine TIMP-2 in our adult mixed intensive care unit (ICU).

Methods: This study enrolled 98 patients who were admitted to the mixed ICU of The University of Tokyo Hospital from July 1st to 2010 to 2011 by consecutive sampling. Urine TIMP-2 and NAG, and plasma NGAL and IL-6 were measured on ICU admission. The results of urine TIMP-2 and NAG, and plasma NGAL and IL-6 were measured on ICU admission. This study was aimed to evaluate whether these biomarkers could predict AKI and its severity, and mortality by ROC analysis.

Results: AKI occurred in 42 (42.9%) patients including 27 (27.6%) severe AKI (KDIGO stage 3). The area under the ROC curve for each marker was shown in Table 1.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMP-2</td>
<td>0.74 (0.63 - 0.83)</td>
</tr>
<tr>
<td>NAG</td>
<td>0.84 (0.74 - 0.90)</td>
</tr>
<tr>
<td>NGAL</td>
<td>0.84 (0.74 - 0.90)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.72 (0.60 - 0.81)</td>
</tr>
</tbody>
</table>

Fifty one (41.8%) patients was complicated with sepsis, including 19 (19.4%) severe AKI. In accordance with previous reports, plasma NGAL and IL-6 were increased by sepsis, however urine TIMP-2 and NAG was increased not by sepsis but by the presence of severe AKI.

In-hospital mortality was 15.3% in this cohort and urine TIMP-2 and NAG, and plasma NGAL and IL-6 were significantly higher in the non-survivors than the survivors, whereas plasma IL-6 was not significantly associated with mortality.

Conclusions: A new urine biomarker of TIMP-2 is increased especially in severe AKI and associated with mortality. Sepsis appeared to have a smaller impact on urine TIMP-2 and NAG compared with plasma NGAL and IL-6. This distinct feature of biomarkers will enable to evaluate the contribution of sepsis to the development of AKI.

Funding: Government Support - Non-U.S.

FR-PO101
Diagnostic Utility of Biomarkers of Acute Kidney Injury in Critically Ill Patients
Claire Hannon, Patrick T. Murray. Dept of Nephrology, Mater Uni Hospital, Ireland; Univ College Dublin, Ireland.

Background: Acute kidney injury (AKI) occurs in 5-10% of hospitalized patients, with a mortality of approximately 50% in a critical care setting. Diagnosis is based on changes in serum creatinine, a late marker of injury. Development of AKI biomarkers may permit earlier detection of AKI and allow improvements in its prevention and therapy.

Methods: All patients admitted to the intensive care unit (ICU) were screened for inclusion in this prospective cohort study. Clinical information and urine was collected daily for 7 days. Urine biomarkers analysed were neutrophil gelatinase associated lipocalin (NGAL), α and β glutathione-S-transferase (GST), albumin and creatinine. AKI was defined by KDIGO criteria using ICU admission creatinine as reference. ROC curves were generated for admission biomarkers and AUC’s were calculated for prediction of AKI and a composite endpoint of death and need for renal replacement therapy (RRT). Admission biomarkers were collected at enrolment, within 24 hours of ICU admission.

Results: 201 patients were enrolled, 90 patients (45.3%) developed AKI. AKI stages: stage 1 (19.9%, n=40), stage 2 (6.5%, n=12) and stage 3 (18.9%, n=38). 201 patients were enrolled, 90 patients (45.3%) developed AKI. AKI stages: stage 1 (19.9%, n=40), stage 2 (6.5%, n=12) and stage 3 (18.9%, n=38). 201 patients were enrolled, 90 patients (45.3%) developed AKI. AKI stages: stage 1 (19.9%, n=40), stage 2 (6.5%, n=12) and stage 3 (18.9%, n=38). Patients with AKI were significantly older (69 ± 5 years, p = 0.003), had a higher incidence of chronic kidney disease (24.4 ± 7.3%, p < 0.001) and a higher mortality (44.4 ± 28.8%, p = 0.011). 40% of patients with AKI needed RRT. Moderate to good AUC’s for AKI prediction were seen with urine NGAL (0.723, p < 0.0001) and albumin (0.689, p < 0.0001). The AUC’s of urine creatinine, α and β GST were non-significant. Combination of admission urine NGAL and urine albumin and APACHE II score improved prediction of AKI with an AUC of 0.770 (p < 0.0001). Prediction of a composite endpoint of death or dialysis using admission urine albumin and NGAL was moderate, with AUCs of 0.639 (p = 0.0008) and 0.596 (p = 0.0186) respectively.

Conclusions: Admission urine NGAL and albumin showed moderate to good ability at AKI prediction, combination with a clinical severity score further improved this. Biomarkers and clinical model combinations may improve AKI diagnosis and prediction.

Acknowledgements: Health Research Board (HRB), Dublin Centre for Clinical Research (DCCR).
Funding: Pharmaceutical Company Support - Astute Medical, INC

FR-PO112
Positive Fluid Balance (PFB) and Hospital Mortality in Severe Septic Patients with or without Acute Kidney Injury (AKI)
Javier A. Neyra, Fabrizio Canepa, John Manollo, Beverley Adams-huet, Robert D. Toto, Jerry Yee. Univ of Texas Southwestern Medical Center, Dallas, TX; Henry Ford Hospital, Detroit, MI.

Background: Severe sepsis causes increased capillary permeability, impaired renal excretion of exogenous sodium and slow vascular rellifing, thereby promoting interstitial edema and adverse outcomes. AKI occurs in up to 70% of those with severe sepsis and intravenous fluid therapy is directed at restoring organ hypoperfusion. The aim of this study is to evaluate the relationship between PFB and hospital mortality in AKI status in non-CKD patients admitted to the ICU with severe sepsis.

Methods: A population-based linked administrative database of 2,786 septics patients was analyzed for the association of PFB (> 5 L) within the first 72 h of ICU admission and death. Our study group comprised 1,854 non-CKD patients (SCr < 1.5 mg/dL within 3 mo prior to admission) stratified by AKI status. Severe sepsis was defined by Infections et al criteria and AKI by Acute Kidney Injury Network. Multivariable logistic regression models were adjusted for age, gender, race, baseline SCr, comorbidities, vasoactive drugs, diuretic exposure, blood transfusion, and SOFA and APACHE II scores.

Results: Mean age (SD) was 65 (16) years: 39% were African American and 39% Caucasian. At time of admission, 47% (867/1,854) had AKI (Group A), 12% (232/1,854) developed AKI (Group B), and 41% (755/1,854) had no AKI within 72 h of admission (Group C). The mean cumulative fluid balance (SD) was 5.3 L (7.3) in Group A, 2.5 L (8.1) in Group B, and 2.8 L (5.4) in Group C. During hospitalization, 398 (21%) died: Group A, 219/867 (25%); Group B, 74/232 (32%); and Group C, 105/755 (14%). In stratified, adjusted models, PFB was significantly associated with hospital mortality in all groups: Group A, OR (95% CI) 2.4 (1.7, 3.4); Group B, 2.3 (1.2, 4.6); and Group C, 1.8 (1.1, 2.9).

Conclusions: In this study population of non-CKD patients with severe sepsis, PFB (> 5 L) was an independent predictor of hospital mortality in patients with or without AKI. These findings highlight the importance of individualized response-based fluid therapy, even in patients with significant increases in SCr within the first 72 h of ICU admission.

Funding: Clinical Revenue Support

FR-PO104
Biomarkers for Acute Kidney Injury in the Emergency Department
Martin Kimmel, Jing Shi, Jorg Latos, Niko Braun, Mark Dominik Alschner. Dept of Internal Medicine, Div of Nephrology, Robert-Bosch Hospital, Stuttgart, Germany; 1Walker Bioscience, Carlsbad, CA.

Background: There is a growing role of emergency departments (ED) for hospital admissions but there are only few studies addressing acute kidney injury in ED. Two novel urinary biomarkers of acute kidney injury (AKI) were recently reported for risk stratification for AKI and the combination of these biomarkers (TIMP-2>uGBBP7) was found to be superior to other known biomarkers of AKI in critically ill hospitalized patients. We have performed an analysis of TIMP-2>uGBBP7 in patients presenting to the emergency department.

Methods: We enrolled 397 patients in the Emergency Department at Robert-Bosch-Krankenhaus, Stuttgart. Daily serum creatinine values and urine output were recorded for AKI staging by KDIGO criteria (302 patients had urine output data). Biomarkers were analyzed in samples collected during the first day (at 0, 6 and 24h) after enrollment. Cystatin C, KIM-1, L-FABP and NGAL were measured in blood and urine and uGBBP7, TIMP2, and IL-18 were measured in urine samples. We examined the association between these biomarkers and KDIGO stage 2 or 3 within 12 hours of sample collection using univariate and multivariate generalized estimating equation (GEE) logistic regression.

Results: All urinary biomarkers tested had a statistically significant (p<0.05) univariable odds ratio for KDIGO stage 2 or 3 within 12 hours of sample collection. The results of the markers measured in blood, only serum creatinine and plasma cystatin C had a significant univariable odds ratio. In a multivariate GEE logistic regression model including all the urine markers and serum creatinine, only TIMP2>uGBBP7 and serum creatinine had statistically significant adjusted odds ratios (standardized odds ratio=2.4 (95% CI, 1.4-4.4) and 1.9 (95% CI, 1.3-2.9), respectively) for patients with urine output data.

Conclusions: In conclusion, our study is the first to report TIMP2>uGBBP7 in urine from a cohort of emergency department patients. Our results show that TIMP2>uGBBP7, associated with mechanical injury, is currently the most promising and sensitive biomarker of AKI, providing valuable information for risk assessment in the emergency department.

Funding: Pharmaceutical Company Support - Astute Medical, Private Foundation Support
Methods: Retrospective chart review of patients admitted to an intensive care unit (ICU) requiring RRT for AKI from January 2011 to January 2012 at a tertiary academic center. Patients initiated on RRT prior to IU admission or for toxic ingestions were excluded. FO was defined as the cumulative fluid balance from IU admission to RRT initiation expressed as a percentage of admit weight. Time-dependent Cox regression was used to assess the association between FO in the first eight days of RRT and mortality, adjusted for sequential organ failure assessment score and history of malignancy.

Results: 149 ICU patients were included: mean age 54 ± 15y, 60% male, 74% white, mean baseline eGFR 81 ± 35 ml/min/1.73m² and mean SOFA score prior to RRT 13 ± 4.

Conclusions: We found that FO at RRT initiation was associated with increased mortality, but this relationship was not significant after adjusting for severity of illness. Conversely, the ability to achieve a negative fluid balance following the initiation of RRT was associated with lower hospital mortality. Further studies are required to determine whether this finding represents an opportunity to positively intervene in this population.

FR-PO014
A New Urinary Scoring System for Differential Diagnosis of Acute Renal Injuries

Kayaho Maeda,1 Yuka Sato, Hiroki Hayashi, Waichi Sato, Seiichi Matsuo,1 Tatsuhiko Hashimoto,1 Rong Chu,1 Hua Xiao Liu,2 Zijing Li,1 Li Yang,1

Background: AKI is a clinical syndrome encompassing various etiologies that involve any of the renal tubules, interstitium, glomerulus or vasculature. We developed a prospective cohort study to explore a new urinary scoring system that may help locate the pathogenic lesions of parenchymal acute renal injuries.

Methods: 165 AKI patients (2012-KDIGO) who were historically proven as parenchymal acute renal injuries from Jun 2011 to June 2013 were enrolled. Urinary sediment examination was performed in the morning of renal biopsy by two independent nephrologists. 24-hour urine protein was tested. A urinary scoring system was made from 50 AKI patients and validated in the following 115 AKI cases using histology as gold standard.

Results: The urinary scoring system originated from 15 cases with acute tubular necrosis (ATN), 13 with glomerular nephropathy, GN, 18 cases with acute tubulointerstitial nephritis (ATIN, 8 with GN), 15 cases with diffuse acute glomerular nephritic lesions (AGN, cellular crescentic GN etc) and 2 cases with vascular injuries.

Validation was performed in 35 ATN cases, 35 ATN cases, 35 AGN cases and 12 vascular injuries cases. The urinary scoring system recognized 76.9% of ATN, 66.7% of ATIN and 92.1% of diffuse AGN. Patients with vascular injuries including TMA and malignant hypertension had “clean” urinary sediment examination and did not fit the scoring system.

Conclusions: Urinary scoring system may help differentiate acute renal parenchymal injuries. More cases are required to enlarge the sample size of the study. Urinary biomarkers, including NAG, a1-MG, KIM-1, NGAL, MCP-1 and IL-18, were tested. Analysis of combining the scoring system and biomarkers is processing.

FR-PO015
Glycosylated Protein CD147 Reflects Renal Dysfunction in Patients with Acute Tubular Necrosis

Hiroshi Kojima, Tomoki Kosugi, Mayuko Maeda,1 Lars O. Uttenthal.

Background: Recently, we demonstrated that CD147 is responsible for chronic inflammation in TECs. We therefore investigated whether plasma and urinary CD147 could reflect disease activity of ATN.

Methods: Experiment (Exp.) 1: Plasma and spot urine samples were collected from the 24 patients, who underwent renal biopsy between 2008 and 2012. They included pathological control (n=12) and ATN (n=12). Exp. 2: 40 patients are registered undergoing open surgery to treat abdominal aortic aneurysms (AAA) in 2004 at our hospital. We collected 160 urine samples from 7 and 33 patients with and without AKI, respectively. In both experiments, plasma and urinary CD147 levels were measured, and its expression in the kidneys was immunohistochemically analyzed. We further examined urinary L-fatty acid binding protein (L-FABP), ATB and 8-OHdG levels.

Results: Exp. 1: CD147 expression, mainly detected in TECs of healthy kidneys, was extremely lower in injured tubules of ATN patients. The NGAL levels and the area under the receiver operating characteristic (AUROC) for the diagnosis of AKI are shown in the table:

Conclusions: CD147 may be a prime candidate for developing a new procedure for the evaluation of AKI.

FR-PO016
Urinary Excretion of Kidney Injury Molecule 1 Predicts the Need for Extra-Renal Replacement Therapy in Cirrhotic Patients Admitted to the Intensive Care Unit

Justine Deves,1 Francois Jouret,2 Yvan Fleury,1 Pierre-francois Laterre,1 Diego Castanarces-zapatero,1 Cliniques Universitaires Saint-Luc (ULC, Brussels); 2Univ of Liege Hospital (ULg CHU, Liege).

Background: Detecting acute kidney injury (AKI) requiring extra-renal replacement therapy (ERRT) remains challenging in cirrhotic patients admitted to the Intensive Care Unit (ICU). Still, AKI is associated with an increased mortality. Here, we prospectively investigated the usefulness of the urinary biomarker of kidney damage, kidney injury molecule 1 (uKIM-1), in predicting the need for ERRT in ICU patients with decompensated cirrhosis.

Methods: Consecutive patients admitted to the ICU of Cliniques Universitaires Saint-Luc, Brussels, for cirrhosis-related complications were prospectively enrolled. Patients with chronic kidney disease were excluded. Serum creatinine levels (sCr) and urinary excretion of KIM-1 were measured at 24h and 48h post admission. A multiple logistic regression for ERRT prediction was performed after adjustment for age, gender, sepsis, MELD score.

Results: The cohort included 109 patients. Main causes of admission were gastrointestinal bleeding (38.5%) and sepsis (33.5%). Twenty-seven patients (24.7%) developed AKI requiring ERRT. No ERRT was initiated before day 2. Mortality rate (74.1% vs 33.5%, p<0.05) and MELD score (27.8 vs 20.1, p<0.05) were significantly higher in ERRT-treated patients. No correlation was found in these patients regarding the evolution of sCr and uKIM-1 within the first 48h. Indeed, sCr decreased over time, whereas uKIM-1 further increased. At day 2, uKIM-1 was significantly higher in patients who required ERRT (17.1 vs 9.7 mg/ml, p<0.027). In logistic regression analysis, uKIM-1 > 10 ng/ml at day 2 predicted the need for ERRT.

Conclusions: At day 2 post ICU admission, uKIM-1 helps better identify patients with decompensated cirrhosis at risk for ERRT.

Funding: Clinical Revenue Support

FR-PO017
The Monomer Is the Major Form of NGAL in Urine and Plasma in Severe Sepsis

Kristian Bangert,1 Alexandra Baer,1 Peter Buhl Hjortrup,2 Anders Perner,2 Lars O. Utenthal.1 BioPorto Diagnostics A/S, Denmark; 2Rigshospitalet, Denmark.

Background: Neutrophil gelatinase-associated lipocalin (NGAL) is a marker of acute kidney injury (AKI), but is also released from neutrophils on phagocytosis of bacteria and as a marker of pro-inflammatory response. It has been reported that the injured kidney releases NGAL in its monomeric form. In contrast, the neutrophils are claimed to release NGAL primarily as homodimer. Patients with severe sepsis have both a high release of NGAL from the neutrophils and a high risk of AKI. We have measured the levels of NGAL monomer and homodimer in urine and plasma samples from patients suffering from severe sepsis.

Methods: NGAL monomer and homodimer were measured with specific ELISAs in sets of urine and EDTA plasma samples from 151 patients suffering from severe sepsis and compared with NGAL measured with a fully automated particle-enhanced turbidimetric immunoassay (The NGAL Test™, BioPorto Diagnostics A/S). AKI was defined as a 50% increase in plasma creatinine levels.

Results: AKI occurred in 83 of the 151 patients. The NGAL levels and the area under the receiver operating characteristics curve (AUROC) for the diagnosis of AKI are shown in the table:

Conclusions: Our results suggest that the monomeric form of NGAL is the major form released in patients suffering from severe sepsis. The combination of plasma and urinary monomeric NGAL could be used as a biomarker of AKI in patients with severe sepsis.
Conclusions: NGAL monomer is the major form of NGAL found in urine and plasma from patients with severe sepsis. The occasional presence of low levels of NGAL homodimer has little impact on the interpretation of results obtained with monomer-reactive, homodimer cross-reactive NGAL assays in samples from patients with sepsis.

FR-PO018

Urine and Plasma Neutrophil Gelatinase Associated Lipocalin (NGAL), the Novel Biomarkers for Leptospirosis Associated Acute Kidney Injury (AKI): Result from the Multicenter Study

Nong,1 Kriang Tungsanga,1 Visith Sitprija,1,2 John A. Kellum.3

Background: AKI is one of the most serious complications of leptospirosis, an important zoonosis in the tropics. NGAL which represents as an early biomarker AKI has never been explored in this specific setting.

Methods: We retrospectively collected kidney specimen and clinical data of AKI patients and then performed three standard techniques (microscopic agglutination test, direct culture, and PCR technique) to confirm the diagnosis of leptospirosis. KDIGO criteria was used as the standard criteria for AKI diagnosis. Recovery was defined as alive and not requiring dialysis during hospitalization or having a persistent KDIGO staging at hospital discharge.

Results: Of the 89 recruited patients, 54 subjects were diagnosed as leptospirosis. Forty-five percent had AKI. Median uNGAL and pNGAL levels in AKI group were significantly higher than the non-AKI group [187.8 (51,7,224.6) vs 10.7 (2.23,56) ng/mL p < 0.001 and [1300 (348,1300) vs 173 (86,238) ng/mL p < 0.001, respectively. uNGAL and pNGAL levels predicted AKI with AUC-ROC of 0.89, and 0.90, respectively. Median uNGAL level in recovery group was significantly lower than non-recovery group [156.7 (38,0,351.2) vs 843.7 (224,8,9,222.2) ng/mL p < 0.001], while pNGAL level was comparable. uNGAL and pNGAL predict renal recovery with AUC-ROC of 0.893 and 0.59, respectively.

Conclusions: From this multicenter study, uNGAL and pNGAL provided the promising result to be a marker for leptospirosis associated AKI. However, only uNGAL showed the potential role to be the predictor of renal recovery in this specific setting.

FR-PO019

The Renal Klotho Expression Is Associated with the Severity of Human AKI


Background: Klotho is highly expressed in the kidney and known to have multiple functions including renoprotection from a variety of insult. Especially, its diagnostic and therapeutic roles in acute kidney injury (AKI) have been demonstrated recently in animal functions including renoprotection from a variety of insult. Especially, its diagnostic and therapeutic roles in acute kidney injury (AKI) have been demonstrated recently in animal.

Methods: We retrospectively collected kidney specimen and clinical data of AKI patients who underwent renal biopsy between January 2001 and December 2012 at Korea university hospital. The protein expression of Klotho was determined by immunohistochemical staining and clinical-pathological correlation was examined.

Results: Among 34 patients who were diagnosed with acute tubular necrosis or acute tubulointerstitial nephritis, a total of 21 patients without chronic histological lesion were included in the study. The mean age was 37.3±18.5 years, and the causes of AKI were ischemic in 1 case (4.8%), infection in 7 (23.3%), drug in 2 (9.5%), rhabdomyolysis in 4 (19.0%) and the others in 7 (23.3%). Their peak creatinine level was 8.16±5.54 mg/dL and 10 patients (46.7%) had received renal replacement therapy (RRT) temporarily. However, most of patients (81%) had functional recovery with creatinine level below 1.3 mg/dL.

Conclusions: This is a first human study which demonstrated that human renal Klotho expression was decreased significantly according to the severity of AKI regardless of etiology, and their low expression was associated with poor short-term outcome.

FR-PO020

Urinary NGAL (Neutrophil Gelatinase-Associated Lipocalin) Excretion at Birth Is Predictive of Susceptibility to Acute Kidney Injury (AKI) in Very Low Birth Weight Infants

Lucia Peruzzi,1 Federica Chiarel,2 Roberta Camilla,1 Giuliana Guidi,1 Claudio Martano,1 Francesco Bertoni,1 Rosanna Coppo,1 Nephrology, Dialysis Transplantation, Regina Margherita Hospital, Italy,1 Neonatology, Univ of Turin.

Background: Preterm infants are susceptible to acute kidney injury (AKI), closure of patent ductus arteriosus (PDA) with prostaglandin inhibitors is a risk factor. Novel AKI biomarkers have not been assessed in their predictive value in very preterm infants.

We evaluated in very low birth weight (VLBW) infants the urinary excretion of NGAL as early AKI biomarker during treatment with ibuprofen for PDA. An association between NGAL excretion at birth and the development of AKI was observed (p=0.005, Mann-Whitney U test). We evaluated in very low birth weight (VLBW) infants the urinary excretion of NGAL as early AKI biomarker during treatment with ibuprofen for PDA.

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

Underline represents presenting author/disclosure.

369A
curve assessing the NGAL plasmatic value accuracy for the need of renal replacement treatment showed an AUC of 0.80 (CI 95% 0.57-0.87, p=0.03) and for the accuracy of death during AKI an AUC of 0.89 (CI 95% 0.54-0.96, p=0.01).

Conclusions: Plasmatic NGAL could be useful to distinguish AKI patients who are at high risk for renal replacement therapy or will die during the event, and also to identify those patients who will recover renal function.

FR-PO023

Urinary Stability Studies for Novel Biomarkers of Acute Kidney Injury

Chirag R. Parikh,1 Isabel Butrymowicz,2 Angela Yu,1 Vernon M. Chinchilli,1 Meyeon Park,2 Chi-juan Hsu,2 William Brian Reeves,3 Prasad Devarajan,3 Paul L. Kimmel,3 Edward D. Stiew,3 Kathleen D. Lui,3 Yale School of Medicine; 4Penn State College of Medicine; 5Univ of California: San Francisco; 6Vanderbilt Univ Medical Center; 7NIDDK/NIH; 8Cincinnati’s Children’s Hospital Medical Center; For the ASSESS-AKI Study.

Background: The effect of variation in storage conditions on biomarker assays may affect accuracy and reliability of measurements. We examined how variations in short-term storage/processing affect measurement of urine Neutrophil Gelatinase-Associated Lipocalin (NGAL), Interleukin-18 (IL-18), Kidney Injury Marker-1 (KIM-1), Liver Fatty Acid Binding Protein (L-FABP) and Cystatin C in ASSESS-AKI, a multi-center study of hospitalized patients with and without AKI.

Methods: The impact of 3 processing conditions were tested: a) centrifugation and storage at +4°C for 48h before freezing at -80°C, b) centrifugation and storage at +25°C for 48h and the reference standard (0.81 (95% CI 0.66,0.96)).

Results: There was excellent CCC (>0.9) for all biomarkers for all processes, except IL-18 at +25°C. Good agreement was observed for IL-18 between samples stored at +25°C for 48h and the reference standard (0.81 (95% CI 0.66,0.96)).

Conclusions: All candidate markers tested showed high stability with short-term storage at +4°C or without centrifugation prior to freezing. For optimal reliability, urine for IL-18 measurement should not be stored at +25°C before long-term storage.

Funding: NIDDK Support, Other NIH Support - National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health

FR-PO024

No Increase in Kidney Injury Molecule-1 and Neutrophil Gelatinase-Associated Lipocalin Excretion Following Intravenous Contrast Enhanced-CT

Judith Kooiman,1 Wilko Van der Kooij,1 Cees van Kooten,1 Ton J. Rabelink.1 Leiden Univ Medical Center; 2Bronovo Hospital; 3St. Lucas Andreas Hospital; 4V. Huisman,1 Sandra W. Van der Kooij,1 Cees van Kooten,1 Yvon J. Koon,1 Angela Yu,1 Vernon M. Chinchilli,5 L. Kimmel,6 Edward D. Siew,4 Kathleen D. Liu.3

Background: Neutrophil gelatinase-associated lipocalin (NGAL) in the 5th quintile. We determined the role of biomarkers in causing AKI through indirect pathways.

Methods: The impact of 3 processing conditions were tested: a) centrifugation and storage at +4°C for 48h before freezing at -80°C, b) centrifugation and storage at +25°C for 48h before freezing, and c) uncentrifuged samples immediately frozen. Biomarker values were log-transformed, and agreement with a reference standard of immediate centrifugation, aliquoting, and storage at -80°C was compared using concordance correlation coefficients (CCC).

Results: There was excellent CCC (>0.9) for all biomarkers for all processes, except IL-18 at +25°C. Good agreement was observed for IL-18 between samples stored at +25°C for 48h and the reference standard (0.81 (95% CI 0.66,0.96)).

Conclusions: All candidate markers tested showed high stability with short-term storage at +4°C or without centrifugation prior to freezing. For optimal reliability, urine for IL-18 measurement should not be stored at +25°C before long-term storage.

Funding: NIDDK Support, Other NIH Support - National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health

FR-PO025

Blood Transfusions Associate with New Biomarkers of Kidney Injury in Cardiac Surgery


Background: Blood transfusion is common in cardiac surgery and is associated with clinically acute kidney injury (AKI). We examined the effect of blood transfusion on biomarkers of kidney injury and serum creatinine in a clinical AKI in a large multicenter (TRIBE-AKI) cohort undergoing cardiac surgery.

Methods: 2120 adults underwent cardiac surgery and were divided into three groups based on the receipt of intraproactively packed red blood cell units: no blood (n=894), ≤ 2 PRBC (n=206) and > 2 PRBC (n=110). AKI was defined as: i) Doubling of serum creatinine from the baseline; ii) first post-operative urinary interluekin (IL)-18 and urinary neutrophil gelatinase-associated lipocalin (NGAL) in the 5th quintile. We determined the relative risk for AKI outcome according to PRBC group after adjusting for pre-operative and surgical variables. Using the Sobel test for mediation analysis, we also evaluated the role of biomarkers in causing AKI through indirect pathways.

Results: Urinary IL-18 and NGAL were higher in those who received >2 PRBC.

Funding: None

FR-PO026

Incidence, Risk Predictive Factors, and Clinical Outcomes of Acute Kidney Injury after Gastric Surgery for Gastric Cancer

Chang Seong Kim, Ha Soo Wan Kim.

Background: The incidence of AKI after Gastric Surgery for Gastric Cancer was high, ranging from 14 to 40%. We aimed to determine the risk factors for AKI and its clinical outcomes by a multicenter study.

Methods: A multicenter study was conducted and the incidence and risk factors for AKI were determined. The patients included in the study were those who underwent gastric surgery for gastric cancer between January 2006 and December 2011. The incidence of AKI was defined as an increase of serum creatinine, change as per the Kidney Disease: Improving Global Outcomes guideline.

Results: Of the 4718 patients, 679 (14.4%) developed AKI. Length of hospital stay and intensive care unit admission rates, and in-hospital mortality rate (3.5% versus 0.2%) were higher in patients with AKI than in those without. AKI was also associated with requirement of renal replacement therapy. Multivariate analysis revealed that male gender [odds ratio (OR) 1.75, 95% confidence interval (CI) 1.37-2.23], hypertension (OR 1.27, 95% CI 1.09-1.49), chronic obstructive pulmonary disease (OR 1.64 95% CI 1.15-2.35), and serum creatinine (< 2 mg/dl) were independent predictors for AKI after gastric surgery. Postoperative AKI and vasopressor utilized a high risk of 3-month mortality after multiple adjustments.

Conclusions: AKI was common after gastric surgery for gastric cancer and associated with adverse outcomes. We identified several factors associated with postoperative AKI; recognition of these predictors may help reduce the incidence of AKI after gastric surgery. Postoperative AKI and vasopressor utilization indicated a high risk of 3-month mortality after multiple adjustments.

Funding: None
FR-PO027

Urine Angiotensinogen to Creatinine Ratio, a Marker of Intravascular Volume Depletion in Patients with Acute Kidney Injury


Background: Intravascular volume depletion is a major risk factor for the development of acute kidney injury (AKI); its prompt identification may prevent the development of AKI. Urinary angiotensinogen/creatinine ratio (uANCR) has been associated with worsening AKI. We hypothesized that uANCR correlates with intravascular volume status.

Methods: 39 adult subjects were recruited in the emergency department. Volume status was determined by the examining physician’s clinical impression. Patients were divided into two groups: intravascularly depleted (n=13) and non-depleted (n=26). The study is ongoing with a goal recruitment of 150 patients and a 1-year follow up chart review. Urinary angiotensinogen was measured by ELISA and corrected for urine creatinine in ng/mg.

Results: There was no difference in frequency between the intravascularly depleted and non-depleted groups by age, gender, use of Renin-Angiotensin System (RAS) blockade or AKI at the time of urine collection. 8 patients had AKI, 18 patients did not have AKI and 13 patients could not be assessed because they did not have a urine creatinine measurement. In the entire group, patients with volume depletion had a significantly higher uANCR of 4.3±11.65ng/mg (median interquartile range) compared to 1.57±2.55ng/mg for the non-depleted patients (p=0.003). uANCR accurately identified volume depleted patients, with an area under the receiver operating characteristic curve (AUC) of 0.793 (p=0.003) for volume depletion. In the subgroup analysis, by AKI status, AUC was 1.0 (p=0.046) for the patients with AKI at presentation compared to an AUC 0.583 for the patients without AKI (p=0.57).

Conclusions: Intravascular volume depletion is associated with a higher uANCR despite similar incidence of AKI at presentation and use of RAS blockade. The subgroup analysis suggests that the differences are driven entirely by patients with AKI. Larger numbers of patients will be required to determine if uANCR can be used clinically to assess volume status among patients with AKI.

Funding: NIDDK Support

FR-PO028

Serum Cystatin C for Defining Acute Kidney Injury in Children Undergoing Cardiac Surgery

Michael Zappitelli, Jason Henry Greenberg, Steven G. Coca, Catherine D. Krawczeski, Simon Li, Heather Thiessen Philbrook, Gang Han, Michael R. Bennett, Prasad Devarajan, Chirag P. Parikh, McGill U.; Yale U.; U. Cincinnati; Maria Fareri Child. Hosp.; U. Western Ontario; Yale U., Translational Research Investigating Biomarkers and Endpoints for AKI Consortium.

Background: In theory, acute serum CysC change can be used to define acute kidney injury (AKI). If CysC, with its fewer limitations, defines AKI more accurately than serum creatinine (SCr), then AKI biomarker associations will be stronger with CysC vs. SCr-AKI definition.

Methods: Three-center prospective study of children (1-mth-18 yrs) post-cardiac surgery. We measured pre and postop SCr, CysC and urine biomarkers (Fig). We defined AKI based on KDIGO, using SCr- and CysC-AKI. We compared biomarker prediction of SCr and CysC-AKI (regression, diagnostic characteristics) and SCr vs. CysC-AKI outcome associations.

Results: 287 children were included. There was poor agreement for SCr- and CysC-AKI Stage50 (κ=0.38); good agreement for St2 AKI (κ=0.78). SCr- and CysC-AKI predicted longer hospital stay (SCr-AKI:7 vs. 4 d, CysC-AKI:7 vs. 5 d, adjusted [adj] p<0.001) and longer ventilation (SCr- and CysC-AKI:2 vs. 1 d, adj p<0.01). In general, 5th quintile (relative to 1st) 0-6hr postop biomarker concentrations predicted St1 or worse CysC-AKI similarly or better than SCr-AKI (Fig, left, regression OR’s); however, prediction was better for St2 or worse CysC-AKI (Fig, right). Except for NGAL, 0-6hr postop biomarker AUCs were higher to predict St1 or worse CysC-AKI (Fig, left); conversely, AUCs were higher to predict St2 or worse SCr-AKI (Fig, right).

Conclusions: AKI biomarkers predicted mild CysC-AKI better than mild SCr-AKI. For more severe AKI prediction, associations were stronger using SCr-AKI. Implications are relevant for future studies using CysC for AKI definition.

Funding: NIDDK Support

FR-PO029

Diagnosis of Acute Pyelonephritis in Renal Allograft: A Possible Role for MicroRNAs

Anjali A. Satoskar,1 Steve Oghumu,1 Uday S. Nori,2 Sergey V. Brodsky,1 Ronald Pelletier,1 Tibor Nadasdy.1 Pathology, Ohio State Univ Wexner Medical Center, Columbus, OH; Internal Medicine, Ohio State Univ Wexner Medical Center, Columbus, OH; Surgery, Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: Acute pyelonephritis (APN) versus acute rejection (AR) is a frequently encountered diagnostic and therapeutic dilemma in clinical transplantation. Biopsy and urine cultures are important diagnostic tools, but they may not always correlate. Variable culture results, overlapping histologic features with AR, persistent graft dysfunction despite antibiotics are frequently encountered. We explored the utility of intragraft microRNA profiles to distinguish between allograft APN and AR.

Methods: Between 2003 and 2011, we identified 49 patients with features of APN on biopsy, performed within the first two years post-transplant. MicroRNA profiling was performed on 20 biopsies (normal kidney, n=4; unequivocal AR, n=5; features of APN, n=11).

Results: Only 32% (16/49) of the patients had concomitant positive urine cultures at biopsy and in 8/16 patients colony count was less than 10^4 CFU/ml. In 14/49 patients, positive urine culture did not coincide with the biopsy and in 19/49 patients, cultures were negative. On microRNA profiling, good clustering was seen among the normal kidneys and among AR biopsies. Among the eleven biopsies with features of APN, four biopsies showed good clustering and a pattern distinct from AR (these four patients recovered graft function with antibiotics); 7/11 biopsies with features of APN showed heterogeneity in microRNA profiles. Three of these seven patients recovered only after steroid treatment, three lost their grafts within one month of the biopsy despite antibiotics and one patient expired. We identified a panel of 21 microRNAs showing significant difference in expression between AR and APN. MR-99b, miR-23b and miRs from let-7, miR-30 family, show promise as markers to distinguish APN from AR.

Conclusions: Allograft pyelonephritis can be a diagnostic and therapeutic challenge. In addition to histology and cultures, differential intragraft microRNA expression may prove helpful to distinguish APN from AR in renal allografts.

Funding: Clinical Revenue Support

FR-PO030

Low VEGF/sFlt Ratio on Admission May Portend the Development of AKI in Critically Ill Patients with Sepsis

Arghya Majumdar, Aditi Jain. Nephrology, AMRI Hospitals, Kolkata, India.

Background: Microvascular alterations in the form of endothelial dysfunction and capillary leak play a key role in sepsis induced AKI.

Methods: To see whether VEGF/sFlt ratio on admission has a correlation with the development of AKI, in critically ill patients with sepsis. Methodology: Prospective observational study, conducted in a multi-specialty ICU, in a tertiary care hospital (AMRI), in Kolkata, India, for 1 year. Included: Adult patients with features of SIRS/sepsis admitted to ICU. Excluded: Patients<18 yrs old, brought in from other health facilities or transferred from other hospitals, pregnant or menstruating women, patients with neoplasm, known cases of CKD and macroalbuminuria. We recorded the time of admission, demographics, symptoms, vital signs, laboratory investigations, antibiotic treatment and outcome. Blood samples were collected for VEGF and sFlt levels were measured from blood and microalbuminuria from urine samples. Clinical data was collated.

Results: An increase of microalbuminuria was noted in the first 24 hours, in the patients who went on to develop AKI, shock (requiring vasopressors) and organ dysfunction, more so in patients with sepsis, despite the fact that both the sepsis and SIRS group had similar APACHE IV and APS scores. The ratio of VEGF/sFlt had a significant correlation with AKI. In patients who developed AKI, VEGF/sFlt at (A) and 24 hours (B), after admission were lower than those who did not.

Funding: Clinical Revenue Support
Conclusions: Endothelial dysfunction and capillary leak plays a pivotal role in pathogenesis of septic AKI. The ratio VEGF/Fli ratio admission was inversely proportional to development of AKI. VEGF plays a key angio-protective role. Low VEGF levels may lead to endothelial cell apoptosis, capillary leak and AKI. Conclusion: Low VEGF/Fli ratio may identify the septic patients at risk of developing AKI, on admission to ICU.

FR-PO031
Performance of Urinary Kidney Injury Molecule-1 (KIM-1) in Acute Kidney Injury (AKI): A Systematic Review Paweena Susantitaphong,1,2 Fouad Chehib,1 Bertrand L. Jaber.1 Medicine, St. Elizabeth’s Medical Center, Boston, MA; 3Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: Urinary KIM-1 is a proximal tubular cell injury marker that has been proposed as a biomarker for early detection of AKI. We conducted a systematic review of diagnostic studies that examined the performance of urinary KIM-1 in AKI.

Methods: We searched MEDLINE (through December 2012), Scopus, Google Scholar, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov for human studies investigating the diagnostic and prognostic performance characteristics of urinary KIM-1 for predicting development of AKI, dialysis requirement, and mortality. We performed bivariate-model and random-effects model meta-analyses.

Results: Of the 41 cohort studies and 8 case-control studies, only 9 prospective cohort studies could be meta-analyzed (2,647 patients). For the diagnosis of AKI, the estimated sensitivity of urinary KIM-1 was 64.7% (95% CI 50.9, 76.5%) and the specificity 81.6% (95% CI 78.0, 86.1%), with a diagnostic odds ratio DOR of 1.83 (95%CI, 1.04, 3.25; P=0.04). For prediction of dialysis requirement (2 studies, 545 patients), the estimated sensitivity of urinary KIM-1 was 42.6% (95% CI 25.7, 61.5%), and the specificity 91.0% (95% CI 49.2, 99.1%). For prediction of mortality (2 studies, 577 patients), the estimated sensitivity of urinary KIM-1 was 71.5% (95% CI 64.8, 98.9%), and the specificity 77.9% (95% CI 62.0, 88.4%).

Conclusions: Although KIM-1 is a promising urinary biomarker in AKI, its potential role needs to be examined in large cohort studies and across a broad range of clinical settings.

FR-PO032
Kidney Injury Molecule-1 and Monocyte Chemotactic Protein-1 as Sensitive Biomarkers for Detecting Cisplatin-Induced Nephropathy in Patients with Lung Cancer Haruka Shinko,1 Yasuaki Ikemi,2 Masami Tadahara,3 Kazuo Matsubara,1 Yasuhiro Fujimoto,1 Yoshinori Kaido,2 Shinji Uemoto,2 Motoko Yanagita,3 Takaharu Ichimura,4 Joseph V. Bonventre,2 Satohiro Masuda.1, 2Dept of Clinical Pharmacology and Therapeutics, Kyoto Univ Hospital, Kyoto, Japan; 3Dept of Pharmacy, Kyoto Univ Hospital, Kyoto, Japan; 4Dept of Respiratory Medicine, Kyoto Univ Hospital, Kyoto, Japan; 3Renal Div, Brigham and Women’s Hospital, Boston, MA; 4Renal Div, Brigham and Women’s Hospital, Boston, MA.

Background: Urinary KIM-1 is a proximal tubular cell injury marker that has been proposed as a biomarker for early detection of AKI. We examined whether the recently discovered urinary biomarkers for AKI can detect cisplatin-induced nephropathy in patients with lung cancer.

Methods: A total of 50 patients were enrolled in this study after providing written informed consent. Patients diagnosed with AKI lacking urine samples at day 3 after treatment were excluded. The urine samples were collected the day before cisplatin (80 mg/sqm) administration and at days 3, 7, and 14. The diagnoses of AKI were based on our local guidelines for AKI.

Results: A comparison of the urinary biomarker concentrations between the AKI (+) group (n = 30 samples) and AKI (-) group (n = 12 samples), revealed that kidney injury molecule-1 (KIM-1) and monocyte chemotactic protein-1 (MCP-1), but not neutrophil gelatinase-associated lipocalin (NGAL), were significantly higher in AKI (+) than that in AKI (-). Composite area under the receiver operating characteristics curve (AUC-ROC) analysis showed that KIM-1 (AUC = 0.855, p = 0.01) and MCP-1 (AUC = 0.828, p = 0.01), but not NGAL (AUC = 0.552, p = 0.05) had high sensitivity for detecting cisplatin-induced AKI. Moreover, the combination of KIM-1 and MCP-1 was significantly higher than that of either one alone (AUC = 0.871, p = 0.001). The cutoff values of KIM-1 and MCP-1 were calculated as 2.45 and 0.25 ng/mg creatinine, respectively.

Conclusions: Both urinary KIM-1 and MCP-1 provide sensitive and specific detection of cisplatin-induced nephropathy in patients with lung cancer.

Funding: Government Support - Non-U.S.

FR-PO033
Urinary Kidney Injury Molecule-1 (KIM-1) Levels Immediately after Surgery Predict the Development of Tacrolimus-Related Chronic Kidney Disease in Liver Transplantation Recipients Haruka Shinko,1 Ayami Tsuchimoto,1 Venkata Sabbisetti,2 Miwa Usugi,1 Emina Hashimoto,1 Kazuo Matsubara,1 Yasuhiro Fujimoto,1 Toshimi Kaido,2 Shinji Uemoto,2 Motoko Yanagita,3 Takaharu Ichimura,4 Joseph V. Bonventre,2 Satohiro Masuda.1, 2Dept of Clinical Pharmacology and Therapeutics, Kyoto Univ Hospital, Kyoto, Japan; 3Renal Div, Brigham and Women’s Hospital, Boston; 1Dept of Surgery, Kyoto Univ Hospital, Kyoto, Japan; 2Dept of Nephrology, Kyoto Univ Hospital, Kyoto, Japan.

Background: The aim of the present study was to examine whether the urinary KIM-1 levels immediately after surgery associates with the occurrence of tacrolimus-related post-liver transplant chronic kidney disease (CKD).

Methods: Twenty-three patients who received de novo living-donor liver transplantation (LDLT) with tacrolimus as a primary immunosuppressant were enrolled after providing written informed consent. Urine samples were collected at postoperative day (POD) 1, immediately before the first administration of tacrolimus. Development of CKD was defined as a 2.0-fold higher than the preoperative level for 3 consecutive months between PODs 1 and 180 (KDQI CKD guidelines).

Results: Urinary KIM-1 concentrations at POD 1 after LDLT were significantly higher than those of healthy subjects. The levels of urinary KIM-1 at POD 1 in patients who ultimately developed CKD were significantly higher than those who did not develop CKD (P < 0.001 by Student-t test). The median value of urinary KIM-1 at POD 1 of all patients was found to be 2.85 mg/mg creatinine. The risk of post-transplant CKD was greater in patients whose urinary KIM-1 values at POD 1 were higher than that median value in comparison to patients with lower urinary KIM-1 level at POD 1 (P = 0.0325 by Fisher’s exact test). However, the frequency of post-transplant CKD was similar when the patients were categorized by the median value of the urinary neutrophil gelatinase-associated lipocalin levels at POD 1 (29.4 mg/mg creatinine, P = 0.582).

Conclusions: Urinary KIM-1 on POD 1 is a prognostic biomarker for the development of tacrolimus-related CKD after liver transplantation.

Funding: Government Support - Non-U.S.

FR-PO034
Is Kim-1 Is a Valuable Diagnostic Tool for Early Diagnosis of Contrast Induced Nephropathy? Derya Akdeniz,1 Huseyn Tugrul Celik,2 Hakki Yilmaz,1 Fatmanur Kazanci,2 Ayse Mukadder Bilgiç,1 Nuket Babvrek,1 Ali Akcay,1 Internal Medicine, Turgut Ozal Univ Faculty of Medicine, Ankara, Turkey; 2Biochemistry, Turgut Ozal Univ Faculty of Medicine, Ankara, Turkey; 3Nephrology, Turgut Ozal Univ Faculty of Medicine, Ankara, Turkey.

Background: Contrast-induced nephropathy (CIN) is a common complication of diagnostic/therapeutic procedures. Serum creatinine levels are sensitive but often lead to diagnostic delays for acute kidney injury (AKI) and potential misclassification of actual injury status. Kidney injury molecule (Kim-1) is a novel early marker of AKI. The aim of our study was to evaluate Kim-1 levels in patients with CIN. We performed a single center, nested case-control study.

Methods: Four hundred eighty six patients who undergone coronary angiography were included into the study. Thirty patients were diagnosed CIN. The diagnosis of CIN was done according to KDIGO 2012 Acute Kidney Injury Guideline criteria. Urinary Kim-1 was measured by enzyme-linked immunosorbent assay before, 6th and 48th hours post contrast. Serumcreatinine was measured before, 24th and 48th hours post contrast.

Results: We showed that Kim-1 levels were significantly increased in the patients with CIN significantly in 6th hour when compared to baseline (p=0.01; median levels 48 and 101.8 mg/dL).

Conclusions: Although Kim-1 is a promising biomarker for the early detection of CIN, further studies are needed to confirm its diagnostic accuracy.

Funding: Government Support - Non-U.S.
FR-PO035
Correlation of Increase in Urinary β2-Microglobulin and CD133 Staining in Renal Biopsy

Background: After filtration through the glomerular, β2-microglobulin is reabsorbed by renal proximal tubules. Increase in urine β2-microglobulin indicates tubular injury, and measurement in urine sediment is useful to determine the source of kidney injury. CD133 has recently been characterized as a progenitor cell marker in the kidney, and also a marker for injured epithelial cells in proximal and distal nephron tubules. This study was designed to evaluate the correlation of urinary β2-microglobulin and CD133 with tubular injury.

Methods: Between 2009 and 2012, 47 patients with renal biopsies had prior RenalVysion™ analysis. Among these, 30 patients had increase in urinary β2-microglobulin. The remainder 17 had normal urinary β2-microglobulin. Immunohistochemical staining for CD133 (1:50 Miltenyi Biotec Inc.) was performed in corresponding renal biopsy specimens. CD133 staining in both proximal and distal tubules was considered positive. We evaluated the correlation of increase in urinary β2-microglobulin with positive CD133 staining in renal biopsy.

Results: 30 patients with increase in β2-microglobulin in the urine, and 25 of these also had CD133 staining positive proximal and distal tubules. In patients with normal β2-microglobulin in the urine, 11 of 17 patients were negative for CD133 staining. Using positive staining for CD133 as the end point for this analysis, sensitivity was 80.6%, specificity was 68.8%, positive predictive value was 83.3%, and negative predictive value was 64.7%.

Conclusions: Detection of β2-microglobulin in urine is a sensitive test of tubular injury, largely paralleled with CD133 upregulation in injured renal tubules. Due to low specificity, this finding should be utilized in conjunction with the patient’s clinical history, urine cytology findings (including casts, tubular cells, and inflammatory cells), urine and serum chemistry.

FR-PO036
Plasma Cystatin C Should Not Be Used to Diagnose AKI after Cisplatin Chemotherapy

Background: Increased plasma cystatin C (pCysC) has been proposed as an alternative to serum creatinine (sCr) for diagnose AKI. We assessed the utility of plasma cystatin C (pCysC) to diagnose AKI after cisplatin-based chemotherapy.

Methods: Plasma and urinary biomarkers were measured at 8 time-points before and after 2 weeks for chemotherapy in 26 patients without CKD. All patients also received dexamethasone, aprepitant and palonosetron antiemetics.

Results: pCysC increased in all patients between 3 and 7 days after cisplatin. pCysC increased by more than 50% (AKI) in 9 patients (35%) whereas only 2 (8%) showed a 50% increase in sCr (p=0.04). pCysC increased more than 25% in 16 patients (61%) whereas only 3 (12%) had a greater than 25% increase in sCr (p=0.001). The mean difference between the percentage increase in pCysC and sCr was 25.0% (95% CI: 15.8% to 34.3%). Kidney injury molecule (KIM)-1, clusterin, interleukin-18 and neutrophil gelatinase-associated lipocalin (NGAL) increased above baseline (p<0.05). Peak KIM-1 and clusterin correlated with peak rise in sCr (r=0.43, p=0.03; and r=0.40, p=0.04 respectively) suggesting the observed modest increases in sCr represented renal injury. Increases in pCysC did not correlate with increases in any other urinary biomarker (0.80–p>0.88).

Conclusions: After cisplatin chemotherapy, pCysC concentrations increase independently of sCr and kidney injury biomarkers in patients treated with contemporary antineumetics. This suggests significant difference, possibly by corticosteroids, neurokinin-1 receptor antagonists or serotonin antagonists warranting further study.

FR-PO037
Mean Daily Fluid Balance and Outcome in Acute Kidney Injury

Background: Acute Kidney Injury (AKI) in critically ill patients carry high mortality. Fluid overload with oliguria leads to increased need for dialysis support and ventilation. The aim of this study is to evaluate the impact of mean daily fluid balance (MDFB) on outcomes in adult ICU patients with AKI.

Methods: This was a prospective study, from January 2009 to December 2010; included 130 patients. Exclusion criteria: Age > 18 years with AKI admitted to ICU; APACHE II and SAPS II scores were calculated. Diagnosis of AKI was based on RIFLE criteria. MDFB was calculated for each day during ICU stay. Outcome was analyzed as survived or deceased. Statistical analysis was done.

Results: Elderly (61 101.8 respectively). Normal 61 1

β2-Microglobulin

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-contrast</th>
<th>48th hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>61 1</td>
<td>101.8</td>
</tr>
<tr>
<td>Increase</td>
<td>25 5</td>
<td>101.8</td>
</tr>
</tbody>
</table>

β2-Microglobulin levels were also significantly different (p=0.001, median levels were 25, 101.8 respectively).

Conclusions: Because creatinine is a sensitive but a late marker of CKD, MDFB may be used for early diagnosis, early initiation of treatment and reduced risk of morbidity.

FR-PO038
Donor Neutrophil Gelatinase-Associated Lipocalin (NGAL) Concentration Predicts Post-Transplant Allograft Function after Kidney Tx

Background: The donor pool for KTx has plateaued worldwide. Expansion of the pool by including LR-donations and donors who previously were not accepted is the only way to increase numbers. Data on specific parameters to predict success/failure of KTx are limited. It has been suggested that NGAL may serve as an early marker for renal injury, but have not as yet been investigated in kidney donors(KD). Therefore, it was the objective to evaluate NGAL in KD as a predictor of early allograft failure after KTx.

Methods: This study prospectively evaluated NGAL (urine, serum) in healthy volunteers (n=30) to compare results with (1) brain dead organ donors (BDOD) before organ procurement (n=58), (2) living related (LR) KD (n=15), (3) KTx recipients who received an allograft from a BDOD (n=58) and (4) KTx recipients who received an allograft from LR donor (n=15). In addition, the study analyzed allograft function in associated kidneys in correspondent recipients that were classified into 2 groups depending on allograft function after KTx: ischemia (IF) vs delayed graft function (DGF). The primary objective was to evaluate the predictive value of NGAL for post Tx allograft function. Secondary objectives were: (1) To compare NGAL levels in BDOD and CKD stage V patients on HD to healthy volunteers, (2) To evaluate NGAL evolution post (LR)KTx by visit, etc.

Results: Study results demonstrate that urine (and serum) NGAL levels in corresponding KD correlate with post transplant allograft function where higher NGAL levels were predictive for DGF.
Conclusions: In summary, our data indicates that NGAL represents a novel, sensitive and non-invasive urinary (and serum) biomarker predictive for primary graft function after KTx. Even in cases where our classical diagnostic parameters do not allow further differentiation of potential KD (marginal donors), NGAL seems to remain a stable and significant indicator.

FR-PO039
Effect of GFR Impairment on the Accuracy of BNP and NGAL as Markers of Cardiac and Renal Failure in Chronic Kidney Disease Patients
Carlo Donadio. Clinical and Experimental Medicine, Univ of Pisa, Pisa, Italy.

Background: Cardio-renal syndromes are characterized by the impairment of cardiac and renal functions. Plasma and urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL), and plasma B-type natriuretic peptide (BNP) are markers of acute kidney injury and renal functions. Plasma and urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) are used in the diagnosis of acute kidney injury (AKI) and heart failure (HF), respectively.

The aim of this study was to assess, in stable chronic kidney disease (CKD) patients in the different functional stages of CKD, the effect of the reduction of GFR on plasma BNP and on plasma and urinary NGAL concentrations.

Methods: GFR (mL/min/1.73m²), plasma BNP, and plasma and urinary concentrations of NGAL and LMWP were measured in 310 CKD patients, clinically stable, at functional stages from 1 to 5. Serum and urinary low-molecular-weight proteins (LMWP), and urinary tubular enzymes (Enz) were measured for comparison. Plasma BNP, NGAL and LMWP were measured in 31 maintenance hemodialysis (HD) patients.

Results: Plasma NGAL increased with the reduction of GFR in CKD patients from stage 2. In the different CKD stages modest differences were found for BNP values. Urinary NGAL slightly but significantly increased in patients at CKD stages 4&5, similarly to urinary LMWP. In HD patients, plasma NGAL and BNP were markedly increased, and high-flux hemodialysis decreased significantly their plasma concentrations.

Conclusions: Plasma NGAL increases markedly with the reduction in GFR, generating a very high number of false positive diagnosis of AKI in stable CKD patients. GFR impairment and etiology of kidney disease have a lower effect on urinary NGAL and on plasma BNP. In any case, specific reference values of NGAL and BNP should be used in CKD patients, according to their functional stage, when assessing AKI, HF, and cardio-renal syndromes in patients with impaired GFR.

Funding: Government Support - Non-U.S.

FR-PO040
Is Mean Arterial Pressure or Use of Norepinephrine, during Cardiopulmonary Bypass, Associated with Acute Kidney Injury?
Kristian Kandler.1 Mathias Ebsesen Jensen,1 Christian Holdtholl Møller,1 Jens C. Nilsson,2 Daniel Steinbrüchel.1 1Dept of Cardiothoracic Surgery, Rigshospitalet, Copenhagen, Denmark; 2Dept of Cardiothoracic Anesthesia, Rigshospitalet, Copenhagen, Denmark.

Background: Acute kidney injury (AKI) after cardiac surgery is common and associated with increased mortality. We wanted to investigate if the mean arterial pressure (MAP) or use of norepinephrine during cardiopulmonary bypass (CPB) were associated with AKI.

Methods: A retrospective analysis of patients who underwent elective or subacute CABG with or without concomitant procedures during the year 2012 was conducted. Exclusion criteria were baseline creatinine > 2.3 mg/dl (200 μmol/l), previous nephrectomy, selective cerebral perfusion and acute procedures within 24 hours of coronary angiography. AKI was defined, using the AKIN criteria, as a total increase in serum creatinine of ≥ 0.3 mg/dl (27 μmol/l) or > 50% compared to the baseline value, within the first 48 hours postoperative. Average MAP during CPB was gathered and calculated from electronic perfusion charts and entered in a binary logistic regression model together with pre- and intraoperative data.

Results: A total of 623 patients were included in the study of which 80% underwent isolated CABG. Mean age was 68.3 ± 9.7 years and 81% were males. AKI was observed in 177 patients (28.4%). Average MAP was 76 ± 6 mm Hg and 45 ± 6 mm Hg (p=0.003) in the AKI- and no-AKI group respectively. Norepinephrine was used, during ECC, in 19% of the AKI patients and 12% of no-AKI patients (p=0.024). Independent factors increasing the risk of AKI were higher age, body surface area, duration of CPB, Euroscore 2 and type of surgery. Preoperative use of renin-angiotensin aldosterone system inhibitors, hypertension and use of norepinephrine when leaving the operating room were also independently increasing the risk of AKI.

Conclusions: Although norepinephrine was used more frequently and the MAP was higher in the AKI group during ECC, the association was not found to be independent, using binary logistic regression analysis.

Funding: Private Foundation Support

FR-PO041
Diagnostic Value of Cystatin C in Contrast-Induced Nephropathy after Percutaneous Cardiovascular Intervention
Peng Li.1 Wong Ka tong,2 Chan Wai Hun,1 Wong Ka Nam.1 1Internal Medicine, Kiang Wu Hospital, Macau, Macau; 2Nephrology Association of Macau, Macau, Macau; 3Emergency Dept, Centro Hospitalar Conde de Sao Januario, Macau, Macau.

Background: Contrast-induced Acute Kidney Injury (CIAKI) is one of most common complications in the patients undergoing percutaneous cardiovascular intervention (PCI) using contrast media (CM) [1]. Many researchers have illustrated that cystatin C was a more sensitive marker of kidney injury since it was less influenced by sex, race, age, protein intake and muscle mass compared with serum creatinine (SCr) [2] and also found that cystatin C might have a better diagnostic accuracy in CIAKI than SCr [3]. We investigated the variation of cystatin C in the patients undergoing PCI in order to further determine the diagnostic value of cystatin C in CIAKI.

Methods: SCr and cystatin C were measured at baseline before contrast exposure, 4 hours and 48 hours after contrast exposure, respectively. Cystatin C levels were detected by particle-enhanced turbidimetric immunoassay (PETIA). Serum creatinine increased 25% within 48 hours is defined as the criteria for the diagnosis of CIAKI [1]. ROC curve analysis was performed for the 24hr and 48hr serum cystatin C.

Results: Among 196 study patients (61 female, 135 Male, mean age: 70.7±11.3yr), 29 patients developed CIAKIAccording to the creatinine criteria. The prevalence of CIAKI was 14.8%. The area under the ROC curve (AUC) of the variation of cystatin C at 48hr showed a better performance than the variation of cystatin C at 24hr (AUC: 0.783 [95% confidence interval (CI): 0.701–0.865, P=0.000] vs 0.691 (95% confidence interval (CI): 0.548–0.774, P=0.006). In the ROC curve of cystatin C at 48hr, the 10% elevation of cystatin C yielded 48.3% diagnostic sensitivity, 83.2% specificity and 90.3% negative predictive value. 25% elevation of cystatin C yielded 27.6% diagnostic sensitivity, 96.4% specificity and 88.5% negative predictive value respectively.

Conclusions: The variation of cystatin C at 48hr presents a better diagnostic value in CIAKI than that of cystatin C at 24hr. Meanwhile, 25% elevation of serum cystatin C at 48hr seems to acquire an excellent specificity for the diagnosis of CIAKI.

Funding: Government Support - Non-U.S.

FR-PO042
Clinical Adjudication Confirms TIMP2*IGFBP7 Results for Acute Kidney Injury
Mitchell H. Rosner.1 Kathleen D. Liu,2 Anitha Vijayan,3 John A. Kellum.4 1Nephrology, Univ of Virginia, Charlottesville, VA; 2Nephrology and Critical Care, Univ of California San Francisco, San Francisco, CA; 3Renal Div, Washington Univ, St. Louis, MO; 4Critical Care Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: We showed that the combination of two biomarkers (TIMP2*IGFBP7) was predictive of AKI as defined by KDIGO stages 2 and 3 (Kshamsi et al. Clinical Research 2013, 17:R25). However, AKI is a clinical diagnosis that does not solely rely on consensus definitions. To further assess the performance of TIMP2*IGFBP7, we assembled a committee of expert nephrologists to adjudicate moderate and severe AKI events.

Methods: Adjudication was done in a cohort of 408 subjects using clinical judgement and consensus definitions. In cases of discordance, the final adjudication was determined by the majority (2 out of 3).

Results: The committee adjudicated 337 (83%) subjects as No AKI and 71 (17%) subjects as AKI. Concordance among adjudicators was 94% (97% for No AKI subjects and 79% for AKI subjects). The KDIGO 2-3 rate (18%) was similar to adjudicated AKI rate, and the agreement between KDIGO staging and adjudication was 97% (98% for No AKI and 92% for AKI subjects). Of the 13 subjects for whom the adjudication and KDIGO staging differed, concordance among the adjudicators was 38% compared to 96% for those subjects for whom the adjudication and KDIGO staging agreed. Adjudication (blinded to biomarker values) agreed more with TIMP2*IGFBP7 levels than did KDIGO staging. The mean TIMP2*IGFBP7 value was significantly (p=0.01) higher for the 6 patients who were adjudicated as AKI but did not reach KDIGO 2-3 (2.78x10^5 ng/mL) compared to the 7 patients who were adjudicated as No AKI but reached KDIGO 2-3 (0.52x10^5 ng/mL). The TIMP2*IGFBP7 area under the receiver operating characteristic curve was 0.82 for detection of AKI as adjudicated by the committee.

Conclusions: Clinical adjudication showed differences compared to non-adjudicated KDIGO staging. This result has important implications for the evaluation of biomarkers and stresses the importance of independent adjudication in biomarker performance trials.

Funding: Pharmaceutical Company Support - Aastute Medical

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
FR-PO043

Urinary Semaphorin 3A Predicts the Progression of Acute Kidney Injury in an Adult Mixed Intensive Care Unit

Kant Doo, Eisie Noiri, Naoki Yahagi, Calpurnia Jayakumar, Ganesan Ramesh, The Univ of Tokyo, Georgia Health Sciences Univ.

Background: Predicting the development of acute kidney injury (AKI) in critical care setting is challenging. Although several biomarkers showed moderately good performance for detecting established AKI even in heterogeneous disease oriented population, identification of new biomarkers that predict accurately the development of AKI is urgently required.

Methods: A single center prospective observational study that was undertaken to evaluate for the first time the reliability of newly identified biomarker semaphorin 3A for AKI diagnosis in heterogeneous intensive care unit populations. Three hundred thirty-nine adult critically ill patients were recruited and urine samples were obtained at ICU admission.

Results: One hundred thirty-one patients (39%) were diagnosed as AKI by the RIFLE criteria; 66 patients were diagnosed as AKI not at ICU admission but eventually within one week after (later-onset AKI). Eighty four AKI patients showed worsening the severity during one week observation (AKI progression). In addition to five urinary biomarkers of L-type fatty acid-binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), IL-18, albumin, and N-acetyl-L-type fatty acid-binding protein (L-FABP), urinary semaphorin 3A was measured at ICU admission. Although other five biomarkers showed higher AUC-ROC values in detecting established AKI compared with detecting later-onset AKI or progression of AKI, semaphorin 3A was able to detect late-onset AKI and AKI progression better than established AKI (AUC-ROC for established AKI: 0.64, later-onset AKI: 0.71, AKI progression: 0.71). Finally, sepsis did not have any impact on semaphorin 3A, while other urinary biomarkers were increased with sepsis.

Conclusions: A new AKI biomarker semaphorin 3A has a distinct predictive use for AKI progression from other AKI biomarkers.

Funding: Government Support - Non-U.S.

FR-PO044

Identification of Superoxide Dismutase [Cu-Zn] as a Prognostic AKI Biomarker

Joseph Alger, Nithin Karakala, Benjamin Neely, Michael G. Janech, James A. Tumlin, Andrew Shaw, John M. Arthur, Medical Univ of South Carolina; Univ of Tennessee College of Medicine in Chattanooga; George Washington Univ; Duke Univ; Durham VA Medical Center; Ralph H Johnson VA Medical Center.

Background: Prognostic biomarkers could be valuable tools for risk assessment during the early phases of AKI. We identified candidate prognostic biomarkers using the combined results of discovery phase proteomics studies (3 human, 1 mouse, 1 rat).

Methods: Thirteen urinary proteins that appeared predictive of AKI across 5 proteomic studies were the development and severity of AKI, determined by AKIN criteria. 2) Rat model of AKI through unilateral nephrectomy (U-NPX), with measurement of sFGF-23 and biochemical parameters at baseline, 3, 7, and 14 days after intervention, with a sham surgery control group.

Results: Prospective comparison of patients admitted to the ICU of our hospital with severe sepsis or septic shock. sFGF-23 was measured at admission, 24 and 48 hours after hospitalization, plus clinical and biochemical parameters. Primary outcomes evaluated were the development and severity of AKI, defined by AKIN criteria. 2) Rat model of AKI through unilateral nephrectomy (U-NPX), with measurement of sFGF-23 and biochemical parameters at baseline, 3, 7, and 14 days after intervention, with a sham surgery control group.

Conclusions: 1) Prospective expansion of patients admitted to the ICU of our hospital with severe sepsis or septic shock. sFGF-23 was measured at admission, 24 and 48 hours after hospitalization, plus clinical and biochemical parameters. Primary outcomes evaluated were the development and severity of AKI, defined by AKIN criteria. 2) Rat model of AKI through unilateral nephrectomy (U-NPX), with measurement of sFGF-23 and biochemical parameters at baseline, 3, 7, and 14 days after intervention, with a sham surgery control group.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO045

Fibroblast Growth Factor 23 Is A Potenital Biomarker of Development of Acute Kidney Injury in Rats and Patients: Preliminary Results

Luis F. Michele, Luis Toro, Centro Estudios Moleculares de la Celula, Facultad de Medicina Universidad de Chile, Santiago, Chile; Critical Care Unit, Hospital Clinico Universidad de Chile, Santiago, Chile.

Background: Acute kidney injury (AKI) is a condition of high incidence in Critical Care Units (CCU). Retrospective studies have shown association between serum Fibroblast Growth Factor 23 (sFGF-23) and AKI in hospitalized patients. The objective of the study is to evaluate in prospective clinical studies and murine models whether sFGF-23 is a predictor of AKI.

Methods: 1) Prospective cohort of patients admitted to the ICU of our hospital with severe sepsis or septic shock. sFGF-23 was measured at admission, 24 and 48 hours after hospitalization, plus clinical and biochemical parameters. Primary outcomes evaluated were the development and severity of AKI, defined by AKIN criteria. 2) Rat model of AKI through unilateral nephrectomy (U-NPX), with measurement of sFGF-23 and biochemical parameters at baseline, 3, 7, and 14 days after intervention, with a sham surgery control group.

Results: Preliminary expansion of patients admitted to the ICU of our hospital with severe sepsis or septic shock. sFGF-23 was measured at admission, 24 and 48 hours after hospitalization, plus clinical and biochemical parameters. Primary outcomes evaluated were the development and severity of AKI, defined by AKIN criteria. 2) Rat model of AKI through unilateral nephrectomy (U-NPX), with measurement of sFGF-23 and biochemical parameters at baseline, 3, 7, and 14 days after intervention, with a sham surgery control group.

Conclusions: 1) Prospective expansion of patients admitted to the ICU of our hospital with severe sepsis or septic shock. sFGF-23 was measured at admission, 24 and 48 hours after hospitalization, plus clinical and biochemical parameters. Primary outcomes evaluated were the development and severity of AKI, defined by AKIN criteria. 2) Rat model of AKI through unilateral nephrectomy (U-NPX), with measurement of sFGF-23 and biochemical parameters at baseline, 3, 7, and 14 days after intervention, with a sham surgery control group.

Funding: Pharmaceutical Company Support - FONDICYIT 1130550,1090223, IMI P09016F, Government Support - Non-U.S.

FR-PO046

Utility of Fractional Excretion of Sodium (FeNa) Compared with the Old-Fashion Clinical History and Urinalysis in the Evaluation of Acute Kidney Injury


Background: Traditionally, it is taught that FeNa can be used in the evaluation of non-oliguric acute kidney injury (AKI) to differentiate the prerenal state from acute tubular necrosis. Accordingly, primary care physicians (PCPs) oftentimes solely focus on obtaining FeNa prior to consulting nephrology for AKI, but not necessarily a complete clinical history or urinalysis (UA) that could be of great diagnostic value. We compared the diagnostic value of FeNa versus those obtained from routine clinical history and UA in the AKI setting.

Methods: This is a prospective study. All consults involving AKI evaluated by the lead author from July 2012-June 2013 were included. Data collected: Age, gender, ethnic background, presenting laboratory findings including Na, K, Cl, HCO3, blood urea nitrogen, creatinine, FeNa, UA, clinical history, and final diagnosis of AKI, recorded as prerenal or "other." FeNa <15%, presence of hyaline casts, urine specific gravity >1.015, or BUN to creatinine ratio (BUN:Cr) = < 20, were considered to be consistent with prerenal state. Sensitivity and specificity of using FeNa, clinical history, UA, either positive clinical history or UA, and BUN:Cr for identifying a prerenal cause of AKI were calculated.

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

Underline represents presenting author/disclosure.
FR-PO047
Assessing Fractional Excretion of Urea for Early Diagnosis of Cardiac Surgery Associated Acute Kidney Injury

Federico Varela, Angel Medina Ayala, Gustavo Cristian Greloni, Matilde Josefa Navarro, Guillermo Javier Rosa diez.
Nephrology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background: AKI is a common complication after Cardiac Surgery (CS). Fractionation of Urea (EFU) has been cited as a precise method to discriminate between early prerenal and established AKI. The aim of our study is evaluate sensitivity and specificity of the EFU, in the early diagnosis of AKI in patients undergoing CS.

Methods: Prospective study of adult patients undergoing CS. AKI was defined by AKIN criteria. CKD patients were excluded. EFU sensitivity and specificity on predictive AKI diagnosis were tested on 1, 6 and 24 hours after CS. Same evaluation was conducted for urinary Ngal. Comparison of AUC (ROC curve) for both methods was made.

Results: Sixty patients, 68 ± 11 years, 25% female, AKI prevalence 26.23%, mortality 3.28%, Staging AKI 56% was AKIN I, 25% was AKIN II and was 19% AKIN III. Thirty-five of patients received diuretics during the first 48 hours. Patients with AKI had significantly lower EFU compared with normal kidney function group (13.3 ± 2.7 vs. 31.6 ± 3.4%, p<0.05) only at 6 hours after CS. N-Gal values also showed statistical difference between both groups at same period.

Conclusions: The results of this study support that EFU measured early after CS, predicts AKI in these patients.

FR-PO048
Renal Outcomes after Liver Transplantation in Fulminant Hepatitis A with Acute Kidney Injury: Comparison with Hepatorenal Syndrome

Jae-yoon Park,1 Jung Pyo Lee,2 Hyung Jun Oh,3 Dong Ki Kim,1 Chun Soo Lim,2 Yon Su Kim.1 Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; Internal Medicine, Tosei Univ College of Medicine, Seoul, Korea.

Background: Liver transplantation (LT) is the treatment of choice for hepatorenal syndrome (HRS). However, the outcome of LT is not well established in acute hepatitis A accompanied by acute kidney injury (AKI). We investigated the outcomes of LT in patients with AKI associated with acute hepatitis A compared with patients with HRS due to other causes.

Methods: We reviewed 1940 consecutive adult recipients undergoing LT at three liver transplantation centers in Korea between 2005 and 2012. 20 patients with acute hepatitis A and AKI (HAV group) were compared with 76 patients with HRS from other causes (HRS group).

Results: There was no difference in the model for end-stage liver disease (MELD) score between groups. Pretransplant estimated glomerular filtration rate (eGFR) was lower in the HAV group compared with the HRS group (20.6 ± 12.7 vs. 28.2 ± 12.8 mL/min/1.73m², p<0.021). Posttransplant patient and graft survival rates were similar between groups. More patients in the HAV group required posttransplant hemodialysis compared with the HRS group (65.0% vs. 38.2%, p=0.043). However, eGFR had been significantly higher in HAV group since posttransplant month 2 (p<0.05). In addition, the HAV group had superior recovery rate of kidney function (eGFR ≥60mld/min 1.73m²) after adjustment for pretransplant renal function or liver function. No patients required long-term renal replacement therapy in either group.

Conclusions: Pre- and immediate posttransplant kidney function is worse in patients with AKI due to acute fulminant hepatitis A, compared to those with HRS due to any cause. However, posttransplant long-term renal outcomes may be better in the HAV group.

FR-PO049
GFR Distributions among Scheduled Contrast-Enhanced Computed Tomography before and after eGFR Self-Report

Yoshinari Yasuda, Kanako Shibata, Shoichi Maruyama, Seiichi Matsuo.
Nephrology/CKD Initiatives, Nagoya Univ, Nagoa, Japan.

Background: Renal insufficiency is the most important risk factor for contrast induced nephropathy (CIN), however it is difficult to assess renal function only by serum creatinine (sCr). Estimated glomerular filtration rate (eGFR) is globally recommended for evaluation of renal function, and eGFR self-report may affect clinical decision making to prevent CIN. Since Akita University Hospital (NUH) started eGFR self-report in December 2009, we analyzed GFR distributions in out-patients prior to scheduled contrast-enhanced computed tomography (CE) in NUH before and after eGFR self-report.

Methods: Study subjects were 6,106 and 6,308 out-patients who were examined by scheduled CE in NUH in 2008 and 2011. Patients under 18 years of age and emergency CE cases were excluded. Age, gender and sCr before CE (until 4 months before) were collected from medical record and eGFR was calculated by Japanese eGFR equation. Implementation rates of sCr measurements and distributions of age, gender and eGFR categories (G1: 90 and above, G2: 60-90, G3a: 45-59, G3b: 30-44, G4: 15-29 and G5: less than 15 mL/min/1.73m²) were compared before and after eGFR self-report. And implementation rates preventive hydration were analyzed among CKD patients with eGFR below 45 mL/min/1.73m².

Results: Age and gender distributions were not different in 2008 and in 2011. Implementation rates of sCr measurements were 78.5% in 2008 and 78.4% in 2011. Proportion of G3b to G5 patients in 2011 was significantly smaller than that in 2008. Implementation rate of preventive hydration was dramatically increased in 2011 (86.7%, compared to 2008 (31.8%), however hydration regimen was not appropriate in some cases.

Conclusions: Distributions of eGFR categories and implementation rate of preventive hydration among patients examined by scheduled CE were different before and after eGFR self-report in NUH, suggesting its preferable effect to prevent CIN.

Funding: Government Support - Non-U.S.

FR-PO050
SIRS, ALI, and AKI Are Established by Four Hours in Experimental Sepsis and Are Not Improved by Post-sepsis Administration of TNF-α Antibodies
Sarah Faubel, Chris Altmann, Ana Andres-herando, Rhea Bhargava, Kayo Okamura. L of CO.

Background: Acute kidney injury (AKI) and acute lung injury (ALI) are complications of sepsis, and the presence of either increases mortality. AKI is often viewed as a late consequence of sepsis and some studies have suggested that AKI occurs as a result of ALI. Notably, the onset of AKI relative to ALI is unclear as routine measures of kidney function (BUN, creatinine) are insensitive and increase late in the study. We hypothesized that AKI and ALI would occur simultaneously due to a shared pathophysiology (i.e., TNF-α mediated systemic inflammatory response syndrome [SIRS]), but that sensitive markers of kidney function would be required to identify AKI.

Methods: Sepsis was induced in male C3H/HeJ mice with 4 different one time doses of intraperitoneal (IP) endotoxin (LPS) (0.0001, 0.001, 0.01, or 0.25 mg). SIRS was assessed by serum inflammatory cytokines (TNF-α, IL-1β, CXCCL-1, IL-6), ALI was assessed by lung inflammation (lung MPO activity), and AKI was assessed by serum creatinine, BUN, and glomerular filtration rate (GFR) (FTTC-labeled inulin clearance) at 4 hours. 20 μg of sTNF-α antibody (Ab) or vehicle was injected IP 2 hours before or 2 hours after LPS.

Results: Serum cytokines and lung MPO activity increased with all 4 doses of LPS; creatinine did not increase with any dose; BUN increased with 0.01 and 0.25 mg. Remarkably, GFR was reduced with all 4 doses of LPS and was 50% reduced in the 0.01 mg dose, demonstrating that dramatic loss of kidney function can occur in sepsis without a change in BUN or creatinine. Prophylactic TNF-α Ab reduced serum cytokines, lung MPO activity, and BUN; however, post-sepsis administration had no effect.

Conclusions: ALI and AKI occur together after sepsis and TNF-α plays a role in the pathogenesis of both. Although failure of anti-TNF-α therapy in clinical trials has generated doubt regarding the role of TNF-α in the pathophysiology of sepsis and called into the question the value of animal models, our data demonstrate that TNF-α mediated ALI and AKI are established early and not amenable to anti-TNF-α treatment; thus, even after just 2 hours, anti-TNF-α therapy cannot be expected to be successful in patients with sepsis.

Funding: Other NIH Support - NHLBI

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

376A
FR-PO051 Activation of Type 1 Angiotensin II Receptors on T Lymphocytes Limits TNF-α-Mediated Acute Kidney Injury Jianzong Zhang, Muhel B. Patel, Jose Gomez, Matthew A. Sparks, Steven D. Crowley. Duke Univ.

Background: Although blockade of type 1 angiotensin (AT1) receptors is a cornerstone of therapy for patients with chronic kidney disease, the role of the renin-angiotensin system (RAS) in the pathogenesis of acute kidney injury remains unclear. In the present experiments, we examined the actions of AT1 receptors specifically on T lymphocytes during acute kidney injury in the cisplatin (CIS) nephropathy model.

Methods: To this end, we intercrossed mice carrying a floxed gene for the AT1 receptor (Agt(loxP/loxP)) with mice harboring Cre recombinase under the control of the CD4 promoter to remove AT1 receptor-mediated responses from T lymphocytes alone (Cre(Agt(loxP/loxP)-Cre)) or from T lymphocytes and cisplatin-treated kidneys (Cre(Agt(loxP/loxP)-Cre)–CIS). Compared to Cre(Agt(loxP/loxP)-Cre) littermates (WT), the TKOs had a ~90% reduction in AT1 receptor mRNA expression solely in T lymphocytes (p<0.0001). We also generated CD4-Cre/miR-17-5p (T cell GFP) mice in which T cells fluoresce green to trace renal infiltration of T lymphocytes.

Results: When subjected to T cell GFP injection to mice (30 mg/kg), we detected green signals in the kidney out to 72 hrs, confirming the renal infiltration of T lymphocytes during the window of nephrotoxicity. At 72hrs, BUN in CIS-treated WT increased dramatically to 185±20 mg/dL, compared to vehicle-treated WT mice (25±5; p<0.001), but CIS-treated TKOs had 96% higher BUNs than WT mice (244±28; p<0.008). Similarly, CIS-treated TKOs had 50% higher serum creatinine (Scr) (1.85±0.21 vs. 1.24±0.23 mg/dL; p<0.02). Moreover, compared to CIS-treated WT, TKOs had augmented renal mRNA expression for the injury marker NGAL (683±203 vs. 1796±645 au; p=0.006). TNF-α expression and renal tubular apoptosis after ischemic AKI when compared to wild type (S1P1Rf/f) mice to mild (20 min) renal IR injury.

Conclusions: We conclude that the fluorescent signal from the T cell GFP injection only modestly decreased compared to wild-type injured kidneys. Markers of extracellular matrix and inflammation are elevated in higher plasma creatinine (1.2, P=0.001) and acute tubular necrosis (15% of kidney section area) compared to subIRI alone (5%, P<0.001). SLPX+subIRI resulted in increased circulating (P<0.009) and infiltrating neutrophils (P<0.001) and renal mRNA expression of Cxcl1 and Il-6 (P<0.003). SLPX Rag1-1 mice were also more susceptible to IR (P<0.001), suggesting the effect of SLPX is not dependent on T or B-cells. Fluorescently labeled cells were observed 3d after reperfusion and persisted only in the ischemic kidney through 7d, suggesting phagocytic cells originating from the spleen localize to renal tissue following AKI.

Funding: NIDDK Support

FR-PO054 Prior Ultrasound Exposure Improves Survival and Modulates the Early Inflammatory Response to Ischemia-Reperfusion Injury in Mice Joseph C. Giuglietti,1 Liping Huang,2 Alexander L. Klubanov,2 Diane L. Rossin,1,3 Kalyani Kitalari,1 Mark D. Okusa,1 1Div of Nephrology and CIIR; 2Div of Cardiology; 3Dept of Pharmacology, Univ of Virginia, Charlottesville, VA.

Background: Inflammation mediates the tissue injury that occurs during acute kidney injury (AKI). We have shown prior ultrasound (US) exposure reduces AKI and inflammation in mice. How US modulates inflammation is unknown. Therefore, the objective of the current study was to determine if prior US exposure modulates the initial inflammatory response to AKI.

Methods: Male C57BL/6 mice were anesthetized and exposed to US (7MHz, MI = 1.2) using Siemens Acuson Sequoia 512 system with a 15LSw transducer. 24h after US exposure, mice were subjected to bilateral renal ischemia-reperfusion injury (IRI). For survival studies, mice were maintained for 7d after IRI. For acute studies, mice were euthanized and tissue samples were collected after 6h (no reperfusion) and 0.5h after IRI. AKI was assessed by measuring plasma creatinine. Neutrophils were quantified by FACS and renal IL-1β mRNA expression was determined by RT-PCR.

Results: Exposure to US prior to IRI significantly improved 7d survival as compared to IRI alone (mortality of 25% vs 87%, P<0.004). The protective effect of US was observed 0.5h after reperfusion, where mice pretreated with US had a 67% reduction (P=0.02) in plasma creatinine compared to mice receiving IRI alone. IRI resulted in a 3-fold increase in renal neutrophils, a phenomenon prevented with prior US exposure (P=0.05). However, prior US did not influence (P=0.99) circulating neutrophils 0.5h after reperfusion, suggesting that US modulates trafficking of neutrophils into the kidney. US reduced (P<0.05) kidney IL-1β mRNA expression by 50% after ischemia alone (no reperfusion), suggesting prior US exposure modulates the response of the kidney to ischemic damage.

Conclusions: The results demonstrate that prior US exposure decreases the mortality associated with IRI in mice. This could be due to an US-induced reduction in ischemic tissue damage, which in turn reduced neutrophil accumulation following reperfusion. Identifying the mechanism responsible will shed light on new therapeutic targets for AKI.

Funding: NIDDK Support

FR-PO055 Macrophage-Specific Deletion of Transforming Growth Factor-β1 Does Not Prevent Renal Fibrosis after Severe Ischemia-Reperfusion Injury Sarah C. Huen, Gilbert W. Moeckel, Lloyd G. Cantley. Yale Univ School of Medicine, New Haven, CT.

Background: The persistence of macrophages is associated with tubulointerstitial fibrosis and progression of chronic kidney disease. Macrophages are known to be major producers of transforming growth factor-β1 (TGF-β1). TGF-β1 has long been implicated as a central mediator of kidney fibrosis. To determine the fibrogenic role of macrophage-derived TGF-β1, we deleted TGF-β1 in lymphoid cells by establish a LysM-Cre;Tgfb1fl/fl transgenic mouse and induced severe unilateral ischemic renal injury (AKI). We have shown prior ultrasound exposure reduces AKI and inflammation in mice. How US modulates inflammation is unknown. Therefore, the objective of the current study was to determine if prior US exposure modulates the initial inflammatory response to AKI.

Methods: Male C57BL/6 mice were anesthetized and exposed to US (7MHz, MI = 1.2) using Siemens Acuson Sequoia 512 system with a 15LSw transducer. 24h after US exposure, mice were subjected to bilateral renal ischemia-reperfusion injury (IRI). For survival studies, mice were maintained for 7d after IRI. For acute studies, mice were euthanized and tissue samples were collected after 6h (no reperfusion) and 0.5h after IRI. AKI was assessed by measuring plasma creatinine. Neutrophils were quantified by FACS and renal IL-1β mRNA expression was determined by RT-PCR.

Results: Exposure to US prior to IRI significantly improved 7d survival as compared to IRI alone (mortality of 25% vs 87%, P<0.004). The protective effect of US was observed 0.5h after reperfusion, where mice pretreated with US had a 67% reduction (P=0.02) in plasma creatinine compared to mice receiving IRI alone. IRI resulted in a 3-fold increase in renal neutrophils, a phenomenon prevented with prior US exposure (P=0.05). However, prior US did not influence (P=0.99) circulating neutrophils 0.5h after reperfusion, suggesting that US modulates trafficking of neutrophils into the kidney. US reduced (P<0.05) kidney IL-1β mRNA expression by 50% after ischemia alone (no reperfusion), suggesting prior US exposure modulates the response of the kidney to ischemic damage.

Conclusions: The results demonstrate that prior US exposure decreases the mortality associated with IRI in mice. This could be due to an US-induced reduction in ischemic tissue damage, which in turn reduced neutrophil accumulation following reperfusion. Identifying the mechanism responsible will shed light on new therapeutic targets for AKI.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Conclusions: Targeting macrophage-derived Tgf-β1 does not appear to be an effective therapy for attenuating progressive renal fibrosis after ischemic kidney injury.

Funding: NIDDK Support

FR-PO056

RGs4 Inhibits Angiotensin II Signaling and Macrophase Localization during Renal Reperfusion Injury Independent of Vasoactive Tone

Paul Pang, Padmaswan Khamlue, Joseph V. Bonventre, Andrew M. Siedlecki. Medicine, Brigham and Women’s Hospital, Boston, MA.

Background: Vascular inflammation is a major contributor to the severity of acute kidney injury. The anti-inflammatory effect of RGs4 in angiotensin II-induced atherosclerosis is known (PNAS, 105:4277, 2008) but has not been studied in the setting of reperfusion injury in the kidney. We hypothesized that RGs4 expression in vascular smooth muscle cells is protective to the kidney after vascular injury.

Methods: We used RGs4 overexpressing (RGs4) and smooth cell-specific RGs4 deleted mice in a model of acute renovascular kidney injury. RGs4-dependent cell signaling was studied in vascular smooth muscle cell (VSMC) culture.

Results: 18 hours after 10-minute unilateral renal artery clamping we observed: no tubular injury, normalized ET-1 levels, and reduced calponin-1 expression.

At the same timepoint blood flow by dynamic MRI was decreased in post-clamp wild type kidneys vs R40X. WT and R40X tissue- AngII levels were elevated in a sub-vasoconstrictive range in kidneys after 12 and 18hrs; confirmed by isolated perfused-kidney technique. By cytokine screen, AngII stimulated VSMC to secrete macrophase chemotractant, RANTES. RANTES expression increased further when RGs4 expression was suppressed. AngII (AT2) inhibition decreased RANTES expression in RGs4-depleted cells implicating Gα protein activation in an AT2-RG54-dependent pathway. Specificity of RGs4 function in VSMC was confirmed with VSMC-specific RG5α-/- that showed high macrophage density by T2 MR imaging compared to Tg and non-Tg. M0 localized to the above region of blood flow disturbance. Tissue AngII in knockouts was also elevated at 12 and 18 hours but in a non-vasoactive range.

Conclusions: We conclude that RGs4 expression, specific to renal VSMC, inhibits AngII mediated oxidative stress and macrophase recruitment during reperfusion injury.

Funding: NIDDK Support

FR-PO057

Regulatory T Cells Recruited to the Kidney by N,N-Dimethylphosphine Ameliorate Lipopolysaccharide-Induced Acute Kidney Injury

Katarzyna Jaworska, Joanna Ratajczak, Brian K. Stevens, Koeun Lee,1 Sang Heon Suh,1 Chang Seong Kim,1 Joon Seok Choi,1 Eun Hui Bae,1 Seong Kwon Ma,1 Jongun Lee,2 Soo Wan Kim.1 Internal Medicine, Chonnam National Univ Medical School, Kwangju, Korea; 2Physiology, Chonnam National Univ Medical School, Kwangju, Korea.

Background: Regulatory T cells (Tregs) exert immunologic tolerance and prevent inflammatory diseases. The present study was aimed to examine whether Tregs recruited to the kidney by N,N-dimethylphosphine (DMS), a sphingosine kinase inhibitor, prevents lipopolysaccharide (LPS)-induced kidney injury.

Methods: Mice were treated with LPS (20 mg/kg, i.p.) with or without DMS (0.4 mg/kg, i.p.). The degree of apoptosis was assessed by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining. The expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), endothelin-1 (ED-1), and Foxp3 was determined by immunoblotting, respectively. PGE2 levels were measured by gas chromatography/mass spectrometry.

Results: Plasma creatinine level was increased after LPS injection for 12 h compared with controls which was attenuated in treatment with DMS. LPS treatment resulted in the elevation of both bax/bcl-2 ratio and number of TUNEL-positive cells in the kidney, which was counteracted by DMS pretreatment. The expression of COX-2, iNOS, and ED-1 was increased in LPS group, which was counteracted by DMS. LPS pretreatment also ameliorated LPS-induced increase in tissue PGE2 concentration. The mRNA expression of Foxp3 was increased in LPS group, which was counteracted by DMS. Using flow cytometry analysis, we investigated the expression of CD4+CD25+ Tregs in the mice spleen and kidney.

Conclusions: These results suggest PD-L1 and PD-L2 have distinct and additive roles in protection from ischemic kidney injury and adoptively transferred Tregs must interact with both PD-L1 and PD-L2 to offer protection from kidney IRI.

Funding: NIDDK Support

FR-PO058

Effect of Endotoxemia on the Expression of the PGE2 Synthetic System, and of Prostaglandin EP Receptors in the Kidney of the Mouse

Klaus Höckerl, Katharina Mederle, Hayo Castrop, Frank Schveda. Univ of Regensburg, Institute of Physiology, Regensburg, Bavaria, Germany.

Background: Septis is one of the leading causes of acute kidney injury (AKI). The present study was undertaken to characterize the biosynthetic pathway of prostaglandin (PG) E2 and to examine the role of PGE, in the pathogenesis of endotoxemia-related AKI.

Methods: Male C57BL/6 mice, 8-10 wk old, were used. Endotoxemia was induced by the injection of lipopolysaccharide (LPS; 3 mg/kg; i.p.). The mRNA and protein levels were measured by q-RT-PCR and by immunoblotting, respectively. PGE2 proteins were determined by assay kits. Glomerular filtration rate (GFR) was determined by FITC-sinistrin clearance in conscious mice.

Results: LPS caused a time-dependent increase in renal COX-2 expression, whereas COX-1 expression was decreased. The LPS-induced increase in PG synthesis was reversed by the administration of dimethylsphingosine (DMS), a general inhibitor of sphingosine kinases. DMS decreased LPS-induced increase in tissue PGE2 concentration. Inhibition of COX-2 did not alter basal GFR, but augmented the LPS-induced decline in GFR. LPS caused an induction of the mRNA for the prostaglandin EP4 receptor, whereas the abundances of the prostaglandin EP1 and EP3 receptors were decreased. The mRNA expression of the EP2 receptor was not altered in response to LPS. In addition, PGE2, exerted a dual effect on renal vascular tone, inducing vasodilatation at lower concentrations and vasoconstriction at higher concentrations in kidneys of control mice. In kidneys from endotoxemic mice, the vasodilator component was more pronounced, whereas the vasoconstrictor at higher PGE2 concentrations was absent.

Conclusions: Our data provide evidence that an activation of the COX-2 / PGs -1 synthetic pathway is responsible for the increased renal formation of PGE2, in response to LPS. Our data further suggest that the vasodilatory effect of PGE2, is enhanced in response to endotoxemia. Thus, agonism of EP2 and/or EP4 receptors may provide a basis for the treatment of sepsis-induced AKI.

Funding: Government Support - Non-U.S.
FR-PO060


Background: Ischemia-reperfusion injury (IRI) is one of the most common causes of Acute Kidney Injury (AKI). In humans, IRI reflects poor renal perfusion in connection with major cardiopulmonary surgery, such as coronary artery venous bypass grafting, and myocardial infarction. The CCR2 chemokine receptor is believed to regulate recruitment of circulating monocytes to the tubulointerstitial space in response to IRI-induced upregulation of the CCL2 chemokine by injured proximal tubular epithelial cells. We describe here the effects of 2 clinical-stage CCR2 inhibitors (CCR2-I) in a mouse model of renal IRI.

Methods: C57Bl/6J WT mice underwent concurrent surgical clamping of both renal arteries for 45 min. Drug treated mice received single intravenous dosing of 25 mg/kg CCR2-I (CCX140 or CCX872) 1h before reperfusion. Control animals received vehicle. Drug efficacy was measured by both plasma creatinine (sCRE) and BUN levels, histological assessment of tubular damage, and number of renal leukocytes.

Results: CCR2-1 treatment significantly reduced sCRE, tubular damage and inflammatory cell infiltration in wild-type and hCCR2KI mice. sCRE: 1.47 and 2.02 mg/dl, CCX872 and vehicle control, respectively; p<0.05; Tubular Damage (% tubules): 41 and 62, CCX872 and vehicle control, respectively; p<0.0001; Total Leukocytes: 1.538 and 12.830 cells/renal kidney, CCX872 and vehicle control, respectively; p<0.001). Similar results were obtained with CCX140 using transgenic hCCR2KI mice.

Conclusions: Robust protection against AKI in a mouse model of IRI was obtained by prophylactic administration of either of two clinical-stage CCR2 inhibitors, one of which, CCX140, is currently being studied in two Phase-2 trials in subjects with T2D diabetic kidney disease. Thus, CCR2 inhibition may represent a novel therapeutic modality in the treatment of human AKI.

FR-PO061


1Tissue Protection and Repair Unit, Sano R&D, Chilly-Mazarin, France; 2III. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 3Diabetes BU, Sano R&D, Frankfurt 65926, Germany; 4SCP Biologics, Sanofi R&D, Vitry-sur-Seine, France.

Background: We describe a novel SIP, agonist, SIP, AGT, which is distinguished from the class of lymphopoenic SIP, functional antagonists for multiple sclerosis.

Methods: SIP, AGT was evaluated in cellular and in vivo models of AKI.

Results: SIP, AGT does not desensitize SIP, which translates to an absence of sustained lymphopenia, and does not show any significant effect on heart rate and AV conduction. SIP, AGT protected renal tubular epithelial cells from tunicamycin-induced apoptosis, inhibited the increase in VCAM, ICAM and P/E-selectins in TNFa-stimulated endothelial cells, and induced survival pathways (pAkt/pErk). In the setting of renal ischemia-reperfusion in rats, SIP, AGT showed almost complete preservation of renal function and consistently reduced tubular necrosis, diminished renal inflammation, maintained endothelial barrier integrity and limited capillary rarefaction. The preservation of renal function was further confirmed in two separate mouse models of AKI induced by glicycerol or tunicamycin.

Conclusions: SIP, AGT displays endothelial protective effects which is in contrast to SIP, functional antagonists which are endothelial-damaging. The observed endothelial protective effects of SIP, AGT, coupled with its epithelial protective and anti-inflammatory effects, represent a new and exciting approach for AKI treatment.

FR-PO062

Natural IgM Protects against Renal Ischemia Reperfusion Injury by Altering Dendritic Cell Function Peter J. Lobo, Kailo H. Schlegel, Liping Huang, Matthew J. Walters, Bajwa, Mark D. Okusa. Dept of Med/CIIR, Univ of Virginia, Charlottesville, VA.

Background: We have shown in prior studies that natural IgM, especially IgM that binds to autologous leukocytes (IgM-ALA), protects against Renal IRI. These studies explore the mechanisms by which protection is conferred. Damage-associated molecular patterns (DAMPs), released following renal ischemia, activate Dendritic cells (DC), which present these autoantigens (especially glycolipids) to NK and NKT cells, initiating the inflammatory process resulting in magnified injury. As we observed high binding of natural IgM on DCs compared to other leukocyte population, we examined if the protective effect of IgM is mediated at the DC stage.

Methods: To test the effect of IgM on DC activation, cultured C57BL/6 (B6) Bone Marrow Dendritic Cells (BMDC) were activated with LPS after pretreatment with either purified natural polycyonal murine IgM from serum, murine IgM, isoacute murine IgM (lacking binding to mouse cells), or albumin. After 24 to 48 hours incubation, supernatant was taken for cytokine, and the BMDCs examined via flow cytometry. The effect of IgM on DC function was tested by L1 transfer of 5x106 pre-treated BMDC into B6 mice given Renal IRI 24 hours later.

Results: IgM inhibited LPS induced TNFa secretion (from 7,150 pg/ml to 3,750 pg/ml) as well as decreasing the up-regulation of CD40 by approximately 40%. We observed no effect of IgM on BMDC expression of CD80, CD1d, MHC class II or on LPS induced TLR4 downmodulation. IgM+LPS treated DCs conferred significant protection against IRI compared to both control IRI or transfer of LPS treated DCs. Kid damage was evaluated by both plasma creatinine and histology.

Conclusions: These studies indicate that Natural IgM, especially IgM-ALA, can provide an innate regulatory mechanism by its effect on DCs.

Funding: NIDDK Support

FR-PO063


1Nephrology and Medicine, Monash Health and Monash Univ, Melbourne, Victoria, Australia; 2III. Medizinische Klinik, Universitätssklinikum Hamburg-Eppendorf, Hamburg, Germany.

Background: Acute kidney injury (AKI) is a major cause of morbidity and mortality. Clinical and experimental data demonstrate that cytokines and leukocytes promote renal inflammation and injury. We sought to define the role of Interleukin (IL)-17A in cisplatin induced AKI.

Methods: We administered cisplatin (15mg/kg) to C57BL/6 wild type (WT) mice and measured kidney inflammation and injury. For reconstitution studies, CD4+ T cells were isolated using magnetic beads and injected into RAG1−/− mice, which lack adaptive immune cells.

Results: Kidney mRNA expression of IL-17A increased significantly after cisplatin treatment. Compared to WT mice treated with cisplatin, functional (serum urea: WT 72.2±10.7 vs. IL-17A−/− 28.2±8.2mmol/L, P<0.001) and histological injury (Injury score: WT 3.3±0.2 vs. IL-17A−/− 1.0±0.2, P<0.001) were decreased in IL-17A−/− mice. While intitial neutrophil recruitment (1.8±0.1 vs. 1.0±0.1, cells/hybrid power field, P<0.001) decreased in the absence of IL-17A, CD4+ T cell recruitment remained intact. Pre-emptive administration of anti-IL-17A antibodies to WT mice attenuated renal injury, serum urea (control antibodies: 54.6±10 vs. anti-IL-17A 25.9±11mmol/L, P<0.05). Neutrophil depletion prior to cisplatin treatment did not significantly reduce renal injury, which only decreased after additional IL-17A neutralization in deficient mice. Depletion of both neutrophils and natural killer T cells significantly protected from AKI, but injury does not further reduced after additional anti-IL-17A treatment, linking these cells with IL-17A induced AKI. While reconstitution of RAG1−/− mice with CD4+ T cells prior to cisplatin treatment increased renal injury, there was no difference after reconstituting with WT or IL-17A−/− CD4+ T cells, demonstrating that IL-17A - producing CD4+ T cells did not enhance AKI. Mice deficient in gammadealta T cells were not protected from AKI.

Conclusions: IL-17A drives AKI and represents a new therapeutic target.

Funding: Government Support - Non-U.S.
**FR-PO064**

Alpha-Lipoic Acid Attenuates Lipopolysaccharide-Induced Kidney Injury

Sang Heon Suh,1 Koeun Lee,1 Eun Hui Bae,1 Seong Kwon Ma,1 Soo Wan Kim,1 Chang Seong Kim,1 Joon Seok Choi,2 Jongun Lee.2

1Depts of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea; 2Depts of Physiology, Chonnam National Univ Medical School, Gwangju, Korea.

**Background:** Kidney is one of the major target organs in sepsis, while effective prevention of septic acute kidney injury has not yet been established. We investigated the protective effect of α-lipoic acid (LA) on lipopolysaccharide (LPS)-induced kidney injury.

**Methods:** Two groups of rats were treated with LPS (20 mg/kg, i.p.), one of which was co-treated with LA (50 mg/kg), while the control group was treated with vehicle alone. Human renal proximal tubular epithelial cells (HK-2 cells) were cultured with or without LPS (10 μg/ml) in the presence or absence of LA (100 μg/ml) for 3 hours prior to LPS treatment.

**Results:** Serum creatinine level was increased in LPS-treated rats, which was attenuated by LA co-treatment. LPS treatment increased both cleaved caspase-3 expression and the number of terminal deoxynucleotidyl transferase dUTP nick end labelling-positive cells in the kidney, which was counteracted by LA. Protein expression of inducible nitric oxide synthase and cyclooxygenase-2 detected by immunoblotting and/or immunohistochemical staining, along with mRNA levels of pro-inflammatory cytokines detected by real-time PCR, was significantly reduced by LA treatment.

**Conclusions:** LA treatment ameliorates LPS-induced kidney injury by suppression of apoptosis, inflammation, and renal tubular dysfunction.

**FR-PO065**

Gender Differences in Murine Ischemia Reperfusion Tolerance Is Extrinsic to the Kidney Itself: Lessons from Treatment Matthew H. Levine,1 Zhonglin Wang,1 Tricia Bhatti,2 Wayne W. Hancock.2

1Depts of Internal Medicine, Tokyo, Japan; 2Depts of Physiology, Academic Medical Center, Amsterdam, Zuid Holland, Netherlands; 3AM Pharma, Bunnink, Netherlands.

**Background:** Gender differences are well described in murine basic renal ischemia reperfusion injury (IRI) models, with females being more tolerant of injury. Whether these differences are driven by differences in the kidney’s resistance to IRI or whether they are due to differences in the host response to IRI are not known.

**Methods:** We utilized a syngeneic murine renal transplant model with male and female kidneys being transplanted into male and female recipients and then, after recovery, undergoing subsequent renal IRI by standardized 25 minute renal IRI protocol. Confirmatory cold ischemia renal experiments were performed with the same four groups, after storage of kidneys at 4 degrees C in UW solution for duration noted below and then subsequently transplanted with standardized transplanation times.

**Results:** Syngeneic kidneys transplanted across genders with subsequent renal IRI showed that kidneys of both genders had similar and enhanced tolerance to IRI in a female host. Conversely, kidneys of both genders tolerated renal IRI equally poorly in a male host, with most mice euthanized in this group by 48 hours due to renal insufficiency.

**Conclusions:** That both CSZ and PBC showed anti-inflammatory effects through different mechanisms.

**FR-PO066**

Recombinant Alkaline Phosphatase Modulates Inflammation and Injury in Two Rat Models of AKI

Sang Heon Suh,1 Kyeong Seon Hwang,1 Eun Hui Bae,1 Seong Kwon Ma,1 Soo Wan Kim,1 Chang Seong Kim,1 Joon Seok Choi,2 Jongun Lee.2

1Depts of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea; 2Depts of Physiology, Chonnam National Univ Medical School, Gwangju, Korea.

**Background:** Purified bovine alkaline phosphatase (AP) has shown intriguing clinical activity treating acute kidney injury in sepsis patients (Heemskerk et al. 2009, Crit. Care Med. 37: 417-23; Pickkers et al., 2012, Crit. Care: 23: R14). A recombinant alkaline phosphatase was designed by swapping the crown domain from intestinal AP with that derived from placental AP enzyme generating a stable human chimeric called recAP.

**Methods:** To study its activity and mode-of-action in models of acute kidney injury (AKI), a single i.v. dose of 1000 U/kg recAP was administered to instrumented Wistar rats (7 per group) within 30 min. after ischemia-reperfusion (I-R) or LPS injection to induce AKI, and compared to saline (n=7). Systemic and local hemodynamics as well as kidney oxygenation were assessed for the duration of the experiment (3 h post-treatment). A control group underwent surgery and insertion of various probes without AKI induction.

**Results:** Saline treated animals developed mild I-R model or severe AKI (LPS model). Systemic hemodynamics was unaffected by recAP, however renal vascular resistance improved in the I-R model (control 2424 ± 370 dyn/s/cm2, 4314 ± 1182 in the saline group vs 2905 ± 1246 after recAP treatment) and renal blood flow significantly improved in the LPS model (control 5.02 ± 1.30 mL/min,saline 8.33 ± 2.98, recAP 6.28 ± 1.89, p<0.001). By immunohistochemistry, recAP modulated inflammatory markers iNOS, IL-6 (p<0.001), as well as peroxidation marker MDA (p<0.001) in the LPS model. Compared to saline, recAP treatment reduced the number of infiltrating MPO+ leukocytes in the cortical peritubular areas (p<0.05). Moreover, recAP reduced expression of renal injury markers L-FABP, NGAL (p<0.001) and pro-apopotic Bax (p<0.01).

**Conclusions:** In conclusion, in rat AKI recAP demonstrated immediate pharmacological effect which included suppression of acute inflammation in the affected kidney and inhibition of tissue injury. This study provides first evidence that recAP is an active protein therapeutic in two rat models of AKI.

**Funding:** Pharmaceutical Company Support - AM Pharma, Bunnink, The Netherlands

**FR-PO067**

Protective Effect of Cilostazol and Probucol on Inflammatory Kidney Injury

Peng He1, Harukiyo Kawamura,1 Kunimasa Yan,2 Minoru Takemoto,1 Koutarou Yokote.1

1Clinical Cell Biology and Medicine, Chiba Univ Graduate School of Medicine, Chiba, Japan; 2Dept of Pediatrics, Kyorin Univ School of Medicine, Tokyo, Japan.

**Background:** The aim of this study is to clarify the protective effect of a combination of cilostazol (CSZ) and probucol (PBC), both of which are prescribed for cardiovascular diseases and exhibit anti-inflammatory properties on inflammatory kidney injury.

**Methods:** In vivo, we employed lipopolysaccharide (LPS) induced acute renal inflammation model mice. In brief, after pretreatment with CSZ, PBC alone or in combination with each other (CSZ/PBC), mice were intraperitoneally injected with LPS. After 24 h, urinary albumin levels were measured by ELISA and expression of MCP1 in glomeruli was analyzed by immunostaining and real-time PCR. In vitro, we treated cultured podocytes with LPS (100 ng/ml) in the presence or absence of CSZ, PBC or CSZ/PBC and then we estimated activation of MAP kinase by immunoblotting, activation of NfκB by immunostaining and reactive oxygen species (ROS) by dihydrodithidium (DHE) staining.

**Results:** In mice glomeruli and cultured podocytes, LPS-induced albuminuria and MCP1 upregulation were considerably suppressed by CSZ/PBC. Among the native cells of glomeruli, podocytes expressed most of MCP1 compared with endothelial and mesangial cells. In cultured podocytes, CSZ and PBC suppressed LPS-induced NfκB activation and MCP1 expression, while the combination of them showed an additive suppressive effect. CSZ increased intracellular cAMP levels and PKA activation which in turn suppressed ERK activation and MCP1 expression downstream. On the other hand, PBC lowered LPS-induced NfκB activation and MCP1 expression by reducing LPS-induced activation of NADPH oxidase and intracellular ROS production.

**Conclusions:** In a LPS-induced acute renal inflammatory mouse model, we confirmed that both CSZ and PBC showed anti-inflammatory effects through different mechanisms. Moreover, the combination of these two drugs had a stronger protective effect on LPS-induced renal dysfunction and glomerular inflammation. This study indicated that combination of CSZ and PBC could be a prospective treatment for inflammatory kidney diseases.

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

Underline represents presenting author/disclosure.

380A
FR-PO068

CXCR2 Knockout Mice Are Protected against Dextran Sulfate Sodium-Colitis Induced Acute Kidney Injury and Inflammation Punitbhavati Vilapakkan Ranganathan, Calpurnia Jayakumar, Ganesan Ramesh. Vascular Biology Center, Georgia Regents Univ, Augusta, GA.

Background: Organ cross-talk exists in many human diseases and in animal models. Recent study had demonstrated that in renal injury, with significant wild type (WT). Further, HSF-1 KO mice have altered T cell infiltration, with significant role in the protection against IR injury seen in HSF-1 KO mice.

Methods: We examined the hypothesis that KC-CXCR2 pathway mediates DSS-colitis induced AKI. Colitis was induced in 8-week old wild-type (WT) and CXCR2 knockout mice by feeding them with 3.5% DSS in drinking water for a period of 8 days. Animals were sacrificed 2 days after removal of DSS. Kidney function was monitored by measuring serum creatinine. Some mice received recombinant KC (100ng/mg) to determine whether exogenous administration of KC exacerbates acute kidney injury. Inflammation and immune cell infiltration were quantified by immunostaining, RT-PCR and ELISA.

Results: WT mice developed severe colitis with DSS treatment which was associated with infiltrative cytokines and chemokine expression and neutrophil infiltration in the colon. DSS-colitis in WT was accompanied by acute kidney injury (serum creatinine: 0.4±0.03mg/dl) and enhanced expression of cytokine (TNFa) and chemokines (MCP-1, IP-10 and KC) in the kidney. However, CXCR2 knockout mice were protected against DSS-colitis as well as acute kidney injury (serum creatinine: 0.2±0.02mg/dl). Moreover, the expression of cytokines and chemokines and neutrophil infiltration was significantly and completely blunted (p<0.001 vs. WT) in CXCR2 knockout mice in colon and kidney. Administration of recombinant KC accelerated DSS-colitis induced acute kidney injury (0.6±0.03 mg/dl; p<0.05 vs. vehicle treated).

Conclusions: Our results suggest that KC and its receptor CXCR2 are critical and major mediators of organ cross talk between colon and kidney in DSS induced colitis and neutrophil infiltration of CXCR2 KO helps to reduce the incidence of acute kidney injury due to ulcerative colitis and crohn’s disease in humans.

Funding: NIDDK Support

FR-PO069

Genetic Depletion of Semaphorin 3A Render Resistance to Ischemia Reperfusion Induced Inflammation and Acute Kidney Injury in Mice Punitbhavati Vilapakkan Ranganathan, Calpurnia Jayakumar, Ganesan Ramesh. Vascular Biology Center, Georgia Regents Univ, Augusta, GA.

Background: Recent studies have shown that guidance molecules that are known to regulate cell migration during development may also play an important role in adult during normal and pathological state. One such molecule called semaphorin 3A (sema3A) is known to be expressed in the kidney and its patho-physiological role in the kidney is unknown.

Methods: To test the hypothesis that sema3A is a mediator of ischemia reperfusion injury of the kidney by increasing epithelial cell apoptosis. Ischemia reperfusion injury in the kidney was induced by clamping renal pedicle for a period of 35 minutes followed by 24h of reperfusion in sema3A knockout (KO) and C3H control mice. Kidney function, inflammation, immune cell infiltration and apoptosis were quantified by measuring serum creatinine, immunostaining, RT-PCR, ELISA and TUNEL assay. Some wild-type received sema3A pathway inhibitor or sema3A blocking peptide 2hr before renal pedicle clamping to determine the effect of pharmacological inhibition of sema3A pathway on ischemic acute kidney injury (AKI).

Results: C3H mice subjected to ischemia reperfusion developed severe renal dysfunction as compared to sema3A KO mice (serum creatinine: 1.7±0.1 vs. 1.0±0.1 mg/dl; p<0.01), which was associated with histological alteration, neutrophil infiltration, increased cytokine and chemokine expression and excretion in urine. These changes were minimal in sema3A KO mice with ischemia reperfusion. Moreover, ischemia reperfusion induced extensive apoptosis in renal epithelial cells which was significantly suppressed in sema3A KO mice. Similarly, administration of sema3A inhibiting peptide or sema3A signaling inhibitor LOXblock-1 protected kidney against ischemia reperfusion induced AKI. Consistent with in vivo pathogenic role of semaphorin 3A, addition of semaphorin 3A to kidney epithelial cells in vitro increased cisplatin induced apoptosis.

Conclusions: Our data suggests that sema3A play a protective role in acute kidney injury through increasing epithelial cell apoptosis and sema3A inhibition may provide protection against human AKI.

Funding: NIDDK Support

FR-PO070


Background: We previously reported that Heat Shock Factor-1 knock-out (HSF-1 KO) mice, are protected against ischemic renal (IR) injury compared with Heat Shock Factor-1 wild type (WT). Further, HSF-1 KO mice have altered T cell infiltration immediately following IR, with significantly fewer CD4+ and CD8+ cells infiltrating HSF-1 KO kidneys than WT kidneys following IR. Our goal was to determine whether T regulatory cells play a role in this protection against IR injury seen in HSF-1 KO mice.

Methods: We compared T regulatory cells (FoxP3+CD25+) in HSF-1 KO and WT kidneys in the sham condition and after reperfusion following 45 minutes ischemia by flow cytometry. The effect of depletion of T regulatory cells on IR injury was studied by injecting HSF-1 KO mice to IR (45 minutes with 24 hours reflow) after treatment with PGC6, anti-CD25 antibody or vehicle control group.

Results: There are significantly more Foxp3+ T regulatory cells in sham operated kidneys of HSF-1 KO mice compared with WT (p<0.02). Early reperfusion after renal ischemia, Foxp3+ did not change in HSF-1 KO kidneys, but increased by 50% in WT kidneys. Treatment of HSF-1 KO mice with PGC6 antibody significantly depleted the renal Foxp3+CD25+ cells when compared with vehicle control group in sham (p<0.008) and following IR insult (p<0.01). PC61 treatment did not affect serum creatinine compared to vehicle control group in sham operated HSF-1 KO mice. However PC61 treatment (causing depletion of intra-renal CD25+ T regulatory cells) resulted in higher serum creatinine in HSF-1 KO than in vehicle treated HSF-1 KO following IR injury (0.89 mg/dl vs 0.48 mg/dl respectively).

Conclusions: Higher endogenous levels of renal T regulatory cells play a role in the protection afforded to HSF-1 KO mice against IR.

Funding: NIDDK Support, Other NIH Support - AI-AID, Private Foundation Support

FR-PO071

Detailed Analysis of Double Negative (CD4–CD8–) T Cells During AKI Maria Noel Martina Lingua,1 Samantha Bandapalle,2 Sanjeev Noel,2 Abdel Hamad,1 Hamid Rabb.2 1Pathology, Johns Hopkins Univ, Baltimore, MD; 2Nephrology, Johns Hopkins Univ, Baltimore, MD.

Background: Double negative (DN) T cells lacking CD4 and CD8 have recently been described to be a resident kidney immune cell (J Leuk Biol 2008). The role of these cells in kidney and how they mediate immune responses are unknown. We hypothesize that DN T cells involved in regulating early immune response could have a suppressive function on cytokine production, potentially protecting kidney from injury.

Methods: Purified T lymphocytes from mice were analyzed for expressing surface markers and cytokines secretion. B6 wild type mice and acute kidney injury mouse model were used. Surface and intracellular staining were done and analyzed with flow cytometry technology.

Results: Double negative T cells comprise a major population in kidney in the steady state (30%). This percentage shows a rapid and transient expansion after acute IRI, increasing after 3h of ischemia up to 60% and decreasing after 24h to 10%. DN T cells showed an activated phenotype in the kidney, expressing markers like CD44 and CD69, and also higher level of co-stimulatory molecules like CD28 and CD40-L compared to CD4+ and CD8+ in kidney. DN T cells exhibit a unique cytokine secretion profile: in steady state express IL-17, IL-10, IFNγ, IL-4 (60%, 10%, 5%, respectively) after in vitro stimulation with PMA/ion, while in ischemic kidneys they increased IL-10 – IL-17 (18%, 68% respectively) secretion and decreased IL-4 (1%). They also express the transcription factor ROR-γu to 20% in steady state.

Conclusions: Our data shows that resident double negative T cells produce a distinct cytokine profile during steady state. After AKI, DN T cells have a significant change in cytokine profile including a change in transcription factor ROR-γ. DN T cells are a newly identified resident kidney cell that can improve our understanding of immune mediated kidney diseases including AKI, glomerulonephritis and transplant rejection.

Funding: Other NIH Support - R21 AI095484

FR-PO072

The Role of Toll-Like Receptors and Reactive Oxygen Species in the Development of Lupus Nephritis Afshar-F Khan,1 Jerome L. Maderet,2 David H. Coyle,3 Eric E. Simon,1 Vecchi Battam,1 1Medicine, Section of Nephrology & Hypertension; 2Peptide Research Laboratory, Tulane Univ School of Medicine, New Orleans, LA; 3Veterans Affairs, SLVHC, New Orleans, LA.

Background: Lupus nephritis is a common and serious manifestation of systemic lupus erythematosus (SLE). We have explored the role of Toll-like receptors (TLRs) and reactive oxygen species (ROS) in the development of kidney disease in a mouse model of SLE. Methods: We used the female New Zealand Black/New Zealand White (NZB/NZW) F1 hybrid (lupus-prone) mouse, which spontaneously develops SLE-like pathology, as a model for lupus nephritis. NZW mice served as the controls. Mice (n = 4) were euthanized at 22, 29 or 41 weeks (wk) of age, and blood and kidneys were harvested to assess renal function and pathology.

Results: Serum creatinine and cystatin C levels and mRNA levels of the genes for the marker genes for monocyte/macrophage in steady state. After AKI, DN T cells have a significant change in cytokine profile including a change in transcription factor ROR-γ. DN T cells are a newly identified resident kidney cell that can improve our understanding of immune mediated kidney diseases including AKI, glomerulonephritis and transplant rejection.

Funding: Other NIH Support - R21 AI095484
Depletion of Macrophage Ameliorates Glycerol-Induced Acute Kidney Injury in Mice Seong Eun Yun, Eunjin Bae, Yeojin Kang, Hyun Soo Cho, Se-Ho Chang, Dong Jun Park. Internal Medicine, Gyeongsang National Univ Hospital, Republic of Korea.

Background: The roles of macrophage in rhabdomyolysis model mice have not been well organized. This study was conducted to elucidate the relative contribution of renal macrophages to the development of acute kidney injury (AKI) by glycerol injection into mice.

Methods: The macrophages were depleted by liposomal encapsulated clodronate (LEC). Mice were distributed into four groups: control group (liposomal vehicle 100 μl, intravenously 24 hour prior to and just before glycerol injection), LEC group (LEC 100 μl, intravenously 24 hour prior to and just before glycerol injection), Gly (50% glycerol (10 ml/kg)), and Gly plus LEC. On day 24 hour, renal function, histology, flow cytometry for macrophages, Western blot and renal tissue immunohistochemistry were assessed.

Results: Glycerol injection increased serum creatinine and blood urea nitrogen (BUN) 24 hours after injection. LEC injections (100 μl/mouse via tail vein) administered 24 h prior to and just before glycerol injection prevented the deterioration of renal function and also tubular damages 24 hours after glycerol injection. Renal macrophages represented by CD45+CD11b+Ly6c+ (0.03%) were significantly decreased by pretreatment of LEC in both normal and myoglobin injured kidney. LEC injection decreased apoptotic death of the tubular epithelial cells by decreasing pro-apoptotic caspase-9 protein and increasing anti-apoptotic Bel-2 protein expression. LEC administration also attenuates activation of ERK and p38 expression 24 h after glycerol administration. NF-κB, MCP-1, and ICAM-1 were also decreased in the damaged tubular epithelial cells by LEC injection. iNOS and COX-2 were decreased in LEC plus glycerol group, compared to and ICAM-1 were also decreased in the damaged tubular epithelial cells by LEC injection.

Conclusions: These results support the hypothesis that depletion of macrophages is effective in prevention of renal dysfunction by abrogating apoptosis and attenuating inflammation in glycerol-induced AKI mice model.

FR-P0074
PKC-α Offers Protection against Programmed Necrosis in Renal Proximal Tubules through Maintaining Functional MPT Pore Grzyna Nowak, Department of Cellular Biology and Anatomy, Mayo Clinic, Rochester, MN, USA.

Background: We have shown that necrosis, but not apoptosis, is the mechanism of cell death in renal proximal tubular cells (RPTC) injured by oxidant. RPTC necrosis is preceded by mitochondrial membrane hyperpolarization and bioenergetic failure. PKC-α activation prevents mitochondrial hyperpolarization, reduces mitochondrial dysfunction and ATP decreases, and decreases necrosis in oxidant-injured RPTC. Overexpression of the inactive mutant of PKC-α induces mitochondrial membrane hyperpolarization in non-injured RPTC.

Methods: To determine specific mechanisms of oxidant-induced RPTC necrosis, monolayers were treated with inhibitors of three different pathways of regulated necrosis and cell viability was assessed following exposure to a model oxidant, tert-butylhydroperoxide. In some experiments, PKC-α was overexpressed and RPTC lysis assessed following THP1 exposure.

Results: THP1 induced 43% RPTC death at 24h after the exposure. Pretreatment of RPTC with cyclosporine A (inhibitor of cyclophilin D) offered no protection at concentration of 1 μM (41% lysis) and exacerbated cell lysis at higher concentrations (58% lysis). Iron chelation by deferoxamine and inhibition of ferroptosis by ferrostatin prevented THP1-induced RPTC death (4% lysis). Necrostatin-1, an inhibitor of necroptosis, decreased RPTC lysis to 12% of controls. Overexpressing PKC-α in RPTC decreased oxidant-induced necrosis to 22% and this protective effect was reversed by cyclosporine A and PKC inhibitor, Go6976. Ferrostatin and deferoxamine augmented PKC-α-mediated protection against oxidant-induced injury (13% and 5% cell lysis, respectively).

Conclusions: These results demonstrate that oxidant-induced RPTC necrosis is iron-dependent and its major mechanism is through ferroptosis. Necroptosis is an additional mechanism involved in RPTC death. However, the opening of the mitochondrial permeability transition pore (MPTP) and loss of ATP, are not mechanisms that mediate oxidant-induced programmed necrosis in RPTC. The protective effects of PKC-α are mediated through maintaining functional MPTP and preventing mitochondrial membrane hyperpolarization.

Funding: NIDDK Support

FR-P0075
FGF/FGFR2 Signaling Protects against Tubular Cell Death and Acute Kidney Injury Zhou Xu, Weichun Chen, Junwei Yang, Chunsun Dai. The Center for Kidney Disease, the Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, China.

Background: Fibroblast growth factors (FGFs) are heparin-binding proteins involved in a variety of biological processes, including cell proliferation, differentiation, survival and angiogenesis. However, the role and mechanism of FGFs/FGFR signaling in tubular cell survival and AKI need further investigation.

Methods: In this study, ischemia/reperfusion or cisplatin injection was used to induce AKI in mice. A mouse model with tubule specific deletion of FGFR2 (Tubule-FGFR2/-) was generated.

Results: In the kidneys with ischemia/reperfusion injury (IRI), the expression of FGFs including FGF2, FGF7, FGF10, FGF12, FGF13, FGF18, and FGF22 were up-regulated. In addition, phosphorylated ERK1/2, a downstream signaling of FGFR was also elevated in the IRI kidneys. To further explore the role of FGF signaling in tubular cell survival and AKI in mice, a mouse model with tubular cell specific FGFR2 gene disruption was generated using Cre-LoxP system. The knockouts were born normal and no obvious kidney function was found within four months after birth. Specific deletion of FGFR2 in tubular cells in mice aggravated the tubular cell death as well as AKI induced by IRI or cisplatin. In cultured NRK-52E cells, recombinant FGF2 protein could induce Erk1/2 phosphorylation and inhibit cisplatin-induced cell death. PD98059, a specific MEK 1/2 inhibitor, abolished Erk1/2 phosphorylation and partly reversed the protective effect of FGF2 in cisplatin-induced cell death.

Conclusions: Together, this study indicates that FGF/FGFR2 signaling is important for protecting against tubular cell death and AKI, which is partly through ERK1/2 signaling activation.

Funding: Government Support - Non-U.S.

FR-P0076
Propidium Iodide Is Cheating on Necrosis Detection: A Multiphoton Microscopy Study Matthias Hackl,1 Andreas Linkermann,2 Bernhard Schermer,1 Thomas Benzing.1 Dept II of Internal Medicine and Center for Molecular Medicine Cologne, Univ of Cologne, Cologne, Germany; 2Clinic of Nephrology and Hypertension, Christian-Albrechts Univ, Kiel, Germany.

Background: There is an ongoing debate, if apoptosis or necrosis is the more prevalent form of cell death after ischemia-reperfusion injury. Propidium iodide (PI) staining has been used as a marker of necrotic cells in many studies. Intact cell membranes prevent the entry of PI into viable cells. PI has been successfully used to detect necrotic nuclei in vivo in the heart, the eye and the brain. Here we tested if PI is a reliable marker of necrosis in the kidney in vivo.

Methods: 6 wk old C57BL6 mice were anesthetized, an arterial cathether was placed and the left kidney was exteriorized for in vivo multiphoton microscopy. 30 μg PI was injected during the acquisition of a time lapse movie. Blood vessels and nuclei were labeled by the injection of 70kDa Texas red dextran and 150μg Hoechst 33342 respectively. Lucifer Yellow was injected to visualize tubular fluid handling. To stop tubular flow the left ureter was ligated three times with 9-0 silk and the animals imaged 2–7 days later.

Results: In healthy and uninjured kidneys a considerable amount of PI was taken up by tubular cells. Time-lapse imaging demonstrated that the nuclei turned red 30–60 minutes after the injection of PI into the circulation. Colabeling with Hoechst 33242 and studies of tubular handling of filtrate showed that only proximal tubular cells (PTC) take up PI. The uptake of PI was markedly reduced 3–7 days after an unilateral ureteral ligation, while Hoechst 33342 staining was unaltered. Imaging of liver and gut showed no uptake in these organs. After the induction of damage with the laser beam some cells immediately took up PI. In healthy kidneys a considerable amount of propidium iodide was taken up by living viable PTs, but this uptake was delayed compared to the uptake of PI in the renal fluid. Distal tubular cells, glomerular cells, the liver and the gut do not show uptake of PI, demonstrating that this uptake is restricted to PTC. Although cells with membrane damage may show a faster PI uptake than viable PTC, the use of PI as a marker for necrotic cells in vivo is limited by the false positive nuclei of viable PTs.

Funding: Government Support - Non-U.S.

FR-P0077
SUMOylation Occurs in Acute Kidney Injury and Plays a Cytoprotective Role Chunyaun Guo, Zheng Dong. Dept of Cellular Biology and Anatomy, Georgia Regents Univ, Augusta, GA.

Background: SUMOylation is a mechanism of post-translational modification where Small Ubiquitin-like Modifiers (SUMO) are covalently attached to target proteins to regulate their localization, stability and functions. SUMOylation has been demonstrated during hypoxia, oxidative, genotoxic and metabolic stresses, suggesting an important role of this modification in cellular stress response. However, it is largely unclear if SUMOylation contributes to the pathogenesis of kidney diseases, such as acute kidney injury (AKI).

Methods: We examined protein SUMOylation in two experimental models of AKI: cisplatin nephrotoxicity and renal ischemia-reperfusion in vitro and in vivo. In addition, we examined the regulation of SUMOylation during cisplatin treatment of cultured rat kidney proximal tubular cells (RPTC) by two ROS scavengers and a pharmacological p53 inhibitor. We further examined the role of SUMOylation during cisplatin treatment of RPTC cells by using ginkgolic acid (GA), a pharmacological inhibitor of the E1-activating enzyme in SUMOylation.

Results: We have demonstrated dramatic increases of protein SUMOylation in both experimental models of AKI. Cisplatin-induced SUMOylation in RPTC cells was partially suppressed by N-acetylcysteine and dimethylurea (two ROS scavengers), supporting a role for oxidative stress in the regulation of SUMOylation. In addition, SUMOylation by SUMO-2/3, but not SUMO-1, was partially suppressed by pifithrin-alpha, a pharmacological inhibitor of p53, supporting a role of p53 in SUMOylation by SUMO-2/3. Pretreatment with GA suppressed SUMOylation during cisplatin incubation and importantly, GA completely reversed necrosis.

Conclusions: Taken together, the results demonstrate the first evidence of SUMOylation in AKI which may result from oxidative stress and p53 signaling and suggest that SUMOylation may play a cytoprotective role in kidney tubular cells.

Funding: NIDDK Support, Veterans Affairs Support
FR-PO078

Two Independent Pathways of Regulated Necrosis Mediate Ischemia-Reperfusion Injury
Andreas Linkermann,¹ Jan Hinrich Braesien,² Maurice Darling,³ Ana Belen Sanz,⁴ Jan O. Heller,⁵ Ricardo Weinlich,⁶ Alberto Ortiz,⁶ Henning Walczak,⁷ Joel M. Weinberg,⁸ Ulrich Kunzendorf,⁹ Stefan Krautwald,¹
¹Clinic for Nephrology and Hypertension, Christian-Albrechts-Univ, Kiel, Schleswig-Holstein, Germany; ²Institute for Diagnostic Histopathology and Cytopathology, Pathology Hamburg-West, Hamburg, Germany; ³Centre for Cell Death, Cancer and Inflammation (CCCI), Cell Death and Inflammation Laboratory, Univ College London, Cancer Institute, London, United Kingdom; ⁴IIS-Fundacion Jimenez Diaz, U Autonoma de Madrid, Redinren, FRIAT, Madrid, Spain; ⁵Dept of Immunology, St. Jude Children’s Research Hospital, Memphis, TN; ⁶Div for Nephrology, Univ of Michigan Medical Center, Ann Arbor, MN.

Background: Regulated necrosis (RN) may result from cyclophilin D (CypD)-mediated mitochondrial permeability transition (MPT) and receptor-interacting protein kinase 1 (RIPK1) mediated necroptosis. It is unclear whether there is one common pathway in which CypD and RIPK1 act in or if separate RN pathways exist.

Methods: Here, we demonstrate that necroptosis in ischemia-reperfusion injury (IRI) in mice occurs as primary organ damage, independent of the immune system, and that mice lacking RIPK1, the essential downstream partner of RIPK1 in necroptosis, are protected from IRI.

Results: Protection of RIPK3-ko mice was significantly stronger than that of CypD-deficient mice. Mechanistically, analysis of cisplatin-induced AKI and hyperacute TNF-Shock models in mice suggested the co-existence of CypD-mediated MPT from RIPK1/RIPK3-mediated necroptosis. We therefore generated novel CypD-RIPK3 double-deficient mice that are viable and fertile without an overt phenotype and that survived prolonged IRI which was lethal to each single knockout. Combined application of the RIPK1 inhibitor necrostatin-1 (Nec-1) and the MPT inhibitor sanglifehrin A (SFA) confirmed the results with mutant mice.

Conclusions: The data demonstrate the pathophysiological co-existence and co-relevance of two separate pathways of RN in IRI and suggest that combination therapy targeting distinct RN pathways can be beneficial for the treatment of ischemic injury.

Funding: Other NIH Support - NIH-DK34275, Pharmaceutical Company Support - Novartis, Fresenius medical care, Intereg4a (MeoMtxs), Private Foundation Support, Government Support - Non-U.S.

FR-PO081

Melittin Induced Acute Kidney Injury through TNF-α/NF-κB/Mitochondria Dependent Apoptotic Pathway
Ling Zhang, Ping Fu. West China Hospital of Sichuan Univ, China.

Background: Mechanism of acute kidney injury (AKI) following multiple bee stings is not clear. Melittin, a main component of bee venom, can induce apoptosis in many cell types. We aimed to investigate the mechanism of melittin induced apoptosis in renal tubular epithelial cells through TNF-α/NF-κB signaling pathway.

Methods: AKI model was established by injecting melittin (40 μg/ml) through the caudal veins of BALB/c mice (n=60). AKI was defined as creatinine (Cr) increased over 2 fold of that in control group. Blood and kidney samples were collected at 0h, 2h, 6h, 12h, 24h and 48h. Cr, urea nitrogen and hemoglobin were measured by Abbott i-STAT blood-gas analyzer. Creatine kinase was measured by immunochemiluminometric assays. Serum TNF-α was measured by ELISA method. Apoptosis of renal tubule cells was detected by TUNEL staining and transmission electron microscopy. Expression of caspase-3, caspase-8, caspase-9, Bcl-2, Bax, and cytochrome c was detected by western blot.

Results: AKI was diagnosed at 6h after injection of melittin (Cr: 1.1±0.3 mg/dl at 6h vs. 0.4±0.1 mg/dl at 0h, p<0.05). Serum TNF-α level increased significantly since 2h after injection. Apoptosis was detected since 2h, and was most notable at 12h. Western Blot showed that p-IκBα/IκBα ratio was significantly decreased in melittin group during 6h to 24h, indicating that NF-κB signal pathway was inhibited. RT-PCR showed that the Bcl-2/Bax ratio was significantly lower in melittin group than control group, indicating that the mitochondrial dependent apoptosis pathway was activated.

Conclusions: We successfully established melittin induced AKI in mice. Melittin might induce mitochondrial dependent apoptosis in renal tubular epithelial cells through activating TNF-α and inhibiting NF-κB signaling pathway.

FR-PO080

Nephron-Specific Kidney Injury Molecule-1 Overexpression Induces Tubular Damage and Kidney Failure in Transgenic Zebrafish
Wening Yiq, Said Movahedi Naini, Dirk M. Hentschel, Joseph V. Bonventre, Renal Div, Brigham and Women’s Hospital, Boston, MA.

Background: Mammalian kidney injury molecule-1 (KIM-1) is upregulated after kidney injury in proximal tubular cells, and serves as a highly sensitive and specific biomarker for acute kidney injury. KIM-1 is also upregulated in many subjects with chronic kidney disease. KIM-1 functions as a phagocytic receptor which mediates the uptake of apoptotic bodies as well as oxidized lipids. Data from our laboratory suggests that prolonged expression of KIM-1 in mice is maladaptive. Here, we characterized zebrafish KIM-1 (zKIM-1) family members, and studied the effect of zKIM-1 overexpression on the zebrafish pronephros.

Methods: We cloned zKIM-1 and related family members and compared biochemical and functional aspects with that of human KIM-1 (hKIM-1) using PCR, western blotting, in situ hybridization (ISH) and immunostaining. We created two zebrafish models of KIM-1 overexpression in the pronephros employing the cdh17 promoter. In one case the expression was constitutive. In the other case a cdh17:CreERT2 transgenic fish line was created that allowed for tamoxifen-induced overexpression of KIM-1 in nephrons initiated at 72 hr post fertilization (hpf).

Results: As with hKIM-1, zKIM-1 was not expressed in healthy nephrons, and was markedly upregulated after gentamicin-induced injury. zKIM-1 also showed a conserved phagocytic activity comparable to hKIM-1. Tissue-specific constitutive overexpression of zKIM-1 in the pronephros under cdh17 promoter control caused pericardial edema, reduced GFR and a higher mortality with defects apparent by 48 hpf. Histologic examination revealed kidney tubular damage in nephrons overexpressing zKIM-1. Cre-mediated overexpression of zKIM-1 initiated at 72hpf caused a similar kidney maladaptive phenotype marked by tubular damage, edema and higher mortality.

Conclusions: zKIM-1 has high structural and functional similarities to hKIM-1. KIM-1 overexpression in the pronephros of the zebrafish results in tubular damage and kidney failure. Enhanced prolonged expression of KIM-1 in human proximal tubules may have maladaptive consequences due to KIM-1-mediated in phagocytosis of tubular components.

Funding: NIDDK Support
DNA Damage Response in Renal Ischemia-Reperfusion and ATP-Depletion of Renal Tubular Cells; Zhengwei Ma, Zheng Dong. Dept of Cellular Biology & Anatomy, Georgia Regents Univ, Medical College of Georgia, Augusta, GA.

Background: Renal ischemia-reperfusion leads to acute kidney injury (AKI) that is characterized pathologically by tubular damage and cell death, followed by tubular repair, atrophy and interstitial fibrosis. Recent work suggested the possible presence of DNA damage response (DDR) in AKI. However, this evidence is scarce and the role and regulation of DDR in ischemic AKI remains elusive.

Methods: In this study, DDR was studied in kidney tissues during ischemia-reperfusion in mice and renal proximal tubular cells (RPTC).

Results: We detected DDR in kidney tissues during ischemia-reperfusion in mice, as shown by increased expression of γH2AX and phosphorylation of ATM, Chk2 and p53. DDR was also induced in vitro during "reperfusion" of RPTC after ATP-depletion. DDR in this model was abrogated by supplying glucose (generate ATP via glycolysis), indicating that the DDR depends on ATP depletion. The DDR was suppressed to various extents by the ATPIm inhibitor Kc5933, the antioxidant N-acetylcysteine, the general caspase inhibitor z-VAD and overexpression of Bel-2.

Conclusions: In conclusion, DDR occurs during renal ischemic AKI in vivo and ATP-depletion injury in vitro. ATM is a sensor in this DDR, which involves oxidative stress and apoptosis.

Funding: NIDDK Support, Veterans Affairs Support

Rector/mTORC2 Protects against Cisplatin-Induced Tubular Cell Death and Acute Kidney Injury; Jingzhong Lai, Weiichun He, Junyang Wang, Chunsun Dai. The Center for Kidney Disease, the Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: The mammalian target of rapamycin (mTOR) plays a critical role for cell growth and survival in many cell types. While substantial progress has been made in understanding the abnormal activation of mTORC1 in the pathogenesis of kidney disease, little is known about mTORC2 in kidney disease such as acute kidney injury (AKI).

Methods: Here a mouse model with tubule specific deletion of Rictor (Tubule-Rictor-/+) was generated and NRK-52E cell, a rat proximal tubular cell line, was used.

Results: The knockouts were normal and no obvious kidney dysfunction or kidney morphologic abnormality was found within 2 months after birth. Cisplatin-induced AKI was exacerbated by the mice and ablation of the Rictor in the tubular cells exacerbated cisplatin-induced AKI compared to those in the control littersmates. Tubular cell apoptosis, Akt phosphorylation (Ser473) as well as autophagy were induced in the kidneys from the control littersmates with cisplatin-induced AKI. Less cell autophagy or Akt phosphorylation and more cell apoptosis in the knockout kidneys were identified compared with those in the control littersmates. In cultured NRK-52E cells, Rictor sRNA transfection sensitized cell apoptosis to cisplatin while reduced cisplatin-induced autophagy. Finally, metformin could abolish cisplatin-induced cell death induced by Rictor sRNA and cisplatin administration.

Conclusions: This study suggests that endogenous Rictor/mTORC2 protects against cisplatin-induced AKI, which is probably mediated by promoting cell survival through Akt signaling activation and autophagy induction.

Funding: Government Support - Non-U.S.

Rapamycin Prevents LPS-Induced Endothelial Cell Dysfunction; Giuseppe Castellano,1 Alessandra Stasi,1 Margherita Gigante,1 Angelica Rapamycin Prevents LPS-Induced Endothelial Cell Dysfunction;

Methods: Here a mouse model with tubule specific deletion of Rictor (Tubule-Rictor-/+) was generated and NRK-52E cell, a rat proximal tubular cell line, was used.

Results: The knockouts were normal and no obvious kidney dysfunction or kidney morphologic abnormality was found within 2 months after birth. Cisplatin-induced AKI was exacerbated by the mice and ablation of the Rictor in the tubular cells exacerbated cisplatin-induced AKI compared to those in the control littersmates. Tubular cell apoptosis, Akt phosphorylation (Ser473) as well as autophagy were induced in the kidneys from the control littersmates with cisplatin-induced AKI. Less cell autophagy or Akt phosphorylation and more cell apoptosis in the knockout kidneys were identified compared with those in the control littersmates. In cultured NRK-52E cells, Rictor sRNA transfection sensitized cell apoptosis to cisplatin while reduced cisplatin-induced autophagy. Finally, metformin could abolish cisplatin-induced cell death induced by Rictor sRNA and cisplatin administration.

Conclusions: This study suggests that endogenous Rictor/mTORC2 protects against cisplatin-induced AKI, which is probably mediated by promoting cell survival through Akt signaling activation and autophagy induction.

Funding: Government Support - Non-U.S.

Funding: Private Foundation Support

Arginase2 Is Up-Regulated in Renal Tubular Cells of AKI and Regulated NO In Vitro and In Vivo; Koji Ogata, Tatsuki Matsumoto, Kazu Hamada, Yoshinori Taniguchi, Yoshiko Shimamura, Kosuke Inoue, Taro Horino, Yoshio Terada. Kochi Univ, Japan.

Background: Arginase (AGase) is an enzyme that breaks down L-arginine and ornithine to urea, and was identified as nitric oxide (NO) metabolism-related factor. AGase2 is expressed constitutively in normal kidneys. However, because the biological role for AGase2 in acute kidney injury (AKI) is poorly understood, we studied the expression/ modulation mechanism and role of AGase2 axis, and the aging effects.

Methods: To clarify the role of AGase2 in AKI, we used a rat ischemia/reperfusion (I/R) AKI model and cultured renal tubular cells (NRK-52E cells). To examine the effects of AGase2 on AKI, we used AGase2 expression vector and siRNA. Moreover, to assess aging effects, we also studied AGase2 expression in aged mice (42- and 87-week-old).

Results: Western blot analysis showed that AGase2 expression was increased at 12-48 h after I/R. The renal expression of AGase1 was very weak and not changed by I/R. Immunohistochemical examination revealed that AGase2 expression was increased in proximal tubules. In vitro AGase2 expression was also increased in NRK-52E cells under hypoxic stimulation. Overexpression of HIF-1a and Amt resulted in increased AGase2 expression. When increased AGase2 under hypoxia was suppressed by AGase2 siRNA, phosphorylation of eNOS (Ser-1177) was increased. Overexpression of AGase2 in NRK-52E cells resulted in suppressed phosphorylation of eNOS. Finally, AGase2 expression was significantly increased in 42- and 87-week-old aged mice, and showed further increase after AKI, in addition to the reduction of phosphorylation of eNOS.

Conclusions: In summary, AGase2 is up-regulated in renal tubular cells under AKI and hypoxic conditions. AGase2 might play a pivotal role on AKI pathogenesis via NO modulation by down arginine and suppress eNOS activity. Furthermore AGase2 might be critical for aging-related AKI pathogenesis.

FR-P0087

Inhibition of PKCδ Protects against Cisplatin-Induced Renal Tubular Cell Apoptosis by Activation of Autophagy through Directly Inhibition of AKT/mTOR Signaling; Zhong Deng,1,2,3 The Second Xiangya Hospital, Central South Univ; 1Dept of Cellular Biology and Anatomy; Medical College of Georgia, Georgia Regents Univ; 1Charlie Norwood VA Medical Center, Augusta, GA.

Background: Inhibition of PKCδ protects against cisplatin-induced acute kidney injury (AKI); however, the underlying mechanism remains[en]un[clear]. Autophagy has recently been recognized as an important mode of cell death. We hypothesized that inhibition of PKCδ may provide renoprotection by increasing autophagy.

Methods: In this study, we examined the role and signaling pathway of PKCδ in autophagy regulation during cisplatin treatment of renal proximal tubular cells (RPTC).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
We further determined if the protective effect of PKCδ inhibitors depends on autophagy using renal proximal tubule–specific Atg5 knockout (PT-Atg5-ko) mice. After activation, PKCδ was shown to directly interact with Akt, resulting in Akt phosphorylation at serine-473. Consequently, Akt phosphorylated and activated mTOR, a major negative regulator of autophagy. Consistently, dominant negative and genetic inhibition of PKCδ during cisplatin treatment blocked mTOR activation, enhancing autophagy for cell survival. Rottlerin, a pharmacologic inhibitor of PKCδ, showed significant protective effect during cisplatin-induced AKI in mice, which was markedly abrogated in PT-Atg5-ko mice.

Conclusions: This study revealed a new signaling pathway mediated by PKCδ and Akt in the regulation of mTOR and autophagy. Moreover, it demonstrates the involvement of autophagy in the renoprotective effect of PKCδ inhibitors in AKI.

Methods: We examined the change of primary ciliary by immunofluorescence and its role in tubular cell apoptosis and AKI induced by cisplatin, a chemotherapy agent with notable nephrotoxicity.

Results: In cultured human proximal tubular HK-2 epithelial cells, cilia became shorter during cisplatin treatment, followed by apoptosis. Knockdown of Kif3a or Polaris (cilia maintenance proteins) reduced cilia and increased apoptosis during cisplatin treatment. We further subcloned HK-2 cells and found that the clones with shorter cilia were more sensitive to cisplatin-induced apoptosis. Mechanistically, cilia-suppressed cells showed hyperphosphorylation or activation of ERK. Inhibition of ERK by U0126 preserved cilia during cisplatin treatment and protected against apoptosis in HK-2 cells. In C57BL/6 mice, U0126 prevented the loss of cilia from proximal tubules during cisplatin treatment and protected against AKI. U0126 up-regulated Polaris, but not Kif3a, in kidney tissues.

Conclusions: It is suggested that ciliary regulation by ERK plays a role in cisplatin-induced tubular apoptosis and AKI.

FR-PO091

Epidermal Growth Factor Receptor (EGFR) Inhibition with Erlotinib Attenuates Cisplatin-Induced Nephrotoxicity in Rats

Takahiro Wada, Masayuki Iyo, Kei Matsuzomo, Yuki Shindo-Hirai, Yoshihiro Kuno, Taihei Suzuki, Ysutaka Yamamoto, Saitou Tomohiro, Ken Iseri, Takanori Shibata. Div of Nephrology, Dept of Medicine, Showa Univ School of Medicine, Japan.

Background: The effects of blocking the EGFR in acute kidney injury (AKI) are controversial. We investigated the renoprotective effect of erlotinib, a tyrosine kinase inhibitor that can block EGFR activity, on cisplatin (CP)-induced AKI.

Methods: C57BL/6j mice were exposed to 7 mg/kg cisplatin (CP, i.p.) on day 0. Groups of animals were given either erlotinib (CP+E, 20 mg/kg, n=14) or vehicle (CP+V, n=14) daily by oral gavage from day -1 to day 3. Five SD rats were used as normal control (NC). All rats were sacrificed on day 4. In addition, we analyzed the effects of erlotinib in signaling pathways that are involved in CP-N by using human renal proximal tubular cells (HK-2).

Results: Compared to the NC rats, the CP+V rats exhibited marked AKI characterized by deterioration of renal function, severe tubulointerstitial (TI) damage, and increase in renal cortical mRNA expressions for proinflammatory cytokines, fibrogenic genes, and pro-heparin-binding EGF-like growth factor. Compared to vehicle, erlotinib treatment significantly prevented BW loss and increased urine volume. Erlotinib significantly improved renal function (Scr: 1.63±0.3 vs. 0.82±0.2 mg/dL, p<0.01) and ameliorated TI injury (the number of casts/HFP: 2.0±0.7 vs. 0.7±0.1, p<0.01). PUNA-positive and TUNEL-positive cells were significantly reduced by erlotinib. Furthermore, renal cortical mRNA for TGFB-β and Bax/Bcl-2 ratio were significantly reduced in CP+E rats compared to CP+V rats. Additionally, we observed that erlotinib significantly reduced the phosphorylation of ERK1/2, which was induced by CP in HK-2.

Conclusions: Our study shows that erlotinib attenuates the CP-induced AKI by degradation of tubular cell apoptosis and proliferation. The inactivation of ERK1/2 is likely one of the fundamental factors involved in apoptosis reduction. These results strongly suggest that erlotinib is useful for preventing AKI in patients receiving chemotherapy including CP.

FR-PO092

Truncated Dnase I Acts as Dominant-Negative Inhibiting Kidney Cell Death Induced by Cisplatin

Alexei G. Basnakian,1 Dmitry D. Zhidano,2 Tariq Fahmy,1 Alena Savenka. 1Pharmacology and Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR; 2Central Arkansas Veterans Healthcare System, John L. McClellan Memorial Veterans Hospital, Little Rock, AR.

Background: DNA fragmentation, generally regarded as the hallmark biochemical event of apoptosis, is the attribute and important mechanistic step in many cell death modes that occurs in vivo and in vitro models of kidney injury. DNA fragmentation induced by cisplatin toxicity to the kidney was shown to be mediated by deoxyribonuclease I (DNase I). The latter, however, was later shown to induce alternative splicing of DNase I. The current study was aimed to determine the role of the alternatively-spliced truncated DNase I, delta4DNase I, generated by EndoG.

Methods: Real time RT-PCR, western blot, TUNEL assay, Annexin and flow cytometry.

Results: Our study demonstrated that cisplatin intoxication induced delta4DNase I in mouse kidneys. The DNase I isoform was shown to be expressed in many other mouse organs, and it was associated with low nuclear endonuclease activity. Reconstituent delta4DNase I completely lacked endonuclease activity, and its acto-binding activity was also strongly diminished. The expression of delta4DNase I decreased mRNA and protein expression of native Dnase I and other apoptotic endonucleases in rat kidney tubular epithelial NRK-52E cells. It also suppressed total DNA activity in the cells, and provided protection against cisplatin toxicity measured by TUNEL assay or Annexin V/PI assay followed by flow cytometry.

Conclusions: This study identified a new native mechanism of kidney tubular epithelial cell protection by DNase I inactivation, which potentially can be applied in future therapies of cisplatin-toxic acute kidney injury.
**FR-PO093**

Epoxyeicosatrienoic Acids Increase Intrarenal Reoxygenation and Prosurvival Signaling and Protect against Renal Ischemia/Reperfusion Injury

W. Sperling,1 M. Zwart,2 D. E. Plunkett,2 J. S. Parrott,3 J. D. M. Zeevi,1,2,4 S. Qi,3 J. D. Bevan,1,2

Conclusions: Our data suggest that renal protection of STC1 is facilitated by a combination of increased AMPK activity and ROS inhibition, which together promote cell survival and recovery.

**FR-PO009**

The Injured Kidney Releases Factors into the Circulation That Cause Increased Mitochondrial Membrane Potential and Increased Antioxidant Gene Expression

J. H. Kim,1 S. M. Danner,2 A. S. Blevins,3 S. A. S. Kelleher,4 K. L. Schaper,3 C. T. Drummond,3 T. H. Lee,1 K. L. W. Shi,1,2,5 M. E. P. Coceani,1,2,6 J. E. D. Anderson,3 J. J. Simpson,2 J. D. Beswick,2,7,8 J. D. Bevan,1,2,4 and S. E. K. Allen1

Conclusions: Our data are the first to explain the mechanism of the involvement of PHDs in AKI and suggest that PHD inhibitors may have potential for the treatment of AKI.

**FR-PO096**

Oxygen-Sensing Prolylhydroxylase 1 (PHD1) in Acute Kidney Injury

S. M. Jin,1 K. L. Schaper,2 A. S. Blevins,3 J. J. Simpson,3 S. A. S. Kelleher,3 S. E. K. Allen1

Conclusions: Our findings provide evidence that STC1 is involved in AMPK activation and ROS reduction, which contribute to the survival and recovery of injured cells.

**FR-PO097**

Stanniocalcin-1 Inhibits Renal Ischemia/Reperfusion Injury via an AMPK-Dependent Pathway

C. T. Drummond,3 J. E. H. Lee,1 J. D. Beswick,2,7,8 J. D. Bevan,1,2,4 and S. E. K. Allen1

Conclusions: These findings suggest that STC1 protects against I/R injury by promoting AMPK activation and ROS reduction, which are essential for renal cell survival and recovery.

---

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

386A
Methods: We subjected wild-type (WT) and STC1 Tg mice to bilateral I/R kidney injury (clamping of renal pedicles for 30 min), concomitant with AMPK inhibition using compound C (CC; single injection at 20 mg/kg).

Results: Kidney baseline activity of AMPK correlated with the expression of stanniocalcins; with the highest activity in STC1 Tg, followed in decreasing order by WT and STC1 knockout (KO) and STC1/2 double KO. I/R in WT kidneys increased AMPK activity and expression of STC1, UC2P and sirtuin 3 (SIRT3) proteins. AMPK induction with CC before I/R abolished AMPK activation and diminished SIRT3 and UC2P expression without affecting STC1 protein expression. Moreover, the kidneys displayed increased production of superoxide and H₂O₂, and worse morphological changes. Pretreatment of STC1 Tg mice with CC restored susceptibility to I/R kidney injury characterized by: decreased creatinine clearance and urine output; morphological changes similar to those observed in WT kidneys after I/R; and increased ROS production. As observed in WT mice, AMPK inhibition in STC1 Tg mice attenuated UC2P and SIRT3 expression at baseline and after I/R.

Conclusions: These data suggest that: 1) STC1 is critical for AMPK activation in the kidney; and 2) STC1-induced protection from I/R kidney injury and expression of UC2P and SIRT3 are AMPK-dependent.

**Funding:** NIDDK Support, Other NIH Support - T32 Training Grant (DK082706), Private Foundation Support

**FR-PO098**
Development of Novel Nrf2 Activator to Treat Acute and Chronic Kidney Disease Sanjeev Noel,1 Sanath Bandapalle,1 Rajesh Thimmulappa,2 Shyam Biswal,2 Hamid Rabhi,2 Dept of Medicine, Johns Hopkins Univ, Baltimore, MD, 1School of Public Health, Johns Hopkins Univ, Baltimore, MD.

Background: Oxidative stress induced by ischemia reperfusion (IR) participates in the development of AKI and its progression to CKD. Treatment with Nrf2 is critical for the induction of antioxidant response during ischemic injury and therefore an attractive therapeutic target for pharmacological augmentation of antioxidant response in kidney diseases. Novel Nrf2 activators such as Trifluoromethyl 2’methoxychalcone (TMC) are needed to protect from IR and to prevent the lipid binding interface. We demonstrate that phosphorylation at a predicted protein kinase A (PKA) phosphorylation site dramatically internalizes the basolateral membrane-localized isolated PLAT domain and full length PC1 in kidney epithelial cell lines. Phosphorylation here abolishes the ability of PLAT to bind to PI4P, as predicted from the structure.

**Methods:** Based on these results, we propose a model for the function of PLAT, in which PLAT binds to specific membrane lipids, in a calcium- and PKA-dependent manner; binding controls the orientation of PLAT and thus the way in which it interacts with partner proteins. These interactions appear to be critical for the localization and function of PKD1 and downstream effectors.

**Funding:** Private Foundation Support

FR-PO1001
Cleavage of PC1 Is Dependent on the Unfolded Protein Response (UPR) Effector Xbp1 Sorin V. Fedele1, Seung H. Lee,1 Rachel Gallagher,1 Ann-Iwhee Lee,2 Stefan Somlo,1 1Internal Medicine, Yale School of Medicine, New Haven, CT; 2Lab. and Exp. Medicine, Well Cornell, New York, NY.

Background: The unfolded protein response is a cellular mechanism that is activated when unfolded proteins accumulate in the ER, with Xbp1 being its most conserved effector. Activation of Xbp1 translocates to the nucleus and activates transcription of chaperones and proteins involved in ER-associated degradation. (ASN, 2011 TH-OR125) we have shown that Sce63, one of the ADPLD genes, and Xbp1 interact genetically in a polycystin-1 (PC1) dependent manner. In the current work we investigated the molecular underpinnings of the Sce63-/-;Xbp1-/-PC1 interaction.

**Methods:** We examined processing of PC1 in kidney tubule cell lines isolated from mice carrying the ImmortoMouse and Pkd1fl/fl;Bac transgenes in addition to inactivating mutations in Sce63 alone (SKO) or in Sce63 and Xbp1 together (DKO). We also analyzed kidney tissues from Pkd1fl/fl;Bac SKO (Sce63+/+;KapCre) and DKO (Sce63fl/fl;Xbp1fli/fl;KapCre) mice.

Results: Full length PC1 (PC1-FL) is cleaved at the GPS to yield the extracellular domain from the region linking the N-terminal and C-terminal domains. The levels of PC1-CTF were reduced in SKO-Pkd1fl/fl;Bac cells while they were almost completely absent in DKO cells where a concomitant increase in PC1-FL was observed, suggestive of a defect in GPS cleavage. Lysates from DKO-Pkd1fl/fl;Bac mice exhibited further reduction in PC1-CTF beyond that seen in SKO-Pkd1fl/fl;Bac kidneys. Re-expression of Sce63 in the DKO cells completely restored PC1-CTF while overexpression of Xbp1 partially restored PC1-GPS cleavage in a dose dependent manner. Thus, activated Xbp1 can compensate for Sce63 deficiency to promote PC1-GPS cleavage. Xbp1 overexpression can also restore PC1 processing in Prkcsh –/–;Pkd1F/H-BAC cells. Finally, the ER chaperone Erdj4, a Xbp1 transcriptional target, modestly increased PC1-CTF levels in DKO cells.

Conclusions: The most conserved effector of the UPR response, XBP1, can modulate the cleavage of PC1 and this may represent a potential therapeutic avenue for PC1-misense mutant backgrounds.

**Funding:** NIDDK Support

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

Underline represents presenting author/disclosure.

**FR-PO100**
Structure and Function of the Polycystin-1 PLAT Domain Xiaojun Xu,1 Andrew J. Streets,2 Peter J. Arntymik,3 Mike P. Williamson,2 Albert C. Orig3 1Academic Nephrology Unit, Univ of Sheffield, Sheffield, United Kingdom; 2MBB, Univ of Sheffield, Sheffield, United Kingdom.

Background: The PLAT (named after Polycystin-1, Lipoxgenase and Alpha Toxin) or L12 (Lipoxgenase Homology 2) domain is located in the 1st intracellular loop of polycystin-1, the protein product of PKD1, the gene mutated in 90% of Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients. This signature domain is found in all PKC paralogues and shows evolutionary conservation in orthologues down to nematodes. PLAT has been predicted to be a lipid-binding domain based on homology to the lipoxigenases although little has been reported about its structure or function.

**Methods:** Nuclear Magnetic Resonance (NMR) studies of the polycystin-1 PLAT domain have resulted in assignment of 90% of its amino acid residues, which has allowed us to calculate a model of its structure. PLAT adopts a beta-sandwich fold composed of two four-stranded beta sheets, and is thus similar in structure to homologous domains in lipoxigenases.

Results: Lipid blot assays show that PLAT binds selectively to certain phospholipids, in particular to the phosphatidylyserine (PS) and phosphatidylglycerol (PG) lipids. Using NMR, we have shown that these lipids have adjacent but different binding sites. We have also identified the binding site for calcium, and demonstrated that binding to PS is calcium dependent. In addition, we have identified a protein/protein interaction site, which is on the opposite face to the lipid binding interface. We have demonstrated that phosphorylation at a predicted protein kinase A (PKA) phosphorylation site dramatically internalizes the basolateral membrane-localized isolated PLAT domain and full length PC1 in kidney epithelial cell lines. Phosphorylation here abolishes the ability of PLAT to bind to PI4P, as predicted from the structure.

Conclusions: Based on these results, we propose a model for the function of PLAT, in which PLAT binds to specific membrane lipids, in a calcium- and PKA-dependent manner; binding controls the orientation of PLAT and thus the way in which it interacts with partner proteins. These interactions appear to be critical for the localization and function of PKD1 and downstream effectors.

**Funding:** Private Foundation Support

**Basic and Animal Studies of PKD**

**Poster/Friday**
Functional Role of GPS Cleavage for Polycystin1 Biogenesis and Trafficking

FR-PO102

Function of GPS cleavage for polycystin1 biogenesis and trafficking was studied. We previously showed that the cleavage (Pc1U) in postnatal developing kidneys and other tissues: (1) heterodimeric Pc1cFL in which generates a previously unrecognized complexity of endogenous Pc1 products. Two distinct polycystin-1 (PC1). PC1 is regulated in part by post-translational modifications by formation of renal cysts and caused mainly by mutations in PKD1, which encode regulators of STAT3 signaling in the kidney and the pathogenesis of ADPKD. STAT3. Whether PKC-zeta activates or represses STAT3 signaling depends on the state of PKC-zeta binds and phosphorylates the PC1 tail and regulates its activation of STAT3. We found that atypical PKC (PKC-zeta) interacts with the cytoplasmic tail of PC1 and regulates its activation of STAT3. This mechanism is consistent with previous reports demonstrating that PKC-zeta interacts with PC1 and regulates its activation of STAT3. Our results demonstrate that two distinct profiles of PKD1 deficiency lead to heart dysfunction and fibrosis in mice. The absence of SAH in HT mice suggests the development of a primary cardiomyopathy associated with decreased polycystin-1 activity. Our findings suggest, on the other hand, that CY mice develop a cardiomyopathy based on two components: primary PKD1 deficiency and cardiac damage secondary to SAH. Our data provide significant insights into human ADPKD heart disease and prove useful for future investigations.

Poster/Friday

Different Patterns of Pkd1 Deficiency Lead to Heart Dysfunction and Fibrosis in Mice

FR-PO105

Methods: We used MDCK cells that were stably transfected with an expression system where expression of full length PC1 or PC1-R4227X mutant can be induced by tetracycline. From these cells, we found that inhibition of the aggresome degradation pathway with tubacin, a specific HDAC6 inhibitor, led to an up-regulation of PC2 expression when PC1 was overexpressed. Importantly, tubacin had no effect on PC1 expression. In addition we found that HDAC6 does interact with PC2 in control MDCK cells where PC1 expression has been knocked down. Over-expression of PC1 not only decreased expression of PC2, but also greatly reduced the interaction of HDAC6 and PC2. On the other hand, PC1 does not interact with HDAC6, suggesting that PC1 accelerates the aggresomal degradation of PC2 via a second messenger that requires the presence of the C-terminal tail of PC1. Consistent with these findings, we observed that overexpression of the PC1-R4227X mutant, which lacks the last 76 amino acids, did not decrease PC2 expression, nor did it decrease the interaction between PC2 and HDAC6.

Conclusions: We have now uncovered a new pathway that explains how PC1 regulates PC2 expression via the aggresome degradation pathway.

Funding: NIDDK Support, Private Foundation Support

Poster/Friday

Polycystin-1 Accelerates Degradation of Polycystin-2 via the Aggresome Pathway

FR-PO104

Background: Autosomal dominant polycystic kidney disease is characterized by formation of renal cysts and caused mainly by mutations in PKD1, which encode polycystin-1 (PC1). PC1 is regulated in part by post-translational modifications by formation of renal cysts and caused mainly by mutations in PKD1, which encode regulators of STAT3 signaling in the kidney and the pathogenesis of ADPKD. STAT3. Whether PKC-zeta activates or represses STAT3 signaling depends on the state of STAT3. These data demonstrate a novel interaction between PKC-zeta, p62/SQSTM1, and PC1. PKC-zeta decreases the interaction between PC1 and PKC-zeta is enhanced by expression of the scaffold protein p62/SQSTM1, which was also found to bind the PC1 tail. PKC-zeta binds and phosphorylates the PC1 tail and regulates its activation of STAT3.

Methods: Cardiac and renal phenotypes were analyzed in two Pkd1-deficiency mouse models: 10-13-wk-old noncystic Pkd1+/+(HT) and its wild-type controls (WT); and 20-23-wk-old cystic Pkd1/+/−(Nestin+/−(CY) and its noncystic controls (Pkd1+/+/−(NC)). Heart function and kidney cystic index (CI) were evaluated by high-resolution ultrasound. Expression of PC1. We identiﬁed the molecular composition of endogenous PC1 resulting from GPS cleavage by various biochemical strategies. We show that GPS cleavage generates a previously unrecognized complexity of endogenous PC1 products. Two distinct forms of cleaved PC1 molecules are produced along with a small amount of uncleaved PC1 (Pc1U) in postnatal developing kidneys and other tissues: (1) heterodimeric Pc1cFL in which NTF is non-covalently associated with CTF. We show that proper Pc1cFL trafficking requires intact CTF and propose a model in which Pc1U is derived from Pc1cFL.

Conclusions: Our data demonstrate that GPS cleavage is a critical regulator of PC1 biogenesis and trafficking plays a crucial role in PC1 trafficking for all PC1 products. This study thus provides new insights into the complex biogenesis and trafficking of functional proteins in a cell type- and stage-dependent manner.

Funding: NIDDK Support

Poster/Friday

PKC-Zeta Phosphorylates Polycystin-1 and Modulates Its Regulation of STAT3 Activity

FR-PO103

We found that inhibition of the aggresome degradation pathway with tubacin, a specific HDAC6 inhibitor, led to an up-regulation of PC2 expression when PC1 was overexpressed. Importantly, tubacin had no effect on PC1 expression. In addition we found that HDAC6 does interact with PC2 in control MDCK cells where PC1 expression has been knocked down. Over-expression of PC1 not only decreased expression of PC2, but also greatly reduced the interaction of HDAC6 and PC2. On the other hand, PC1 does not interact with HDAC6, suggesting that PC1 accelerates the aggresomal degradation of PC2 via a second messenger that requires the presence of the C-terminal tail of PC1. Consistent with these findings, we observed that overexpression of the PC1-R4227X mutant, which lacks the last 76 amino acids, did not decrease PC2 expression, nor did it decrease the interaction between PC2 and HDAC6.

Conclusions: We have now uncovered a new pathway that explains how PC1 regulates PC2 expression via the aggresome degradation pathway.

Funding: NIDDK Support, Private Foundation Support

Poster/Friday

Over-Expression of the Polycystin 1 C-Terminal Tail Leads to Disappearance of Acetylated α-Tubulin

FR-PO106

Methods: We used MDCK cells that were stably transfected with an expression system where expression of full length PC1 or PC1-R4227X mutant can be induced by tetracycline. From these cells, we found that inhibition of the aggresome degradation pathway with tubacin, a specific HDAC6 inhibitor, led to an up-regulation of PC2 expression when PC1 was overexpressed. Importantly, tubacin had no effect on PC1 expression. In addition we found that HDAC6 does interact with PC2 in control MDCK cells where PC1 expression has been knocked down. Over-expression of PC1 not only decreased expression of PC2, but also greatly reduced the interaction of HDAC6 and PC2. On the other hand, PC1 does not interact with HDAC6, suggesting that PC1 accelerates the aggresomal degradation of PC2 via a second messenger that requires the presence of the C-terminal tail of PC1. Consistent with these findings, we observed that overexpression of the PC1-R4227X mutant, which lacks the last 76 amino acids, did not decrease PC2 expression, nor did it decrease the interaction between PC2 and HDAC6.

Conclusions: We have now uncovered a new pathway that explains how PC1 regulates PC2 expression via the aggresome degradation pathway.

Funding: NIDDK Support, Private Foundation Support

Poster/Friday

Different Patterns of Pkd1 Deficiency Lead to Heart Dysfunction and Fibrosis in Mice

Bruno E. Balbo, Andressa Godoy Amaral, Jonathan Mackowiak Fonseca, Vera Mc Salem, Luiz F. Onuchic. Nephrology, Univ of Sao Paulo, Brazil.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a systemic disorder associated with cardiovascular manifestations, including hypertension (SAH) and ventricular hypertrophy. Although fibrosis impacts on kidney disease progression, its role in ADPKD cardiac phenotype remains uncertain.

Methods: Cardiac and renal phenotypes were analyzed in two Pkd1-deficiency mouse models: 10-13-wk-old noncystic Pkd1+/+(HT) and its wild-type controls (WT); and 20-23-wk-old cystic Pkd1+/−(Nestin+/−(CY) and its noncystic controls (Pkd1+/+/−(NC)). Heart function and kidney cystic index (CI) were evaluated by high-resolution ultrasound. Expression of PC1. We identiﬁed the molecular composition of endogenous PC1 resulting from GPS cleavage by various biochemical strategies. We show that GPS cleavage generates a previously unrecognized complexity of endogenous PC1 products. Two distinct forms of cleaved PC1 molecules are produced along with a small amount of uncleaved PC1 (Pc1U) in postnatal developing kidneys and other tissues: (1) heterodimeric Pc1cFL in which NTF is non-covalently associated with CTF. We show that proper Pc1cFL trafficking requires intact CTF and propose a model in which Pc1U is derived from Pc1cFL.

Conclusions: Our data demonstrate that GPS cleavage is a critical regulator of PC1 biogenesis and trafficking plays a crucial role in PC1 trafficking for all PC1 products. This study thus provides new insights into the complex biogenesis and trafficking of functional proteins in a cell type- and stage-dependent manner.

Funding: NIDDK Support

Poster/Friday

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder that presents with renal cysts. Mutations in PKD1 or PKD2 genes lead to ADPKD, which results in polycystin-1 (PC1) and polycystin-2 (PC2) gene expression in primary renal cysts of PKD1 and PKD2 respectively. Up-regulation or down-regulation PC1 or PC2 leads to polycystic kidney disease in mice suggesting that polycystins must be regulated within a functional window to avoid cyst formation. We have shown previously that PC1 regulates PC2 expression (un-published data). Here we further investigated the regulation of the PC2 degradation pathway by PC1. Misfolded and unfolded proteins are refolded by chaperones.

Results: Proteins that cannot be refolded usually end up degraded by proteasomes. Proteins that are not degraded by proteasomes precipitate as aggresomelike aggregates and are transported by Histone deacetylase 6 (HDAC6) towards the aggresome for degradation.

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

Underline represents presenting author/descriptor.
**FR-PO107**

**Polycystin-1 Regulates Actin Cytoskeleton Organization and Directional Cell Migration through a Novel PC1-Pacsin 2-N-Wasp Complex**

Gang Yao,1 Vy Nguyen,2 Kristina A. Roberts,1 Ayumi Takakura,1 Markus Plomann,1 Jing Zhou,1 Han Xiao,3* Harvard Center for Polycystic Kidney Disease Research, Brigham and Women’s Hospital, Boston, MA; 3Center for Biochemistry, Univ of Cologne, Cologne, Germany.

**Background:** Formation of a tubule with defined length and lumen diameter is a fundamental step for epithelial and endothelial cells to make many vital organs. Autosomal dominant polycystic kidney disease (ADPKD), the most common life-threatening monogenic disorder that manifests itself in cyst formation in multiple epithelial organs, is the result of the loss of control of tubule lumen size. One of the prerequisites for proper tubulogenesis in vitro and in vivo is directional cell migration.

**Methods:** In this study, we utilized yeast two-hybrid screens, biochemistry, cell biology, and live cell imaging to discover proteins that interacts with ADPKD protein polycystin-1 (PC1) and to study the consequence of the identified interaction.

**Results:** Yeast two-hybrid screens using the C-terminus of PC1 as bait, identified Pacsin 2, a cytoplasmic phosphoprotein that has been implicated in cytoskeletal organization, vesicle trafficking, cell intercalation during gastrulation, and more recently in kidney tubule development, and repair of ischemia-reperfusion injured kidneys. PC1 C-tail binds to a 107-residue fragment containing the a 3 helix of the F-BAR domain of Pacsin 2. Pacsin 2 expression and localization are altered in Pkd1 mutant kidneys. Kidney epithelial cells deficient in either PC1 or Pacsin 2 migrate at a slower speed with reduced directional persistency, and exhibit defects in lamellipodium formation and tubulogenesis in 3-dimensional (3D) collagen gels. We further demonstrate that PC1, Pacsin 2, and N-Wasp are in the same protein complex, and both PC1 and Pacsin 2 are required for N-Wasp/Arp2/3-dependent actin remodeling.

**Conclusions:** Our study suggests that PC1 modulates actin cytoskeleton rearrangements and directional cell migration during tubule development and regeneration through the Pacsin 2-N-Wasp complex, which consequently contributes to the establishment and maintenance of the sophisticated tubular architecture.

**Funding:** NIDDK Support, Other NIH Support - DK51050, DK40703, and P50DK074030

**FR-PO108**

**Polycystin Signaling Is Required for Lymphatic Development**

Patricia Outeda Garcia,1 Gregory G. Germirli,2 Terry J. Watnick,1 1Dept of Medicine, Div of Nephrology, Univ of Maryland, School of Medicine, Baltimore, MD; 2National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD.

**Background:** Edema is a universal feature of all Pkd1 and Pkd2 targeted alleles reported in the literature to date and has been variably attributed to vascular fragility and/or cardiac defects. Since the lymphatic system plays a critical role in tissue fluid homeostasis, we speculated that a defect in the lymphatic vasculature might contribute to edema in Pkd1 mutant embryos.

**Results:** We harvested E14.5 Pkd1 embryos and controls (WT) and performed whole mount staining of dorsal skin with the lymphatic endothelial cell (LEC) marker, Lyve1. We found that both Pkd1+/- and Pkd2+/- mice exhibited a more dilated and disorganized lymphatic network with decreased branching. Next, we focused on an earlier stage of lymphatic development and stained sections from the jugular area of E11.5 embryos and the LEC marker, Prox1. At this stage Prox1 positive LECs were budding from the dorsolateral aspect of the cardinal vein in both mutant and wild type embryos. In wild type embryos LECs were found in a narrow, restricted dorsolateral area. In contrast, in Pkd1+/- embryos the distribution of Prox1 positive cells appeared to be more random. We found that the area of distribution of Prox1 positive cells in the dorsolateral aspect of the cardinal vein was significantly increased in Pkd2+/- embryos, suggesting an abnormality in polarized cell migration. We used a cell culture system to show that both Pkd1 and Pkd2 depleted, lymphatic cells have an intrinsic defect in directed migration that may contribute to the edema phenotype.

**Conclusions:** Our work establishes a role for polycystins in lymphatic development and identifies a new signaling pathway that is involved in lymphangiogenesis.

**Funding:** NIDDK Support, Other NIH Support - DK51050, P01DK095036, P30 DK090868

**FR-PO109**

**The Role of Phosphorylation in Polycystin-2 Trafficking and Channel Activity**

Yuijung Cai,1 Yiana Y. Kuo,2 Hongzhi Quan,1 Kathryn Stone,3 Ke Dong,1 Xin Tian,1 Ming Ma,1 Seung H. Lee,1 Tran Chen,1 Barbara E. Ehrlich,2 Stefano Somlo.1 1Internal Medicine, Yale Univ School of Medicine, New Haven, CT; 2Pharmacology, Yale Univ, New Haven, CT; 3WM Keck Biotechnology Resource Laboratory, Yale Univ, New Haven, CT.

**Background:** Loss of polycystin-2 (PC2), a cation channel, results in autosomal dominant polycystic kidney disease (ADPKD). PC2 has been localized to cilia and is abundantly expressed in the endoplasmic reticulum (ER). Our previous studies have shown that PC2 is constitutively phosphorylated at residue Ser812 and that loss of phosphorylation at Ser812 results in a 10-fold decrease in sensitivity to Ca2+ activation of PC2 but has no effect on PC2 localization at the ciliary membrane (Cai et al, 2004).

**Methods:** We identified additional phosphorylation sites in PC2 by phosphoproteomic analysis of TiO2 enriched immunoprecipitated PC2 prepared from either cultured epithelial cells stably overexpressing PC2 or from native mouse kidney tissues. Cultured renal epithelial cells stably overexpressing the PKD2 C-terminus with combinations of the mutations in both isoforms of phosphorylation sites(s) were examined for PC2 function. The functional assays examined the effects of PC2 phosphorylation on: 1) the association of PC2 with PC1 or with itself; 2) PC2 ciliary trafficking; 3) stabilization of PC1-CTF by PC2; and 4) cellular Ca2+ transient activity of PC2.

**Conclusions:** Phosphorylation of PC2 plays a role in regulation of PC2 channel activity and trafficking to cilia. Understanding the molecular basis for the regulation of PC2 phosphorylation may enhance understanding the mechanism of cyst growth in ADPKD.

**Funding:** NIDDK Support

**FR-PO110**

**Sorting Nexin 3 Regulates the Trafficking and Surface Localization of Polycystin-2**

Shuang Feng, Andrew J. Streets, Albert C. Ong. Academic Nephrology Unit, Univ of Sheffield, Sheffield, United Kingdom.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD), is caused by mutations in PKD1 (85%) or PKD2 (15%). Although the ADPKD proteins, polycystin-1 (PC1) and polycystin-2 (PC2) have been shown to form a receptor-ion channel complex, the surface expression of PC2 appears to be regulated by protein phosphorylation and interaction with key adaptor proteins.

**Methods:** To identify additional regulators of PC2 sorting and trafficking, we conducted a yeast-2-hybrid (Y2H) screen using the PC2 C-terminal domain as bait. Here, we report a functional interaction between PC2 and two isoforms of sorting nexin 3 (SNX3). The SNXs are a family of proteins first identified in yeast which share a Phox (PX) domain with affinity for PtdIns(3)P and which regulate endosomal sorting. In mammals, 30 SNXs have been identified. The retromer complex comprises two subcomplexes: a trimer (Vps26b-29-35) which functions as a cargo-selective adaptor and a membrane delensing adapter (consisting of a sorting nexin (SNX) heterodimer). In mammals, there are two distinct mammalian retromer complexes distinguished by either a SNX-BAR homodimer or by monomeric SNX3.

**Results:** We identified a new SNX3 isoform (102aa, isoform 5) as a new binding partner to the C-terminus of PC2 at a site distinct from the classical SNX3 isoform (162aa, isoform 1). In-vitro binding studies confirmed that this interaction was direct. Unexpectedly, we found that SNX3-162 could also bind to PC2 indirectly via the retromer complex; PC2 binds to VPS35 directly via its N-terminal domain. The localization of PC2 was distinct within SNX3+/-102 examined in blasticulae vesicles where it binds to AP2 whereas SNX3-162 is expressed in early endosomes where the retromer complex is expressed. Knockdown of both SNX3 isoforms in polarized kidney cells resulted in a two fold increase in surface PC2 expression by biotinylation.

**Conclusions:** Our results reveal for the first time that PC2 internalisation and recycling is regulated by a new SNX3 isoform as well as a SNX3-retromer complex. Since SNX3 expression can be modulated by different drugs, this could represent a potential new target for patients with ADPKD.

**Funding:** Private Foundation Support

**FR-PO111**

**Deletion Mutant of Pkd1 and Pkd2 Gene Cause Cyst Formation in Transgenic Mice**

Yasunobu Ishikawa,1 Saori Nishio,2 Tomotsune Miyamoto,2 Seikyui Shibazaki,1 Hitoshi Hashimoto,2 Yuko Wakamatsu,2 Tatsuya Asumi.1 1Medicine II, Hokkaido Univ, Sapporo, Hokkaido, Japan; 2Bioscience and Biotechnology Center, Nagoya Univ, Nagoya, Aichi, Japan.

**Background:** Autosomal dominant polycystic kidney disease is the most common monogenic disorder resulting in cystic kidneys and liver. Several genetic mechanisms probably contribute to the phenotypic expression of the disease. A two-hit mechanism has been proposed to explain how cysts develop. However, the dominant pattern of inheritance would argue for a gain of function, haploinsufficiency, or a dominant negative mechanism.

We established four different transgenic medaka models to investigate whether a dominant negative mechanism may cause cyst formation.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Methods: We cloned the medaka Pkd1 and Pkd2 genes by homolog search. Next we generated 4 transgenic medaka models named as Pkd1 EF1α, Pkd2 EF1α, Pkd1 Tet-On and Pkd2 Tet-On that expresses translation elongation factor 1 subunit alpha (EF1α) promoter linked to deleted exons 6-27 in Pkd1 or exons 12-15 in Pkd2 respectively. In lines Pkd1 Tet-On and Pkd2 Tet-On, we used the Tet-On system that induces gene expression upon doxycycline (DOX) administration. We carried out a series of analyses including gene expression by real time PCR, histology, cell proliferation and apoptosis in Medaka at specific time points of 1, 2, 3, 4 and 5 months of age.

Results: Pkd1 gene expression in the Pkd1 transgenic medaka ranged from 2- to 5-fold increase relative to Pkd1 endogenous levels from control medaka arbitrarily set at 1. Pkd2 expression levels in Pkd2 transgenic medaka ranged from 3- to 50-fold relative to Pkd2 endogenous levels from control medaka arbitrarily set at 1. All four models developed kidney cysts, however both Pkd1 EF1α and Pkd1 Tet-On showed very small and fewer cysts compared with Pkd2 EF1α and Pkd2 Tet-On. Proliferating Cell Nuclear Antigen positive cells increased in cyst lining cells of all models. But the overall number of apoptotic nuclei seen in low power fields in cystic kidneys was very low and did not differ significantly among all models.

Conclusions: Overexpression of Pkd1 and Pkd2 deletion mutants in medaka results in cyst formation via a dominant negative mechanism.

FR-PO112
Biochemical Analysis of the ADPKD PKD2-D511V Patient Mutation Alexis Hoffer,
Michael Kottgen.
Div of Nephrology and General Medicine, Univ Medical Centre Freiburg, Freiburg im Breisgau, Baden-Württemberg, Germany.
Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited mendelian disorder in humans. Mutations in the PKD2 gene account for approximately one out of four cases. PKD2 encodes the transient receptor channel polycystin-2 (TRPP2), a non-selective Ca2+-permeable cation channel. There are multiple types of mutations causing ADPKD. The Mayo ADPKD Mutation Database lists a total of 2959 different mutations in PKD2, including 77 frame-shift, 42 non-sense and 37 splice mutations as well as 26 substitutions. However, rather little experimental data investigating the disease mechanism of these mutations is available.

Methods: Here we analyze the biochemical properties of the pathogenic missense variant PKD2-D511V, which has been previously characterized as a channel-dead mutant. Cellular expression systems and a Drosophila melanogaster PKD2 knock-out model are used for in vitro and in vivo studies, respectively.

Results: The D511V mutation causes significantly reduced (85.2%) TRPP2 expression levels compared to wild-type protein in heterologous expression systems. The mutant protein used for variant as well as 26 substitutions. However, rather little experimental data investigating the disease pathogenesis. The mutant protein used for in vitro and in vivo studies, respectively.

Results: The D511V mutation causes significantly reduced (85.2%) TRPP2 expression levels compared to wild-type protein in heterologous expression systems. The mutant protein used for variant as well as 26 substitutions. However, rather little experimental data investigating the disease mechanism of these mutations is available.

Methods: Here we analyze the biochemical properties of the pathogenic missense variant PKD2-D511V, which has been previously characterized as a channel-dead mutant. Cellular expression systems and a Drosophila melanogaster PKD2 knock-out model are used for in vitro and in vivo studies, respectively.

Results: The D511V mutation causes significantly reduced (85.2%) TRPP2 expression levels compared to wild-type protein in heterologous expression systems. The mutant protein used for variant as well as 26 substitutions. However, rather little experimental data investigating the disease mechanism of these mutations is available.

Methods: Here we analyze the biochemical properties of the pathogenic missense variant PKD2-D511V, which has been previously characterized as a channel-dead mutant. Cellular expression systems and a Drosophila melanogaster PKD2 knock-out model are used for in vitro and in vivo studies, respectively.

Results: The D511V mutation causes significantly reduced (85.2%) TRPP2 expression levels compared to wild-type protein in heterologous expression systems. The mutant protein used for variant as well as 26 substitutions. However, rather little experimental data investigating the disease mechanism of these mutations is available.

Methods: Here we analyze the biochemical properties of the pathogenic missense variant PKD2-D511V, which has been previously characterized as a channel-dead mutant. Cellular expression systems and a Drosophila melanogaster PKD2 knock-out model are used for in vitro and in vivo studies, respectively.

Results: The D511V mutation causes significantly reduced (85.2%) TRPP2 expression levels compared to wild-type protein in heterologous expression systems. The mutant protein used for variant as well as 26 substitutions. However, rather little experimental data investigating the disease mechanism of these mutations is available.

Methods: Here we analyze the biochemical properties of the pathogenic missense variant PKD2-D511V, which has been previously characterized as a channel-dead mutant. Cellular expression systems and a Drosophila melanogaster PKD2 knock-out model are used for in vitro and in vivo studies, respectively.

Results: The D511V mutation causes significantly reduced (85.2%) TRPP2 expression levels compared to wild-type protein in heterologous expression systems. The mutant protein used for variant as well as 26 substitutions. However, rather little experimental data investigating the disease mechanism of these mutations is available.

Methods: Here we analyze the biochemical properties of the pathogenic missense variant PKD2-D511V, which has been previously characterized as a channel-dead mutant. Cellular expression systems and a Drosophila melanogaster PKD2 knock-out model are used for in vitro and in vivo studies, respectively.

Results: The D511V mutation causes significantly reduced (85.2%) TRPP2 expression levels compared to wild-type protein in heterologous expression systems. The mutant protein used for variant as well as 26 substitutions. However, rather little experimental data investigating the disease mechanism of these mutations is available.

Methods: Here we analyze the biochemical properties of the pathogenic missense variant PKD2-D511V, which has been previously characterized as a channel-dead mutant. Cellular expression systems and a Drosophila melanogaster PKD2 knock-out model are used for in vitro and in vivo studies, respectively.

Results: The D511V mutation causes significantly reduced (85.2%) TRPP2 expression levels compared to wild-type protein in heterologous expression systems. The mutant protein used for variant as well as 26 substitutions. However, rather little experimental data investigating the disease mechanism of these mutations is available.

Methods: Here we analyze the biochemical properties of the pathogenic missense variant PKD2-D511V, which has been previously characterized as a channel-dead mutant. Cellular expression systems and a Drosophila melanogaster PKD2 knock-out model are used for in vitro and in vivo studies, respectively.

Results: The D511V mutation causes significantly reduced (85.2%) TRPP2 expression levels compared to wild-type protein in heterologous expression systems. The mutant protein used for variant as well as 26 substitutions. However, rather little experimental data investigating the disease mechanism of these mutations is available.
FR-PO116

Ciliary Defects in Induced Pluripotent Stem Cells from Patients with Polycystic Kidney Disease and Ciliopathies

Benjamin S. Freedman, Albert Q. Lam,1 Jamie L. Sundsbak,1 Rossella Iatrino,1,2 Xuexing Su,1 Sara J. Koon,3 Maqing Wu,1 Peter C. Harris,3 Jing Zhou,1,2 Joseph V. Bonventre,1,2

Background: Induced pluripotent stem cells (iPSCs) are a powerful new technology for investigating human disease in diverse cell types. We tested the potential of iPSCs to reveal ciliary defects specific to polycystic kidney disease (PKD) or related ciliopathies.

Methods: Fibroblasts from patients with autosomal dominant (ADPKD) and autosomal recessive (ARPKD) polycystic kidney disease (PKD) and related ciliopathies Bardet-Biedl Syndrome (BBS) and Meckel Syndrome (MKS), were retrovirally reprogrammed into iPSCs, sequenced for mutations, and compared to cells from healthy patients for PKD-related defects.

Results: PKD iPSCs elaborated primary cilium and expressed endogenous polycystin-1 (PC1), polycystin-2 (PC2), and fibrocytin/pydactin at levels similar to healthy controls. However, in ADPKD iPSCs or derived somatic epithelial cells, PC2 was detectable in cilia at only 25-50% of the frequency seen in ARPKD and healthy control lines. Unique PKD1 heterozygous mutations were identified in fibroblasts from all three ADPKD patients, and iPSCs from two of these. A possible “second hit” was found at the mutation site in iPSC lines from one patient. Overexpression of wild-type PC1, but not a carboxy-terminal truncation mutant, increased endogenous ciliary PC2–3-fold in ADPKD iPSC-derived hepatoblasts or cultured mouse kidney cells. Neither BBS nor MKS iPSCs exhibited reduced ciliary PC2.

Conclusions: iPSCs can be a powerful tool for investigating human disease in diverse cell types. We tested the potential of iPSCs to reveal ciliary defects specific to polycystic kidney disease (PKD) or related ciliopathies.

Funding: FUND SD, National Institutes of Health (R01DK107483-04)

FR-PO117

Fluid Shear Stress (FSS)-Mediated mTORC1 Regulation Is Aberrant in Cystic Epithelial Cells

Robin L. Mayer,1 Darren P. Wallace,1 Xiangyi Lu,1 Kidney Inst, Univ of Kansas Med Ctr, Kansas City, KS; 1Inst of Environmental Health Sciences, Wayne State Univ, Detroit, MI.

Background: Mammalian target of rapamycin complex 1 (mTORC1) is a major regulator of cell growth, division and metabolism. In autosomal dominant polycystic kidney disease (ADPKD), mTORC1 activity is increased and is thought to play a role in disease pathogenesis, but the underlying mechanism(s) is completely understood. For example, FSS has been shown to modulate mTORC1 by a primary ciliary-dependent, but polycystin-2/calcium-independent mechanism, while polycystin-1 can inhibit mTORC1 via a polycystin-2/calcium-independent mechanism. However, co-regulation of mTORC1 by both polycystin 1 and 2 and FSS is not well understood.

Methods: Mouse inner medullary (IMCD3) and cortical (M1) collecting duct cell lines, cultured mouse kidney cells, human ADPKD cells, IMCD3 and M1 cell lines, were examined in the presence or absence of FSS at frequencies of 10-100Hz. The effect of FSS on mTORC1 was determined by western blot analysis.

Results: Static conditions were set as 100% activity, and FSS frequencies of 0, 5, 10, 20, 50, and 100Hz were examined. FSS induced a dose-dependent decrease in mTORC1 activity for IMCD3 cells. In M1 cells, FSS induced a dose-dependent increase in mTORC1 activity.

Conclusions: These studies reveal a FSS-dependent pathway of mTORC1 regulation that is different in IMCD3 and M1 cells. The results suggest that FSS can have opposing effects on mTORC1 activity, depending on the cell type.

Funding: FUND SD, National Institutes of Health (R01DK107483-04)

FR-PO118

mTORC1 and 2 Signaling in Polycystic Kidney Disease

Iram Zafar,1 Zhibin He,1 Charles L. Edelstein,1 UC Denver; 1ISIS Pharmaceuticals.

Background: We have previously reported that Pkd2−/− mice, an orthologous model of human ADPKD involving mutation of the Pkd2 gene, show reduced cilia and periciliary PC2. A possible “second hit” was found at the mutation site in iPSC lines from two of these. A possible “second hit” was found at the mutation site in iPSC lines from two of these. A possible “second hit” was found at the mutation site in iPSC lines from two of these.

Methods: The effects of BIT-11 on phosphorylated AMPK (P-AMPK) and S6 kinase (P-S6K), a downstream target of mTOR, were determined by western blot analysis. To test the drug’s effect on Cl- transport, ADPKD monolayers were incubated in the absence and presence of BIT-11. The effect of BIT-11 on short circuit current. For FR-PO120

A Novel LBK-1 Activator Inhibits mTOR Signaling and Proliferation of Human ADPKD Cells

Gail Reif,1 Archana Raman, Bailee Lynn Slack, Cibele S. Pinto, Bhaskar Chandras Das, Darren P. Wallace. Kidney Institute, Kansas Univ Medical Center, Kansas City, KS.

Background: In autosomal dominant polycystic kidney disease (ADPKD), elevated mTOR activity contributes to the aberrant proliferation of ciliated epithelial cells. Stimulation of AMP-activated protein kinase (AMPK), an energy sensor that regulates mTOR activity contributes to the aberrant proliferation of cyst-lining epithelial cells. 

Methods: A novel LBK-1 activator inhibitor of mTOR signaling and proliferation of human ADPKD cells was designed and synthesized. The effects of BIT-11 on phosphorylated AMPK (P-AMPK) and S6 kinase (P-S6K), a downstream target of mTOR, were determined by western blot analysis. To test the drug’s effect on Cl- transport, ADPKD monolayers were incubated in the absence and presence of BIT-11.

Conclusions: The LBK-1 activator inhibitor of mTOR signaling and proliferation of human ADPKD cells was designed and synthesized. The effects of BIT-11 on phosphorylated AMPK (P-AMPK) and S6 kinase (P-S6K), a downstream target of mTOR, were determined by western blot analysis. To test the drug’s effect on Cl- transport, ADPKD monolayers were incubated in the absence and presence of BIT-11.

Funding: FUND SD, National Institutes of Health (R01DK107483-04)
**Results:** BIT-11 caused a concentration-dependent increase in P-AMPK/AMPK levels in ADPKD cells. BIT-11 (1 μM) decreased P-S6K/S6 and the rate of ADPKD cell proliferation, consistent with inhibition of mTOR signaling. The drug also inhibited cAMP-induced anion secretion across ADPKD cell monolayers and significantly reduced in vitro cyst growth.

**Conclusions:** Activation of mTOR may be a therapeutic approach to reduce mTOR activity, cell proliferation and CT-dependent fluid secretion in ADPKD.

**Funding:** NIDDK Support

---

**FR-PO121**

**Evaluation of Selective Inhibitors of Nuclear Export for the Treatment of ADPKD**

**Robert H. Weiss,** 1 Hiromi Inoue Wettersten, 1 Matthew Tan, 1 Michael Kauffman. 2,7 **UC Davis; 2 Karyopharm.**

**Background:** Capitalizing on the recent excitement in the ADPKD field with the connection between cancer and PKD, we have extended our RCC therapeutic innovations to evaluate the role of pharmacologic inhibitors of nuclear export to cystic disease characterized by uncontrolled RTE cell proliferation. We previously showed that blockade of Exportin 1 (XPO1), also known as chromosome region maintenance protein 1 (CRM1), by a Selective Inhibitor of Nuclear Export (SINE), attenuates renal cell carcinoma (RCC) growth by confining p53 and p21 proteins to the nucleus and thus decreasing their degradation (J Urol. 2013, 189:2317). Given that low p21 levels are characteristic, and ADPKD cells, primary normal human kidney cells (NHK), mouse ADPKD cells (pkd1Δ−/Δ−), and control mouse kidney cells were incubated with the SINE XPO1 inhibitors, KPT-251 and -330, and cell viability assay, cell cycle analysis, apoptosis assay, immunoblotting, immunohistochemistry, and PCR were performed.

**Results:** Both KPT-251 and -330 caused cell cycle arrest at G1/S and led to apoptosis in all ADPKD cell lines tested. While XPO1 inhibitors attenuated XPO1/CRM1 protein levels in ADPKD cells as was seen in RCC cells, the inhibitors did not affect p53 and p21 protein levels in ADPKD cells in vitro but decreased levels of the cell cycle relevant proteins CDK4 and 6.

**Conclusions:** We introduce a novel therapeutic approach to the treatment of ADPKD, based on our earlier findings in RCC, using SINES. These compounds attenuate key cell cycle regulatory proteins, and decrease proliferation, in human ADPKD cells. In vivo studies examining the efficacy of these XPO1 inhibitors in cyst growth and renal function preservation are currently underway; these studies have the potential to revolutionize ADPKD treatment.

**Funding:** NIDDK Support, Other NIH Support - NCI, Veterans Affairs Support

---

**FR-PO122**

**Downregulating Hedgehog Signaling Attenuates Renal Cystogenesis in Mouse Models of Cystic Kidney Disease**

**Pamela Virgin Tian, 1 George Talbot, 1 Annick Doan, 1 Darren T. Jacobs, 2 Luciana M. Silva, 1 Michael P. Schoenfeld, 1 Anthony W. Wettersten, 1 Barry Prysak-Gehrke, 2 David Beier. 1,2 **Anatomy and Cell Biology and the Kidney Institute, Univ of Kansas Medical Center; Kansas City, KS, 2 Genetics Div, Brigham and Women’s Hospital/Harvard Medical School, Boston, MA; 3 Center for Developmental Biology and Regenerative Medicine, Seattle Children’s Research Institute, Seattle, WA.**

**Background:** Mutations associated with renal cystic diseases reside in genes encoding proteins that localize to primary cilia. These cilia proteins can disrupt ciliary structure or function and participate in the Hedgehog (Hh) signaling pathway. We examined renal cystogenesis in a Thm1 conditional knockout (cko) mice, a model generated using a ubiquitous, tamoxifen-inducible Cre recombinase.

**Results:** Thm1 deletion at E11.5 caused cystic kidney disease in adult mice, with elevated cAMP and increased proliferation. To determine if proliferation initiates Thm1 cKO renal cystogenesis, we examined kidneys at earlier time points. At P15, Thm1 cKO renal tubular dilations were evident and proliferation levels were high but similar to levels in wild-type kidneys. At P20, proliferation was markedly reduced in wild-type and mutants, but not in Thm1 cKO kidneys. These data suggest that proliferation alone is insufficient to initiate renal cystogenesis and that the ciliary defect may keep the kidney in a developmental state. In Thm1 cKO kidneys, expression of Hh signaling genes was upregulated. Importantly, transcripts of Hh target genes were also increased in cJek and Pkdl cKO kidneys. To determine a functional role for enhanced Hh activity in renal cystogenesis, we are genetically downregulating Hh signaling in these mouse mutants. Preliminary data suggest that ablation of Glis2, the main transcriptional activator of the Hh pathway, attenuates Thm1, cJek and Pkdl cKO kidney disease.

**Conclusions:** Thus enhanced Hh activity may play a general role in renal cystogenesis and may present a novel potential therapeutic target.

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

---

**FR-PO123**

**Inhibition of Macrophage Migration Inhibitory Factor Delays Renal Cyst Growth in ADPKD**

**Li Chen, 1 Xia Zhou, 2 Katherine Swenson-Fields, 3 Xiaogang Li. 1,2 **Dept of Internal Medicine; 1Dept of Anatomy and Cell Biology, Univ of Kansas Medical Center; Kansas City, KS.

**Background:** Macrophage migration inhibitory factor (MIF) can stimulate tumor cell proliferation, suppress apoptosis, facilitate invasion of the extracellular matrix and promote angiogenesis. Elevated levels of MIF have been found in the urine of ADPKD patients. However, the cellular origin of MIF in ADPKD and the potential contribution of this factor to disease progression have not been determined.

**Results:** MIF expression was assessed in the kidneys and cells from Pkd1-deficient mice by RT-PCR and immunoblot analysis. The contribution of MIF to proliferation and proliferation signaling was determined by following treatment of cystic renal epithelial cells with either MIF siRNA or its inhibitor, ISO-1, in vitro. The functional effect of MIF on renal cyst growth was tested by treating Pkd1 conditional knockout mice with ISO-1.

**Results:** MIF was upregulated in Pkd1 mutant renal epithelial cells and tissues of Pkd1 conditional knockout mice vs Pkd1 wild type mice. Furthermore, MIF was secreted and found in the cyst fluid of kd1fl/fl-Ksp-Cre mice and Pkd1fl/fl-Kdpcre mice. Knockdown of MIF with siRNA or inhibition of MIF with ISO-1 in Pkd1 mutant renal epithelial cells did not decrease cystic renal epithelial cell proliferation as analyzed by the MTT assay; and 2) decreased the expression of Cyclin D1, phospho-Stat3, and phospho-mTOR, which are aberrantly upregulated and are known to contribute to cystic epithelial cell proliferation in ADPKD. These results suggest that MIF promotes cystic renal epithelial cell proliferation potentially through activation of these pathways. We also found that treatment with ISO-1 decreased monocyte chemotactic activity in ADPKD cyst cell conditioned medium (CM). Most importantly, the administration of ISO-1 to Pkd1fl/flKsp-Cre mice delayed cyst growth and improved renal function.

**Conclusions:** Inhibition of MIF decreases a potent anti-proliferative and anti-monocytic chemotactic effect in cystic renal epithelia and CM respectively, and delays cyst formation. These results support MIF as a potential therapeutic target in ADPKD.

**Funding:** NIDDK Support

---

**FR-PO124**

**Effects of 2-OH Estradiol and Bicarbonate Loading on the Development of Polycystic Kidney Disease (PKD) in the PCK Rat**

**Xiaofang Wang, Hong Ye, Christopher James Ward, Vicente E. Torres. Mayo Clinic.**

**Background:** 2-OH estradiol (2-OHE) alleviates PKD in Han:SPRD cy/+ rats by an undefined mechanism associated with up-regulation of P21 and mTOR inhibition (AJP Renal Physiol 302:F636, 2012). Since 2-OHE inhibits soluble adenylyl cyclase (SAC) in vitro and bicarbonate loading markedly aggravates PKD in PCK rats, likely by activating SAC (unpublished observation), we sought to determine whether 2-OHE administration would be protective in this Pkd1 model and prevent the detrimental effect of bicarbonate.

**Methods:** Four groups of PCK rats (10M and 10F per group) were treated with vehicle or 2-OHE (10 μg/kg/hr) via osmotic pumps and given water or 100mM sodium bicarbonate to drink between 3 weeks and sacrifice at 10 weeks of age. Linear regression analysis was used to assess the effect of treatment comparisons adjusted for gender.

**Results:** In PCK rats 2-OHE moderately inhibited SAC and PKD development without affecting renal cAMP levels; 2) Bicarbonate loading markedly increased renal SAC activity, cAMP levels and PKD severity; 3) 2-OHE did not reduce cAMP levels or prevent the bicarbonate induced aggravation of PKD, possibly because of insufficient SAC inhibition; 4) 2-OHE stunned growth and had no effect on liver cystic disease.

**Conclusions:** These results support MIF as a potential therapeutic target in ADPKD.

**Funding:** NIDDK Support

---

**FR-PO125**

**COX-2 Inhibition in the PCK Rat**

**Xiaofang Wang, Hong Ye, Katharina Hopp, Peter C. Harris, Vicente E. Torres. Mayo Clinic.**

**Background:** Cyclooxygenase (COX)-2 is up-regulated in the kidneys of Han:SPRD cy/+ rats and COX-2 inhibitors have a protective effect in this model (AJP Renal Physiol 293:F821, 2007; Mol Biol Rep 39:7743, 2012). Furthermore, antagonists of two PG2E2 GsCPRs, EP2 and EP4, inhibit cAMP signaling in human and/or murine tubular epithelial cells and in vitro cystogenesis (AJP Renal Physiol 293:F1622-F1632, 2007; Prost & Lipid

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

Underline represents presenting author/disclosure.
Med 98;11, 2012). We sought to quantify renal mRNA expression of COX isozymes, PG2 synthases (PGEs), and EP receptors and renal PG2 levels in PCK compared to wild-type rats, and the effect of the COX-2 inhibitor celecoxib (CBX) on the development of PKD in this Pkd1 model.

Methods: mRNA expression was quantified using real-time PCR. Four groups of PCK rats (1 control, C, and 3 treatment groups fed 250, 500 and 1000ppm CBX in powdered chow, 10M and 10F per group) were studied between 3 weeks and sacrifice at 10 weeks of age. Linear regression analysis was used to assess the effect of treatment comparisons adjusted for gender.

Results: COX-2 mRNA levels were significantly increased in PCK compared to wild-type kidneys. CBX administration was associated with relatively higher kidney volumes in both genders and blood pressures in male rats only (Table). Despite significant reductions in tissue PG2, AMP levels remained unchanged. CBX had no detectable effect on the renal cystic disease.

Conclusions: COX-2 mRNA expression and renal PG2 levels are increased in PCK rats. However, inhibition of COX-2 increased BP in male rats and had no protective effect on PKD development, possibly because PG2 acting on different receptors exerts antagonistic effects.

Funding: NIDDK Support

FR-PO126

Multi-Target Treatment in ADPKD

Yane Liu,1 Johannes Loffeing,2 Alexandre Arcaro,3 Andreas L. Serra,4

1Institute of Physiology, Univ of Zürich, Switzerland; 2Institute of Anatomy, Univ of Zurich, Switzerland; 3Dept of Clinical Research, Univ of Bern, Switzerland; 4Div of Nephrology, Univ Hospital Zurich, Switzerland.

Background: Targeting the mammalian target of rapamycin (mTOR) by mTOR inhibitors has only modest effects on PKD progression. CBX administration was associated with relatively higher kidney volumes in both genders and blood pressures in male rats only (Table). Despite significant reductions in tissue PG2, AMP levels remained unchanged. CBX had no detectable effect on the renal cystic disease.

Conclusions: COX-2 mRNA expression and renal PG2 levels are increased in PCK rats. However, inhibition of COX-2 increased BP in male rats and had no protective effect on PKD development, possibly because PG2 acting on different receptors exerts antagonistic effects.

Funding: NIDDK Support

FR-PO128

Alicraken Ameliorates Cyst Progression by Suppressing the Intrarenal Renin-Angiotensin System Activity in Autosomal Dominant Polycystic Kidney Disease

Tsukasa Nakagaki,1 Saori Nishio,1 Yasunobu Ishikawa,2 Sekiya Shibazaki,2 Akira Nishiyama,2 Stefan Somlo,3 Hiroyuki Kobori,2 Tatsuya Atsumi,1 Internal Medicine II, Hokkaido Univ Graduate School of Medicine, Sapporo, Japan; 2Dept of Pharmacology, Kagawa Univ School of Medicine, Kagawa, Japan; 3Dept of Internal Medicine, Yale Univ School of Medicine, New Haven, CT.

Background: Hypertension is a well-recognized complication of autosomal dominant polycystic kidney disease (ADPKD) and is significant independent risk factor for progression to end stage of renal disease. Involvement of the renin-angiotensin system (RAS) has been postulated, but no consistent relationship has been found between blood pressure and plasma renin activity.

The purpose of this study is to examine the effects of antihypertensive drugs for Pkd1 conditional knockout mice and to evaluate the participation of intrarenal RAS in this model.

Methods: We generated Pkd1 conditional knockout mice carrying the Cre transgene under the control of the Mx1 promoter (Pkd1(Mx1-Cre) mice). All mice were injected with polyinosinic-polycytidylic acid (pI:pC) to induce the expression of Cre recombinase and to inactivate Pkd1 at 2 weeks of age. To evaluate the effects of antihypertensive drugs, Pkd1(Mx1-Cre) mice were treated with osmotic mini-pumps with amlopidine or olmesartan or aleskiren or vehicle for 12 weeks. Blood pressure was measured by the tail-cuff method. Kidney weight to body weight ratio (KW/BW), and renal cystic index were used to assess efﬁcacy of treatment. Intrarenal RAS activity was examined by measurement of urinary angiotensinogen (AGT) excretion and immunohistochemistry for renin, angiotensin II, and AGT in the kidneys.

Results: Blood pressure was almost similar among the treatment groups. There was no difference in KW/BW and renal cystic index, between amlopidine, olmesartan and vehicle. Alicraken treatment signiﬁcantly reduced the KW/BW, renal cystic index, BUN, urinary albumin excretion, and intrarenal RAS activity.

Conclusions: These studies suggest RAS inhibition with aliskiren may be effective in slowing cyst growth by suppressing the intrarenal RAS activity in ADPKD.

FR-PO129

H2-Relaxin Modulates Expression of Fibrosis-Related Genes in Normal and Cystic Human Renal Epithelial Cells

Heather Hilary Ward,1 Paul C. Grimm,2 Angela Wandering,3 Internal Medicine, Nephrology Div, Univ of New Mexico, Albuquerque, NM; 2Pediatric Nephrology, Stanford Univ, Stanford, CA; 3Pathology, Univ of New Mexico, Albuquerque, NM.

Background: In autosomal dominant polycystic kidney disease (ADPKD), renal inflammation, abnormal extracellular matrix (ECM) deposition, and fibrotic progression are concurrent with cyst growth and collectively destroy renal architecture, resulting in irreversible loss of kidney function. To date, the opportunity to circumvent these additional factors that promote the loss of renal function has been insufficiently studied.

Methods: We used computer-assisted quantiﬁcation of picrosirius red staining and real-time PCR to evaluate the effect of H2-relaxin on matrix metabolism in cystic kidneys and speciﬁc renal cell types.

Results: We demonstrated that H2-relaxin in the C57r/12 model of ADPKD decreased expression of genes that regulate ECM synthesis and degradation, and these data correlated with trends of decreased renal interstitial matrix content. Relaxin actions lead directly on fibroblasts and endothelial cells, but little is known about relaxin-mediated signaling in epithelia. In vitro, real-time PCR data showed that human ADPKD renal epithelia expressed abnormal levels of ECM components in the absence of other fibrotic drivers. When normal and ADPKD renal epithelia were incubated with H2-relaxin in the presence of a fibrotic stimulus (TGFβ1), H2-relaxin differentially inhibited up-regulation of matrix-synthesis genes, tissue inhibitors and mesenchymal markers in normal and ADPKD epithelia. Hence, as expression levels of genes related to ECM synthesis and degradation were strongly up-regulated upon TGFβ1 stimulation in normal and ADPKD renal epithelia, when compared to respective vehicle-treated control cell types.

Funding: NIDDK Support

FR-PO127

Combination Therapy with Tolvaptan and Pasireotide Has Enhanced Effectiveness in the Pkd1 R3277C Model

Katharina Hopp, Xiaofang Wang, Hong Ye, Cynthia J. Hommerding, Peter C. Harris, Vicente E. Torres. Mayo Clinic.

Background: Animal and human studies have identified elevated levels of cAMP as a basic defect in Autosomal Dominant Polycystic Kidney Disease (ADPKD). Further, indirect targeting of Atp2b1 has been shown as an effective means to lower cAMP levels and slow the rate of cyst growth by using two therapeutic, tolvaptan and pasireotide, that act through antagonizing the stimulatory V2R or stimulating the inhibitory sSRTs, respectively.

Methods: Here, we utilize the Pkd1 R3277C mouse model, which genetically and phenotypically mimics human ADPKD, to test the value of a combined treatment. Both drugs (tolvaptan, 0.1% via food; pasireotide, 10μg/kg via osmotic pump) were administered over a 5-month period, starting at 1 month. Statistical analyses were performed by 2-Way ANOVA and a Tukey HSD post-hoc test.

Results: At 6 months the %Kd/BW was 1.9±0.2 in the control (C, n=22), 1.7±0.2 in the tolvaptan (T, n=21), 1.6±0.1 in the pasireotide (P, n=18), and 1.4±0.2 in the T+P groups (n=18). A significant impact of tolvaptan treatment (p=1.4E-9). Pairwise comparisons showed the greatest significance for the combined treatment (C vs. T: p=1.0E-2; P vs. 2.3E-4; B vs. 5.5E-10) with a marked additive effect over single treatments (B vs. T: p=1.9E-4; P vs. p=1.8E-2). Both treatments reduced cyst volume (μl, C: 91.8±31.7, T: 73.7±19.9, P: 50.4±20.6, B: 12.7±5.6, p<0.001 for significance of C vs. P, T, B vs. P=3.3E-4) and C vs B (p=5.8E-8). Further, CAMP levels (pmol/mg protein) were significantly reduced to WT levels by the combined treatment (C: 4.5±1.5, T: 1.1±1.3, P: 3.9±1.4, B: 3.3±0.6, WT: 3.3±0.9; C vs B, p=1.7E-2). No significant differences were found between treatment T to wild-type/pasireotide or males/females.

Conclusions: The strengths of this study are the use of an orthologous model with slowly progressive renal cystic disease and long-term treatment. Further, this study shows for the first time an additive effect between tolvaptan and pasireotide, reinforcing the central role of cAMP and cAMP in ADPKD pathogenesis and the likely benefit of combination therapy for ADPKD patients.

Funding: NIDDK Support

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

Underline represents presenting author/disclosure.
Conclusions: These studies provide the first detailed mechanistic analyses of the utility of relaxin for dissecting fibrotic mechanisms in renal epithelia. Pinpointing the mechanisms underlying fibrosis in ADPKD has important implications for identifying effective therapeutics, such as H2-relaxin, to prevent or reverse the process of fibrosis in ADPKD patients.

Funding: Other NIH Support - K12GM088021 from the NIGMS, UL1 TR000041 from the NCRR and NCATS

FR-PO130
Pyroluridine Dithiocratesmate Reduces Kidney Enlargement and Proteinuria in Experimental Polycystic Kidney Disease Michelle Ts, Padmeshree Rao, Mayuresh Korgaonkar, Sheryl L. Foster, Anthony Peduto, David C. Harris, Gopala K. Rangan. 1 Centre for Transplant & Renal Research, Westmead Millennium Institute, Sydney, Australia; 2Brain Dynamics Centre, Westmead Millennium Institute, Australia.

Background: The proinflammatory transcription factor family, nuclear factor (NF)-κB, is upregulated in experimental PKD, and NF-κB inhibition reduces cyst growth in Pkd1-/- mice. NF-κB, is upregulated in experimental PKD, and NF-κB inhibition reduces cyst growth in rodent PKD.

Methods: Male LPK rats (N=8/PNP99/horn with diverse collagenic deposit dilatation) received i.p. of either vehicle (V) or PDTC [40mg/kg once (x1), or twice daily (x2)] from postnatal wks 4 until 11. Total kidney volume (TKV) was assessed by 3D MRI at wk 5 and 10.

Results: PDTC reduced proteinuria by 66%, but did not alter renal dysfunction (Table). By serial MRI, the relative within-rat increase in TKV was 1.3-fold greater in V + PDTC (p<0.01). PDTC also attenuated 2KW:BW ratio by 25% and interstitial CD68+ cells (x1 wk 5 and 10.

Conclusion: Low-dose PDTC is effective in reducing renal cystogenesis and proteinuria in experimental PKD.

Funding: Millennium Institute, Australia.

FR-PO131
Phosphodiesterase 1A Rescue of Renal Cytogenesis and Examination of Additional PDEs in Zebrafish Caroline R. Sussman, Christopher James Ward, Amanda Christie Leightner, Peter C. Harris, Victoria E. Torres. Mayo Clinic.

Background: Substantial evidence indicates the importance of elevated cAMP in polycystic kidney disease (PKD). Preclinical and clinical trials have shown the feasibility of therapies (vasopressin V2 receptor antagonists and somatostatin analogs) acting on G protein coupled receptors to inhibit Adenylyl Cyclase activity and production of cAMP. We have previously shown that pde1a depletion significantly upregulated in the cystic epithelium of CPK, hydrocephalus, and body curvature in zebra fish.  Data are consistent with PDE1A effects downstream of PC2 and upstream of PKA inhibitor, H89, partially rescued the formation of renal cysts, hydrocephalus, and body curvature in zebra fish.  These data are consistent with previous data from PDE1A loss of function studies, providing further evidence of an integral role of PDE1A in renal cystogenesis in PKD setting.

Methods: To test whether modulating cAMP hydrolysis also affects renal cystogenesis, we have altered activity of the Phosphodiesterase, PDE1A, in zebra fish.  Data are consistent with PDE1A effects downstream of PC2 and upstream of PKA, and indicate the utility of zebra fish for analysis of additional PDEs. In addition, these data suggest a role for zebra fish in evaluating PDE-targeted therapy for PKD.

Results: These data are consistent with previous data from PDE1A loss of function studies, providing further evidence of an integral role of PDE1A in renal cystogenesis in PKD setting.

Conclusions: PDE1A is an important role in cell proliferation and differentiation and has a key role in kidney development and in kidney diseases. However its role in PKD is not yet defined. We hypothesized that Notch signaling may be an important pathogenic feature of autosomal dominant (ADPKD) and autosomal recessive (ARPKD) PKD.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Affairs Support, Private Foundation Support

FR-PO133
Abnormal Uregulation of Notch3 Pathway in Polycystic Kidney Disease Madhulika Sharma, Trisha Home, Lynn Magenheimer, Gayl Reif, Brenda S. Magenheimer, Robin L. Maser, Darren P. Wallace, James P. Calvet. Internal Medicine (Nephrology and Hypertension), Univ of Kansas Medical Center, Kansas City, KS; 2Biochemistry and Molecular Biology; Univ of Kansas Medical Center, Kansas City, KS.

Background: Abnormal proliferation of tubular epithelial cells is a hallmark of polycystic kidney diseases (PKD). Despite recent advances, a better understanding of the molecular mechanisms involved in cyst development is needed. Notch signaling plays an important role in cell proliferation and differentiation and has a key role in kidney development and in kidney diseases. However its role in PKD is not yet defined. We hypothesized that Notch signaling may be an important pathogenic feature of autosomal dominant (ADPKD) and autosomal recessive (ARPKD) PKD.

Methods: Immunohistochemistry (IHC) was performed in kidney paraffin sections obtained from CPK mice (a model ADPKD) and PKD1 null/HoxB7 conditional mice (a model of ARPKD) at one and two weeks of age. These mice develop rapidly progressive cystic disease and by 20 days of age the mice die due to end stage renal disease. We also obtained kidney sections from ADPKD patients undergoing a nephrectomy. We used commercially available antibodies for Notch1, Notch2, Notch3 and Notch4 (Notch receptors); Jagged1, Jagged2, Delta like1, Delta like4 (D14) (Notch ligands); and Hey1 and Hey2 (Notch targets). Signals from IHC were quantified using Image J Analysis. Comparisons were made with littermate controls or with normal human kidney samples.

Results: Notch3 was found to be distinctively upregulated in the cystic epithelia of all the models of PKD tested. Uregulation of Notch3 expression correlated with disease progression in CPK mice. Among the ligands, D14 expression was most significantly upregulated in the cystic epithelium. In addition both Hey1 and Hey2 targets of Notch pathway were found to be significantly upregulated in the cystic epithelium of CPK, PKD1 null/HoxB7 mice and ARPKD patients.

Conclusions: Upregulation of the Notch signaling pathway in ADPKD and ARPKD suggests that small molecule inhibitors of this pathway may have therapeutic potential in the PKD setting.

Funding: Private Foundation Support

FR-PO134

Background: Recent data demonstrated the renno-protective effect of vitamin D analogs via anti-inflammatory, immunomodulatory and anti-fibrotic effects. Polycystic kidney disease (PKD) is the most common inherited disease characterized by multiple cysts formation accompanied by renal fibrosis. However, there have been no studies investigating whether vitamin D imposes any effects on cyst formation, growth & renal fibrosis in PKC.
We aimed to examine the effect of active vitamin D analog, paricalcitol on in-vitro cyst formation as well as phenotype transition and apoptosis of cyst-lining epithelial cells. We used an in-vitro cyst model system of forskolin-treated Madin-Darby canine kidney (MDCK) cells to study the effect of paricalcitol (20 nM) on cyst development. Effect of paricalcitol on TGF-β (10 ng/ml)-induced phenotype transition and apoptosis of ADPKD cyst-lining epithelial cells (WT-12 cell) was also evaluated with an assessment of phosphorylation of p38 and ERK1/2, MAPK, GSK-3β and nuclear translocation of β-catenin. Results: Paricalcitol significantly inhibited forskolin-induced cyst formation of MDCK cells with an attenuation of both ERK1/2 MAPK activation and GSK-3β phosphorylation. Paricalcitol also inhibited TGF-β-induced expression of vimentin and fibronectin in WT-12 cells with a significant reduction of p38 and ERK1/2 MAPK activation, GSK-3β phosphorylation and nuclear translocation of β-catenin. Paricalcitol protected ADPKD cyst-lining cells from TGF-β-induced apoptosis with down-regulation of Bax, Cytochrome C, cleaved caspase-3 and -9. Conclusions: Paricalcitol ameliorated cyst formation, pro-fibrotic phenotype transition and apoptosis of renal tubular cells, which can be one of the therapeutic options targeting early and late mechanisms of renal disease progression in PCK.

FR-PO135

Macrophage-Cyst Cell Interaction in ADPKD Promotes Production of Fibrogenic Factors Katherine Swenson-Fields, Jacqueline D. Peda, Sally M. Salah, Brad M. Davis, Darren P. Wallace, Timothy A. Fields. The Kidney Institute, Univ of Kansas Medical Center, Kansas City; KS.

Background: In polycystic kidney disease (PKD), the destructive compression of parenchyma responsible for loss of kidney function is driven by both expanding cysts and fibrosis. We have shown that interaction between cyst epithelial cells and macrophages (MΦs) promotes cyst cell proliferation and expansion. MΦs are known to promote fibrosis in chronic kidney disease and thus are likely to do so in PKD. However, the specific contribution of MΦ epithelial cell interactions to the creation of a pro-fibrotic environment in PKD has not been examined. In this study we co-cultured MΦs with primary human epithelial cyst-lining epithelial cells with either PKD cysts or non-cystic kidneys to generate conditioned media (CM), which was assessed for fibrogenic effects on renal fibroblasts.

Methods: RAW 264.7 cells (mouse MΦ-like line) or MΦ-differentiated THP-1 cells (human monocyte lineage) were co-cultured with PKD cyst cells or collecting duct cells from non-cystic kidneys (NKC) either directly or in transwells (0.4 um pores). CM was collected and incubated with NRK-49F cells (rat renal fibroblast line), and the effects on cellular morphology and the production of fibrogenic markers [type-1 collagen (COL1A1) and smooth muscle actin (SMA)] were assessed.

Results: CM from co-culture of MΦs and either PKD cells or NHK cells but not CM from any cell-type alone induced dramatic morphological transformation in fibroblasts. Fibroblasts treated with co-culture CM displayed a bipolar or stellate morphology with markedly elongated cellular extensions, which was similar to but distinct from that produced by TGFβ1 treatment. Also, treated cells accumulated in nodular foci. These effects were observed whether the MΦ-cyst epithelial cell co-culture was direct or via transwell. Immunoblots showed COL1A1 was induced specifically by treatment with co-culture CM or with TGFβ1. However, myofibroblast marker SMA was induced only by TGFβ1.

Conclusions: Interaction between MΦs and renal tubule epithelial cells results in production of fibrogenic factors. This interaction may be a viable therapeutic target in PKD and other chronic kidney diseases.

Funding: Private Foundation Support

FR-PO136

Amphiregulin, an Epidermal Growth Factor Receptor Ligand, and BRP39 in the Pathogenesis of Cystic Kidney Fibrosis Seung H. Lee, 1 Sung Hyun Son, 2 Sorin V. Fedele, 3 Rachel Gallagher, 1 Stefan Somlo, 1 Dept. of Internal Medicine, Section of Nephrology, Yale Univ, School of Medicine, New Haven, CT; 2 Dept. of Internal Medicine, Section of Nephrology, BHS Han Seo Hospital, Busan, Republic of Korea.

Background: Fibrosis plays an important role in the progression of polycystic kidney disease (PKD). Disregulated EGFR signaling has also been implicated in the pathogenesis of PKD. We sought to determine whether there may be an inter-relationship between fibrosis signaling pathway, EGFR activation and mediators of the fibrogenic/inflammatory response in PKD.

Methods: Fibroblast cells (NIH3T3) and kidneys from an ADPKD orthologous gene model (Pkd1+/−Pkd1-Cre) were used to examine mRNA and protein levels of TGF-β1 targets (PAI-1, SMAD2), EGFR ligands amphiregulin (AR) and HB-EGF, EGFR downstream effectors Akt and ERK and the marker of tissue fibrosis/inflammation BRP39 by quantitative PCR (qPCR) and semi-quantitative Western blot.

Results: TGF-β1 activation of NIH3T3 cells resulted in increased AR expression and activation of EGFR targets p-Akt and p-ERK and associated fibroblast cell proliferation. The proliferative response to TGF-β1 was inhibited by EGFR inhibitor AG1478. We next examined P24 kidney tissues from cystic Pkd1+/−Pkd1-Cre and non-cystic controls for evidence of up-regulation of these fibrosis related pathways. Cystic kidney tissue at P24 showed up-regulation of the TGF-β1 targets PAI-1 and AR and the fibrosis and inflammatory disease marker BRP39 by qPCR.

Conclusions: The data support further testing of the hypothesis that TGF-β1 mediated fibrosis in PKD may in part be mediated by amphiregulin and EGFR signaling and by the inflammatory mediator BRP39. These pathways may prove to be reasonable therapeutic targets for treating renal fibrosis in ADPKD.

Funding: Private Foundation Support

FR-PO137

Computer Model of Renal Cyst Formation Julio M. Belmonte, 1 Sherry G. Clendennon, 1 James A. Glazier, 2 Robert L. Bacallaio, 2 1Physics/Biocomplexity Institute, Indiana Univ, Bloomington, IN; 2Medicine, Indiana Univ, Indianapolis, IN.

Background: Recently we have shown that ectopic cadherin-8 expression can initiate cyst formation. We utilized a 3D multi-cell simulation of renal tubules to investigate mechanisms behind this observation. Our model predicts that loss of cell-cell adhesion in a single cell suffices to trigger cysts and the pattern differs from contact-inhibition changes.

Methods: CompuCell 3D is an open source simulation environment for running multicell simulations. The program numerically solves matrices that model cell-cell, cell-ECM adhesion and cell-volume constraints. Cell adhesion was analyzed over a continuum of values and predictions confirmed by hanging drop assay.

Results:

PKD simulation. (A) Starting from a stable tubular structure we model cadherin-8 phenotype by changing macroscopic properties of the microinjected cell (blue cell in panel). Increased surface tension between wild type and cadherin-8 expressing cell leads to deformation of cell contact-inhibition, proliferation and formation of a single ectopic cyst. (B) 3D view of a similar simulation showing two formed cysts. (C) Images of cysts (arrows) stained for cadherin-8 (green) (D-E) Hanging drop assays show (D) compacted spheres of N-cad expressing cells and (E) loosely associated sheets of cadherin-8 expressing cells. The prediction that cadherin 8 decreased cell-cell adhesion in renal epithelial cells was confirmed in hanging drop assays. Cadherin 8 transfected HK-2 cells had fewer cell aggregates and aggregate size was decreased compared to N-cadherin transfected cells.

Conclusions: in silico modeling of renal cyst formation makes discrete predictions about cell-cell adhesion properties that are confirmed by cell-cell adhesion assays. This approach allows for rapid identification of biological pathways that alter normal epithelial morphogenesis pathways.

Funding: Government Support - Non-U.S.

FR-PO138


Background: Infections are the second most common cause for hospitalization in chronic HD patients. CLABSIS remain a major health concern and focus of quality improvement programs. However, CLABSIs continue to occur in select groups.

Methods: Review of baseline characteristics and outcomes of CLABSIs at a single tertiary care center.

Results: From 01/2007-06/2012, 99 chronic HD patients were treated for CLABSIs. CLABSIs were equally distributed over the 4.5 years; range 16-20/year. Mean age was 62±17 years, 52% male, and 77% Caucasian. Diabetes (55%), coronary artery disease (57%), and heart failure (64%) were frequent comorbidities. Others included: immunosuppression (24%), intracardiac device (22%), joint arthropathy (15%), and prosthetic heart valve (10%). Diabetes was the main (28%) renal failure cause. The majority (94%) had tunnelled central venous catheters (CVC) and few had temporary CVCs (6%). The most common pathogens are shown.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>gram-positive staphylococci</td>
<td>32%</td>
</tr>
<tr>
<td>enterococcus species</td>
<td>22%</td>
</tr>
<tr>
<td>methicillin-susceptible staphylococcus aureus (MSSA)</td>
<td>12%</td>
</tr>
<tr>
<td>methicillin-resistant (MRSA)</td>
<td>34%</td>
</tr>
</tbody>
</table>

CVCs were removed in 78% with salvage attempted in others. At index hospitalization, infective endocarditis (IE) was confirmed (5 patients) or suspected (6). Over a 6-month period, 2 were later diagnosed with IE. A second CLABSI occurred in 23 patients within 12 months. Overall survival rate was reduced at 6 (67%) and 12 months (47%).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Conclusions: Chronic HD patients hospitalized with CLABSI have a high prevalence of comorbidities that complicate decision-making. Even with being high risk, few patients developed IE from CLABSI. Better prediction tools to identify those at highest risk for CLABSI despite modern infection prevention protocols merit further investigation.

FR-PO139
Risk of Catheter-Related Bloodstream Infections in Elderly Patients on Hemodialysis
Margana Murea, Kimone M. James, Gregory B. Russell, Anthony J. Bleyer, John M. Burkart, Barry I. Freedman. Wake Forest School of Medicine, Winston-Salem, NC.

Background: Elderly patients are more likely to require tunneled central vascular catheters (TCVC) for dialysis than younger patients. Unfortunately, there is little data on the risk of catheter-related bloodstream infections (CRBSI) in this population.

Methods: We collected data regarding CRBSI on prevalent and incident adult patients undergoing HD using TCVC at 9 Wake Forest Outpatient Dialysis centers between 2005 and 2007. Subjects who had a TCVC for <21 days were excluded. Cox proportional hazards regression analysis was performed with an event defined as CRBSI and censoring for death, end of study, or CRBSI no longer needed.

Results: 374 adult (age <75 years) and 90 elderly (age ≥75 years) subjects of mean±SD age 54.8±12.3 and 81.3±4.9 years, dialysis vintage 1.8±3.3 and 1.5±2.9 years (p=0.47), and race distribution (European-American, African-American, other) 43.8%, 51.9%, 4.3%, and 73.3%, 26.7%, 0%, respectively (p<0.0001) were evaluated. CAD and CHF were more prevalent in elderly (51.1% and 48.9%) vs. adult patients (27.0% and 26.5%), (p<0.001), while diabetes, HTN, and PVD had similar prevalence between groups. Mean total at-risk catheter-days were 272±243 in adults and 318±240 in the elderly. There were no significant differences in catheter site, use of anti-microbial catheter lock solutions, and bacterial culture results between groups. 208 total CRBSI events occurred (190 in adults, 18 in elderly), with CRBSI incidence per 100 catheter-days 0.20±0.46 in adults and 0.06±0.16 in elderly, (p<0.0001). Using Cox regression analysis adjusted for sex, ethnicity, diabetes, catheter site and antimicrobial catheter lock solution, the hazard ratio (HR) for CRBSI in the elderly vs. adults was 0.33 (95% CI 0.20-0.54; p<0.0001). Risk of CRBSI declined by 11% per each 5 year age increment (HR, 0.89, 95% CI, 0.85-0.93, p<0.0001).

Conclusions: Elderly patients on HD using TCVC are at a significantly lower risk of CRBSI than younger patients. These results suggest that TCVC may be a more suitable option in elderly patients if permanent vascular access is problematic.

FR-PO140
Reduction in Catheter-Associated Blood Stream Infections in a Pediatric Dialysis Unit
Kera E. Luckritz, Maureen M. Shanley, Theresa A. Mottes, Matthew Niedner. 1Pediatric Dialysis, Univ of Michigan, Ann Arbor, MI; 2Center for Acute Care Nephrology, Cincinnati Children’s Hospital, Cincinnati, OH; 3Pediatric Critical Care, Univ of Michigan, Ann Arbor, MI.

Background: Hemodialysis (HD) is the most common dialysis modality in children with a tunneled catheter as the vascular access in >75% of the patients. The USRDS 2012 report cites a central line-associated bloodstream infection (CLABSI) incidence of 14.5% among pediatric patients. CLABSI can lead to morbidity including hospitalization and access failure, making prevention a priority in this population.

Methods: A CLABSI eradication team of pediatric nephrologists, dialysis/apheresis nurses, an infection control practitioner, a physician assistant who specializes in dialysis catheter insertions and an administrator was established. A bundle of evidence-based best practices was developed for the care of dialysis catheters and exit sites. A checklist of 10 steps was used as a tool to prompt desired practices and capture self-auditing process measures. Audits were performed with an “all or none” compliance methodology. Only trained dialysis/apheresis nurses who received 1.1 education regarding the accessing procedure from a member of the CLABSI team were allowed to access dialysis catheters. Audits were completed over 18 months and results were reviewed monthly by the team with feedback from the staff on challenges to compliance. After each infection, a root cause analysis was performed. Follow up communication with the dialysis staff emphasized lessons learned, preventability and patient impact.

Results: In the first 3 months, self-reported and observed compliance were 32% and 41% respectively, which rose to 82% and 67%. CLABSI rates are shown in a control chart, with statistically significant special cause variation patterns circled.

Conclusions: Minimizing the number of personnel accessing HD catheters and standardizing the technique with constant monitoring and feedback can reduce CLABSI rates.

FR-PO141
Fibrin Sheath Disruption during Catheter Exchange: Association with Bacteremia and Catheter Patency
Amanda M. Valliant, Muhammad K. Chaudhry, Alexander S. Yevzlin, Brad C. Astor, Micah R. Chan. Univ of Wisconsin Hospitals and Clinics, Madison, WI.

Background: Tunneled dialysis catheters are the most common form of vascular access among incident dialysis patients in the United States. Fibrin sheath formation is a frequent cause of late catheter dysfunction requiring an exchange procedure with balloon disruption of the fibrin sheath. It is unknown whether fibrin sheath disruption is associated with increased incidence of bacteremia or catheter failure.

Methods: We reviewed all tunneled dialysis catheter exchange procedures at the University of Wisconsin between January 2008 and December 2011. The primary outcome was incidence of bacteremia, defined as positive blood cultures within 2 weeks of the procedure. Catheter failure, requiring intervention or replacement, was examined as a secondary outcome. Baseline characteristics examined included diabetic status, gender, race and age.

Results: A total of 163 procedures were reviewed; 67 (41.1%) had fibrin sheath disruption and 96 did not. There was no difference in the prevalence of bacteremia among those with (3/67; 4.5%) and those without fibrin sheath disruption (3/96; 3.1%; p=0.65). Fibrin sheath disruption was not significantly associated with the risk of catheter failure (adjusted hazard ratio [AHR] = 1.34; 95% confidence interval [CI]: 0.87-2.10; p=0.18). Diabetes was associated with greater risk of catheter failure (AHR = 1.88; 95% CI: 1.19-2.95; p=0.006), whereas higher age was associated with a lower risk of catheter failure (AHR per 10 years = 0.83; 95% CI: 0.72-0.96; p = 0.01).

Conclusions: This study demonstrates for the first time, to our knowledge, that there is no significant association between fibrin sheath disruption and bacteremia or catheter patency. These results are encouraging given the large numbers of patients utilizing tunneled catheters for initial hemodialysis access and the known rates of fibrin sheath formation leading to catheter failure.

FR-PO142
MRSA and MSSA Carriage in a Cohort of Haemodialysis Patients: Prevalence, Eradication and Short Term Outcomes
Nadia Sarween, Anna Price, Jyoti B. Baharani. Renal Medicine, Birmingham Heartlands Hospital, Birmingham, United Kingdom.

Background: Haemodialysis (HD) patients with Staphylococcus aureus (S. aureus) bacteremia have an increased risk of adverse outcome including death, compared to bacteremia caused by other pathogens. Nasal colonisation of MRSA has been shown to increase the risk of subsequent endogenous infection with the organism in dialysis patients.

Methods: We performed a retrospective study in chronic haemodialysis patients to estimate the prevalence of S. aureus nasal carriage (for both MSSA and MRSA), to define patient groups at risk of colonisation and to look at the short-term outcomes following a decolonisation programme.

Results: All established HD patients (666) were screened 4 monthly for 24 months (between June 2009 and May 2011). At least two swabs; from the nose and access site were taken. Those with a positive result completed a course of decolonisation treatment. Data was gathered retrospectively using hospital electronic records and the renal unit data base for a period of 18 months following the date of the initial swab. Statistical analysis was performed using SPSS.

Results: The prevalence of colonisation with S. aureus was 47.7% (MRSA 9% MSSA 91%). 59% were male and median age was 65 years. 18.9% were in the high-risk co-morbidity group using Charlson Index. After decolonisation treatment 34% remained
FR-PO143


**Background:** The colonization of the inner catheter lumen is the first step in the pathogenesis of most CRBSI. The aim of the study was to analyze the results of a protocol established in our hemodialysis (HD) unit, based on surveillance cultures (SCs), to prevent CRBSI.

**Methods:** Prospective study (April 2011–April 2012) in HD patients (pts) with tunnel cuffed central venous catheters (TCCs). Endoluminal colonization was assessed every 15 days by SCs: mixture of hematocrit (≤ 2 mL) and blood (≤ 3 mL) extracted from the TCC just before connecting the pts. SCs were inoculated into aerobic culture bottles and incubated 48-72 hours (Bact/Alert, Biomerieux). Based on the microorganism and the time to positivity (TTP), an algorithm was designed: Group 1 (negative): continue surveillance; Group 2 (Coagulase-negative Staphylococcus [CoNS], TTP>14 hours): draw a new SC in a week. If the result was repeated, antibiotic lock therapy (ALT) was indicated (vancomycin or daptomycin 5 mg/mL, 2 weeks); Group 3 (CoNS, TTP<14 hours): ALT; Group 4 (other microorganism, any TTP): diagnosis of CRBSI and management according to guidelines.

**Results:** We included 104 pts with 129 TCCs. 56 pts were male and the median age was 73.0 (IR:54.5-80.0). The Charlson comorbidity index adjusted for HD was 7.0 (IR: 6.0-9.0), and the TCC vintage was 118 days (IR:18-364). The most common causes of renal impairment were diabetic nephropathy (26.9%) and renal vascular disease (22.1%). The median of follow up was 262.5 days (IR: 135-365). A total of 1734 SCs were collected (median n: 18 [IR:10-24]) and 100 (5.8%) were culture positive. According to the protocol TCC colonization was detected in 28 occasions: 19 from groups 2 and 3, and 9 from group 4. Six pts carrying 7 TCCs had 7 CRBSI. The rate of CRBSI was 0.27/1000 catheter-days.

**Conclusions:** SCs, based on easily accessible samples, may contribute to reduce CRBSI in HD pts. Thereby, ALTs would be restricted to pts at high risk of CRBSI.

FR-PO144

Sustained Infection Reduction in Outpatient Hemodialysis Centers Participating in a Prevention Collaborative

**Background:** When blood flow is low during hemodialysis (HD) line reversal is often undertaken, which can lead to high recirculation (RC). Catheter (C) tip design is considered a key factor that affects RC. We compared RC with a split-tip versus symmetrical tip C. Methods: A prospective trial of split-tip and symmetrical tip tunnelled C performance included a pre-planned ultrasound blood flow sub-study. Consenting adult chronic HD subjects were randomized to either: 1. A symmetrical tip catheter, Covidien’s Palindrome™ catheter with side slots; 2. A split-tip catheter, Bard® Hemosplit® catheter. In 206 subjects, the distal recirculation velocity measurement was used to capture blood flow rates (BFR) and RC during week 1, 5 and 11 after C insertion. BFR and RC, and arterial (AP) and venous pressures (VP) were recorded in both forward flow (FF) and after line reversal at flow rates of 350, 400, and 450 mL/min, between 30 and 90 minutes following initiation of HD. The primary objective of the sub-study was RC in reverse flow (RF).

**Results:** Median RC in RF was 3.8% in the split-tip C and 3.2% in the symmetrical tip C (P = 0.096). The following additional variables were analyzed. 1) RC in FF flow was higher in the symmetrical tip C (median 3.7 versus 0. P = 0.001); 2) The symmetrical tip C had a higher mean BFR during week 5 at all 3 pump settings (all P ≤ 0.038) but no different at other measurements; 3) The difference between the prescribed and actual BFR was -20.4±25.9 vs. -9.8±21.1, split-tip vs. symmetrical tip C (P = 0.018) during week 5 at all pump settings.

**Conclusions:** There was no statistically significant difference in recirculation after line reversal between a split-tip and symmetrical tip HD catheter.

**Funding:** Pharmaceutical Company Support - Covidien
Comparison of a Split-Tip versus Symmetrical Tip Hemodialysis Catheter Hariprasad S. Trivedi,1 Tushar J. Vachharajani,2 Nand K. Wadhwa,1 Mark Vannorsdall,1 Jean Lee,3 Klemens B. Meyer.4 Medical College of Wisconsin; W.G. (Bill) Hefner VAMC; Stony Brook Univ Medical Ctr; Temple U; Maine Health; Tufts Med Ctr.

Background: In a multi-center, randomized, open-labeled trial we compared the performance and longevity of a split-tip versus symmetrical tip hemodialysis (HD) catheter.

Methods: Adult subjects requiring chronic HD scheduled to receive a tunneled C for vascular access were considered for the trial. Key study criteria included a patent internal jugular vein and absence of active infection. Eligible and consented subjects were randomized in a 1:1 ratio to either: A symmetrical tip catheter, Covidien’s Palindrome™ catheter with side slots; 2. A split-tip catheter, Bard® Hemosplit® catheter. Subjects were followed until study completion which was defined as 35 weeks after catheter placement, study catheter removal, or death. The primary end-point was “time to catheter-induced complication or TCIC” defined as time to first incidence of intervention for malfunction due to thrombosis, poor flow requiring administration of tissue plasminogen activator (tPA), mechanical problems requiring surgical/radiological intervention, catheter displacement, or failure due to catheter related blood stream infection.

Results: 15 US centers enrolled 661 subjects of whom 568 had at least one post-baseline visit measurement for the primary end-point. Mean age was 59.4 ±14.8 years, 51.6% were female, 52.8% were African American, 8.3% were Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity. The most common cause of end-stage renal disease was type 2 diabetes mellitus (38.6%). 89 subjects were female, 52.8% were African American, 8.3% were of Hispanic/Latino ethnicity.

Conclusion: The results of this multi-center randomized open-labeled clinical trial show that the split-tip HD catheter has improved performance and longevity compared with a symmetrical tip catheter. Thus, the split-tip HD catheter could be a suitable alternative to the conventional symmetrical tip catheter in patients requiring HD for chronic kidney disease.
Funding: Clinical Revenue Support

FR-PO154
Citrte versus Heparin L ock for Hemodialysis Catheter: A Systemic Review and Meta-Analysis of Randomized, Controlled Trials 

Yuliang Zhao,1 Ling Zhang,2 Ping Fu,1 Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan Province, China; 1Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan Province, China; 2Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan Province, China; 3Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan Province, China; 4Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan Province, China; 5Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan Province, China; 6Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan Province, China.

Background: Citrate solution has been suggested as an effective and safe catheter lock in hemodialysis. However results from studies comparing citrate with heparin locks remain inconclusive.

Methods: We collected data from PubMed, Ovid, the Cochrane Library, Web of Science databases and major nephrology journals. A systemic review and meta-analysis was performed of all eligible randomized controlled trials.

Results: 13 randomized controlled trials (1770 patients, 22106 catheter-days) met the inclusion criteria. Pooled analyses found that Citrate locks could significantly reduce the incidence of catheter related bloodstream infection (RR=0.37, 95%CI=0.28-0.49, P<0.001). Subgroup analysis showed citrate alone, citrate + gentamicin, citrate + taurodolene were all superior to heparin lock in the prevention of catheter related bloodstream infection (P<0.002, <0.001, <0.002 respectively).

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

Results: 13 randomized controlled trials (1770 patients, 22106 catheter-days) met the inclusion criteria. Pooled analyses found that Citrate locks could significantly reduce the incidence of catheter related bloodstream infection (RR=0.37, 95%CI=0.28-0.49, P<0.001). Subgroup analysis showed citrate alone, citrate + gentamicin, citrate + taurodolene were all superior to heparin lock in the prevention of catheter related bloodstream infection (P<0.002, <0.001, <0.002 respectively).

Conclusions: Our results indicate geographic disparities in AVF placement with decreased rates of AVF as the first access created in the metropolitan and rural populations compared to the micropolitan populations.
Factors Predicting Failure of AV “Fistula First” Policy in the Elderly

Background: An arteriovenous fistula (AVF) is the preferred access for HD. The goal of this study was to identify factors associated with AVF failure in the pre-dialysis period in an elderly HD population.

Methods: We used USRDS. Medicare claims data to identify incident HD patients ≥67 year old from 01/05 to 12/31/08 with first pre-dialysis access placed being an AVF (n=20,360; 76.2±6.02 year old, 58.5% males). AVF failure, defined as failure of using the AVF for the first outpatient dialysis, was used as the outcome. Logistic regression model was used to identify factors associated with AVF failure.

Results: Of patients who had an AVF placed pre-dialysis, 48% initiated dialysis using the AVF and 52% using a catheter or an AVG. The following variables were found to be associated with AVF failure when an AVF was created at least 4 months pre-HD initiation: age ≥67 yr, female gender, race, history of diabetes mellitus, cardiac failure and shorter duration of pre-ESRD nephrology care. Odds ratio for AVF failure for the entire cohort showed similar findings.

<table>
<thead>
<tr>
<th>Early AVF placement group</th>
<th>Reference group</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI) P Value</td>
<td>OR (95% CI) P Value</td>
</tr>
<tr>
<td>Age at ESRD onset</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.91 (0.90-0.92)</td>
</tr>
<tr>
<td>Female</td>
<td>1.01 (1.00-1.02)</td>
</tr>
<tr>
<td>Race: White</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.99 (0.98-1.00)</td>
</tr>
<tr>
<td>Female</td>
<td>1.02 (1.01-1.03)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.22 (1.19-1.25)</td>
</tr>
<tr>
<td>No</td>
<td>1.21 (1.20-1.23)</td>
</tr>
<tr>
<td>Pre-ESRD care</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Early A VF</td>
<td>0.72 (0.69-0.74)</td>
</tr>
<tr>
<td>Late A VF</td>
<td>0.75 (0.72-0.77)</td>
</tr>
</tbody>
</table>

Conclusions: In an elderly HD population, there is an association of older age, female gender, race, diabetes failure and shorter duration of pre-ESRD care with predialysis AVF failure. These results might help to identify populations at risk in order to assure adequate AVF maturation or AVG creation as primary access.

Optimal Time for AVF Placement in the Elderly. “The Earlier the Better”–A Myth or a Truth?

Background: AVF is the preferred access for hemodialysis (HD). However, many AVFs fail to mature or develop stenosis/thrombosis prior to starting dialysis, especially in the elderly. That results an undesirable increased incidence of catheter use.

Methods: We used USRDS. Medicare claims data to identify incident HD patients ≥67 year old from 01/05 to 12/31/08 with first pre-dialysis access placed being an AVF (n=20,360; 76.2±6.02 year old, 58.5% males). AVF failure, defined as using the AVF for the first outpatient dialysis. Our second outcome was the number of pre-dialysis vascular access procedures. Time between AVF placement and dialysis start was our primary variable of interest. Using a logistic regression model we further analyzed subgroups divided by gender, race, presence/absence of diabetes and CHF.

Results: Of patients who had an AVF placed pre-dialysis, 54.9% initiated dialysis using the AVF and 45.1% using a catheter or an AVG. The OR for success increased with longer times between AVF placement and dialysis start. This trend was also present in the subgroups studied.

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>OR for success (95% CI) P Value</th>
<th>Procedures Mean (SD) P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>0.99 (0.98-1.00) 0.003</td>
<td>4.31 (6.64) 0.001</td>
</tr>
<tr>
<td>6-12</td>
<td>0.93 (0.91-0.95) 0.005</td>
<td>3.37 (1.38) 0.001</td>
</tr>
<tr>
<td>12-24</td>
<td>0.91 (0.89-0.93) 0.001</td>
<td>3.14 (1.22) 0.001</td>
</tr>
<tr>
<td>&gt;24</td>
<td>0.90 (0.88-1.11) 0.006</td>
<td>2.72 (1.21) 0.001</td>
</tr>
</tbody>
</table>

Conclusions: We suggest that placing an AVF more than 6-9 months in advance of HD initiation in the elderly might be counterproductive as it is not associated with better AVF maturation, but might lead to greater number of access procedures.
FR-PO160
Choice of Permanent Vascular Access for Dialysis in Elderly Patients (> 75 yo): A Multicenter Observational Study
Mauricio Gallieni,1 Marcello Napoli,2 Andrea Bandera,2 Decenzio Bonocchi,2 Antonio Granata,2 Monica Spina.3 Ospedale San Carlo Borromeo, Milano; 2Scientific Committee, Vascular Access Study Group, Italian Society of Nephrology, Roma, Italy.

Background: Currently, patients over 75 yo represent about 30% of the dialysis population in Italy. Median age at start of dialysis in Italian patients rose from 62.8 years in 1999 to 67.2 years in 2009. A concomitant increase in the prevalence of central venous catheters (CVC) was observed. This observational study aimed at better defining the status of vascular access and the clinical policies of Italian nephrologists in elderly dialysis patients.

Methods: In 31 dialysis units which spontaneously adhered to this observational study, data were collected regarding all permanent vascular access interventions (AV fistula, CVC, grafts) performed between Jan 2009 and Dec 2011 in a large cohort of elderly dialysis patients (over 75 years old). Both incident and prevalent hemodialysis patients were included.

Results: In 1346 patients (811 males, 60.3%), 1584 access interventions were recorded. Mean (±SD) age was 81.0±4.6 years. Comorbidities included diabetes mellitus (25%), heart disease (34%), cancer (13%), central or peripheral vascular disease (35%). In the total population, the chosen procedure was an AV fistula for 51.3% of patient, for 45.2% the insertion of a tunneled CVC and for 3.5% a graft. Gender was a relevant factor in determining outcome: females had higher chances of having a CVC as dialysis access (54.4 vs. 39%, p = 0.005) and conversely lower chance of having an AV fistula (42.1 vs. 57.5%, p = 0.002), while grafts were similar (3.6 vs. 3.5%, p: ns). Presence of one or more comorbidities did not affect the patient distribution for dialysis access type. Among the cohort, 356 patients (RR: 1.02, 95% CI 0.94 to 1.02) and the proportion of AVFs used for dialysis (2 studies, 288 patients: RR 1.11, 95% CI 0.96 to 1.29) were not increased by vessel mapping compared with standard care.

Conclusions: In almost half of patients older than 75 years a tunneled CVC is the dialysis access of choice. Elderly females, but not diabetics, are more likely to receive a tunneled CVC.

Funding: Government Support - Non-U.S.
FR-PO164
Barriers to Timely Dialysis Access Creation: South Texas University Health System Experience
Christina Mehanni, Faraz M. Khan, Padam Hirachan, Jonathan A. Gelfond, Shweta Bansal. Div of Nephrology, Univ of Texas Health Sciences Center at San Antonio, San Antonio, TX.

Background: An arteriovenous fistula (AVF), graft (AVG) and peritoneal dialysis catheter are the recommended accesses to start dialysis therapy, however, about 80% of patients in the US start dialysis using a catheter. We assessed the rate of suboptimal dialysis start defined as initiation of dialysis with a catheter with the aim to identify barriers to timely access creation at the University Health System in San Antonio.

Methods: Charts of consecutive incident dialysis patients were reviewed from January 2010 to December 2012. A total of 154 patients were identified.

Results: Mean age ± SD of study population was 52.4 ± 13 years, 47% were males and 82% were Hispanics. End stage renal disease was attributed to diabetic nephropathy in 75% patients. Suboptimal starts occurred in 80% of the patients (19% had an immature AVF or AVG at the time of initiation). Patient’s demographics, medical history and lab parameters were not different between the suboptimal and optimal start groups. Ninety-two percent patients in the optimal group were seen by a nephrologist for >6 months compared to 66% patients in the suboptimal group (p<0.003). Physician and nurse pre-dialysis education was noted for 86% and 84% patients, respectively in optimal starts versus 33% and 28%, respectively in the suboptimal starts (p<0.001). Among the suboptimal starts, lack of regular health care prior to initiation (40%) and patient related delays (36%) were major barriers to timely access creation. Wait times (median [IQR] in days) to nephrology consult (90[48, 169]), vascular mapping (23[12, 49]), surgery consult (41[27, 62]) and access creation (44[23, 106]) were same between the two groups. On multivariate regression analysis, care by a nephrologist for >6 months was the only predictor for an optimal start (OR=13.95, CI 2.72).

Conclusions: Initiation of dialysis with suboptimal access is common in our system. Lack of regular health care prior to initiation and patient related delays were the major barriers to timely access creation, which are partly modifiable. This study provides the opportunity to test methods to prevent suboptimal starts.

FR-PO165
Vascular Access Vulnerability in Intensive Hemodialysis: A Significant Achilles’ Heel?
Tom Cornelis, Len A. Usvyat, Peter Kotanko, Yuedong Li, Tom Hui, Jonathan A. Gelfond, Shweta Bansal, Jeroen Kooman. 1Maastricht Univ Medical Center, Maastricht, Netherlands; 2Renal Research Institute, New York; 3Univ of California - Santa Barbara, Santa Barbara.

Background: Frequent hemodialysis (HD) may be associated with an increased risk of vascular access complications as compared to conventional HD, especially for arteriovenous fistulas (AVF) and grafts (AVG) due to the increased cannulation frequency. Studies addressing vascular access outcomes in frequent HD so far have shown conflicting results.

Methods: We searched Medline and Embase for all trials looking at vascular access outcomes in frequent HD as compared to conventional HD.

Results: Nineteen studies met the inclusion criteria; 3 studies used a randomized design, 9 studies used a non-randomized design, and 7 studies used a non-randomized design with matching. Mean age ± SD of study population was 52.4 ± 13 years, 47% were males and 82% were Hispanics. End stage renal disease was attributed to diabetic nephropathy in 75% patients. Suboptimal starts occurred in 80% of the patients (19% had an immature AVF or AVG at the time of initiation). Patient’s demographics, medical history and lab parameters were not different between the suboptimal and optimal start groups. Ninety-two percent patients in the optimal group were seen by a nephrologist for >6 months compared to 66% patients in the suboptimal group (p<0.003). Physician and nurse pre-dialysis education was noted for 86% and 84% patients, respectively in optimal starts versus 33% and 28%, respectively in the suboptimal starts (p<0.001). Among the suboptimal starts, lack of regular health care prior to initiation (40%) and patient related delays (36%) were major barriers to timely access creation. Wait times (median [IQR] in days) to nephrology consult (90[48, 169]), vascular mapping (23[12, 49]), surgery consult (41[27, 62]) and access creation (44[23, 106]) were same between the two groups. On multivariate regression analysis, care by a nephrologist for >6 months was the only predictor for an optimal start (OR=13.95, CI 2.72).

Conclusions: Initiation of dialysis with suboptimal access is common in our system. Lack of regular health care prior to initiation and patient related delays were the major barriers to timely access creation, which are partly modifiable. This study provides the opportunity to test methods to prevent suboptimal starts.
FR-PO168
Initial Vascular Access Type in Failed Renal Transplant Recipients
Michael R. Chan,1 Ahmed I. Al-Absi,1 Janet Bellingham,2 Maureen J. Wakeen,2 Alexander S. Yezzlin,3 Brad C. Astor,1 Nephrology, Univ of Wisconsin, Madison, WI; 2Transplantation, Univ of Wisconsin, Madison, WI.

Background: Permanent hemodialysis vascular access is crucial for ESRD patients and in those with failed renal transplant as central venous catheters (CVC) are associated with greater risk of infection and mortality than arterio-venous fistulae (AVF) or arterio-venous grafts (AVG). As renal transplant patients are closely followed by transplant physicians, it would be expected that they have a higher prevalence of AVF/AVG at the time of hemodialysis initiation than those with native kidney failure.

Methods: We examined data from USRDS on 16,728 patients with failed renal transplant and 509,643 patients with native kidney failure who initiated dialysis between 1/1/2006 and 9/30/2011.

Results: At the initiation of dialysis, 27.7% (n=4,656) of patients with a failed transplant started with an AVF, 6.9% (n=1,146) started with an AVG, and 65.4% (n=10,946) started with a CVC. Conversely, 80.8% (n=411,997) patients with native kidney failure initiated dialysis with a CVC (p<0.001).

Conclusions: There was no statistical difference in survival associated with choice of vascular access for dialysis in elderly patients. Therefore a joint decision between patient and clinician should be considered, encompassing patient preference, fitness for surgery and realistic prognosis related to therapy.

FR-PO169
MicroRNA-30 Family Inhibits Calcineurin Signaling in Podocytes
Junnan Wu, Wanfen Zhang, Shaolin Shi, Zhi-hong Liu. Research Institute of Nephrology, Jinling Hospital, Nanjing Univ School of Medicine, Nanjing, China.

Background: Calcineurin signaling has recently been implicated in the injury of podocytes. Several reagents, including TGF-beta, Lipopolysaccharides (LPS) and puroromicinaminocucleoside (PAN), can induce calcineurin signaling in podocytes, but the underlying mechanisms are unknown. We have recently found that miR-30 members are abundantly expressed in podocytes, but all downregulated by TGF-beta, LPS or PAN, leading to podocyte injury. Thus, miR-30s may protect podocytes by inhibiting calcineurin-calcineurin signaling, and downregulation of miR-30s by TGF-beta, LPS or PAN would enhance calcineurin signaling, leading to podocyte injury.

Methods: Conditionally-immortalized human podocyte cell line treated with TGF-beta, LPS or PAN, treated rats, and the biopsies of FSGS patients were used for the study. miR-30 target validations were performed by luciferase reporter assay and western blotting.

Results: We treated podocytes with TGF-beta, LPS or PAN, and found an increase in calcineurin activity, accompanied by downregulation of miR-30s and upregulations of calcineurin signaling components (PPP3ca and NFATc3, which are the predicted miR-30 targets) in the cells. However, exogenous miR-30 expression that sustained the overall level of miR-30s in the podocytes prevented the increase of calcineurin activity and upregulation of calcineurin signaling components (PPP3ca and NFATc3 in the treatment of TGF-beta, LPS or PAN). In f30 miR-30a treated rats, upregulation of PPP3ca and NFATc3 and downregulation of miR-30s were also observed in the podocytes. However, transferring exogenous miR-30a to the podocytes of the rats prevented the upregulation of PPP3ca and NFATc3 and ameliorated podocyte injury. Calcineurin (PPP3ca)upregulation was also found in the podocytes of FSGS patients, in which miR-30s were downregulated. Finally, luciferase reporter assays confirmed that PPP3ca and NFATc3 are the direct targets of miR-30s ipodocytes.

Conclusions: miR-30s inhibit calcineurin signaling in podocytes by directly targeting calcineurin-calcineurin signaling components. Downregulation of miR-30s and the consequent upregulation of calcineurin signaling may be an alternative mechanism by which TGF-beta, LPS or PAN damages podocytes.

Funding: Government Support - Non-U.S.

FR-PO170
The Paracrine Function of Myofibroblast Was Regulated by miRNA-21 in 5/6 Nephrectomy Mice
Yiwen Li. ZheJiang Province Hospital.

Background: Myofibroblast is very important to maintain the normal cardiac function and the cardiac remodeling in pathologic condition. Our previous study found that the paracrine dysfunction of myofibroblast may be responsible for the left ventricular remodeling in uremic cardopathy. However, the mechanism of paracrine disruption of myofibroblast is unknown.

Methods: CRF was induced in adult male mice by 5/6 nephrectomy. The mice were killed at 12 weeks after operation. Myofibroblast was derived from sham mice and 5/6 nephrectomy mice. miRNA-21 was analyzed by PCR. IL-1ß, IL-6, TNF-α, TGF-ß were also decreased in medium. The in vitro study, normal medium, and medium with uremic patients serum were used for the myofibroblast culture.

Results: Myofibroblasts derived from 5/6 nephrectomy mice showed a significant increased expression of miRNA-21 accompanying increased concentration of IL-1ß, IL-6, TNF-α, TGF-ß in medium. The uremia patient serum increased the expression of miRNA-21 in normal cultured myofibroblasts accompanying increased expression of p-AKT, p-ERK1/2, and p-STAT5. Inhibited the miRNA-21 expression by siRNA significantly reduced the overexpression of p-AKT, p-ERK1/2 and p-STAT5 caused by uremic serum. In the same time the concentration of IL-1ß, IL-6, TNF-α, TGF-ß were also also decreased in medium.

Conclusions: The current study elucidated that myofibroblast paracrine function was regulated by miRNA-21 through p-AKT, p-ERK1/2 and p-STAT5 signals pathways in 5/6 nephrectomy mice.

Funding: Clinical Revenue Support

FR-PO171
Number and Function Impairment of Resident c-kit+ Cardiac Stem Cells in Mice with Renal Dysfunction Caused by 5/6 Nephrectomy
Yiwen Li. ZheJiang Province Hospital.

Background: Cardiac stem cell (CSC) dysfunction exists in various kinds of cardiovascular diseases, and may be responsible for the insufficient regeneration of cardiac myocytes and coronary vessels. However, whether chronic renal failure (CRF) affected CSC is unknown.

Methods: CRF was induced in adult male mice by 5/6 nephrectomy. The mice were killed at 12 weeks after operation. C-kit+ CSC numbers was evaluated by flow cytometer. Apoptosis and DNA damage of C-kit+ CSC in the control and CRF mice was analyzed by immunohistochemistry. In the in vitro study, normal medium, and medium with uremic rat serum were used for the CSC culture.

Results: CSC counts attenuated significantly in the chronic renal failure model, whereas apoptosis cells and 8-OHdG-positive cells significantly increased. CSC derived form 5/6 nephrectomy mice heart showed an impaired anti-oxidant potential. In the cultured cells, CSCs subjected to uremic rat serum showed a higher frequency of TUNEL stain-positive and 8-OHdG-positive cells. The uremia rat serum reduced the expression of hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) in CSC.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only
Conclusions: The current study elucidated that CSC number and function disorders existed in mice with chronic renal insufficiency. Apoptosis, oxidative stress and reduced angiogenic factors secretion caused by uremic toxins in serum are contributors to CSC dysfunction.

FR-PO172
MicroRNA-22 Is a Master Regulator of Bone Morphogenetic Protein-7/6 Homeostasis in the Kidney
Junyin Long,1,2 Shawn S. Badal,1,2 Yin Wang,1,2 Farhad R. Danesh,1,2 1Dept of Medicine/Nephrology, Baylor College of Medicine, Houston, TX; 2Section of Nephrology, The Univ of Texas MD Anderson Cancer Center, Houston, TX.

Background: Accumulating evidence suggests that microRNAs (miRNAs) contribute to a myriad of kidney diseases. However, the regulatory role of miRNAs on the key molecules implicated in kidney fibrosis remains poorly understood. Bone morphogenetic protein-7 (BMP-7) and its related BMP-6 have recently emerged as key regulators of kidney fibrosis. Using the established unilateral ureteral obstruction (UUO) model of kidney fibrosis, we examined the regulatory role of miRNAs on BMP-7/6 signaling.

Methods: We employed several in silico analyses to identify conserved, putative, BMP-7/6 targeting miRNAs. Isolation of renal fibroblasts, real-time qPCR of mRNA and miRNA, miRNA in situ hybridization, oligonucleotide-directed mutagenesis, and lucerase reporter assays were carried out as previously described.

Results: miR-22 was predicted to target BMP-7/6 in silico and validated to downregulate BMP-7/6 expression in vitro. To further assess the effect of miR-22 in vivo, we generated a miR-22 null mouse using a targeted strategy to delete the whole exon containing pri-miR-22. We found that knockout of miR-22 significantly attenuated renal fibrosis in the UUO kidney fibrosis model. Interestingly, targeted deletion of miR-22 led to robust elevation of BMP-7/6 protein expression and downstream signaling in vivo. We further demonstrated that miR-22 directly binds to 3’-untranslated region (UTR) of BMP-7, BMP-6 and BMP1B miRNAs in vitro. Importantly, transfection of miR-22 mimic into primary renal fibroblasts isolated from miR-22-deficient mice partially restored the pro-fibrogenic genes induced by TGF-β1. Finally, we found that miR-22 by itself is induced by BMP-7/6, and identified two BMP-responsive elements (BREs) in the proximal promoter region of miR-22 gene.

Conclusions: Our data suggest that miR-22 serves as a master regulator of BMP signaling cascade and renal fibrosis. Our findings also indicate that miR-22 and BMP-7/6 form a regulatory feedback circuit, where not only miR-22 inhibits BMP-7/6, but miR-22 by itself is induced by BMP-7/6 signaling.

Funding: NIDDK Support

FR-PO173
The Mechanism of Pleiotropic Effect in Endothelial Cells with Pitavastatin Treatment
Tsuyoshi Inoue,1,2 Yasuharu Kanki,1,2 Tatsuhiko Kodama,1,2 Youichiro Wada,1 Masaomi Nangaku,1 Takashi Maejima. 2
1Dept of Clin Lab, Univ of Fukui Hosp, Fukui, Japan; 2Dept of Nephrology and Endocrinology, The Univ of Tokyo; 3Laboratory for Systems Biology and Medicine, Research Center for Advanced Science and Technology, The Univ of Tokyo.

Background: CKD is an important risk factor for progression of atherosclerosis related cardiovascular disorders. Patients are widely-used cholesterol lowering drugs. Multiple lines of evidence, including randomized clinical trials, suggested that statins also directly protect the kidney and vascular cells. These, so-called “pleiotropic effects” are supposed to occur, in part, through alterations in vascular cell gene expression.

Methods: We used various epigenetic methods such as Chromatin Immunoprecipitation assay with deep sequencing (ChIP-seq), Chromatin Interaction Analysis by Paired-End Tag Sequencing (ChIA-PET) and Chromosome Conformation Capture (3C)-PCR assay to dissect the molecular mechanism of the gene expression.

Results: Detailed investigation of HIF1 dependent gene expression led us to realize the importance of crosstalk between PPARβ/δ and HIF1 signaling axes. Migration assay showed that synergistic enhancement with these two stimuli, and ANGPTL4 was identified as the common target gene by the combination of microarray and ChIP-seq analysis. The reporter assay combined with ChIP-seq identified the functional hypoxia responsive element (HRE) and PPAR responsive element (PPRE) in the promoter and intron regions of ANGPTL4. The profile changes of the enhancer histone mark (H3K27ac) under hypoxia, PPARβ/δ ligand, and dual stimulations suggested that the spatial proximity of two response elements was the crosstalk cause of the synergistic transcription induction. ChIA-PET supported the interaction between the two regions, and further, newly developed quantitative 3C-PCR assay showed the quantitative change of the frequency of proximity.

Conclusions: These results imply that hypoxic and PPARβ/δ stimulations are important for activation of ANGPTL4 expression, and the synergistic activation is achieved by spatial proximity formation in ANGPTL4 loci.

Funding: Government Support - Non-U.S.

FR-PO174
The Mechanism of ANGPTL4 Induction, a Mediator of Neprotic Syndrome, through Its Chromatin Conformational Change
Tsuyoshi Inoue,1,2 Imari Mimura,1 Takahide Kohro,1 Yoshiya Tanaka,2 Hiroyuki Kamiyama,1 Naoki Takahashi,1 Kenji Kasuno,2 Haruyoshi Yoshida,3 Masayuki Iwano. 1Dept of Clin Lab, Univ of Fukui Hosp, Fukui, Japan; 2Dept of Nephrology and Endocrinology, The Univ of Tokyo; 3Laboratory for Systems Biology and Medicine, Research Center for Advanced Science and Technology, The Univ of Tokyo.

Background: Angiopoietin-2 (ANGPTL4) has been identified as a cause of minimal change nephrotic syndrome recently, but the mechanism of this gene induction has not been elucidated yet.

Methods: In addition to Chromatin Immunoprecipitation (ChIP) assay with deep sequencing (ChIP-seq) analysis of hypoxia inducible factor (HIF) 1α, peroxisome proliferator-activated receptor (PPAR) β/δ and RNA polymerase (Pol) II, we used epigenetic methods including ChIP-seq of histone marks, Chromatin Interaction Analysis by Paired-End Tag Sequencing (ChIA-PET) and Chromosome Conformation Capture (3C)-PCR assay to dissect the molecular mechanism of the gene expression.

Results: Detailed investigation of HIF1 dependent gene expression led us to realize the importance of crosstalk between PPARβ/δ and HIF1 signaling axes. Migration assay showed that synergistic enhancement with these two stimuli, and ANGPTL4 was identified as the common target gene by the combination of microarray and ChIP-seq analysis. The reporter assay combined with ChIP-seq identified the functional hypoxia responsive element (HRE) and PPAR responsive element (PPRE) in the promoter and intron regions of ANGPTL4. The profile changes of the enhancer histone mark (H3K27ac) under hypoxia, PPARβ/δ ligand, and dual stimulations suggested that the spatial proximity of two response elements was the crosstalk cause of the synergistic transcription induction. ChIA-PET supported the interaction between the two regions, and further, newly developed quantitative 3C-PCR assay showed the quantitative change of the frequency of proximity.

Conclusions: These results imply that hypoxic and PPARβ/δ stimulations are important for activation of ANGPTL4 expression, and the synergistic activation is achieved by spatial proximity formation in ANGPTL4 loci.

Funding: Government Support - Non-U.S.

FR-PO175
Vascular Endothelial Growth Factor-C Production Stimulated by TNF-α through p38/HSP27 Pathway and Its Therapeutic Reduction in Human Proximal Renal Tubular Cells
Hideki Kimura,1 Daisuke Mikami,2 Kazuko Kamiyama,2 Naoki Takahashi,2 Kenji Kasuno,2 Haruyoshi Yoshida,3 Masayuki Iwano. 1Dept of Clin Lab, Univ of Fukui Hosp, Fukui, Japan; 2Dept of Nephrology and Endocrinology, The Univ of Tokyo; 3Laboratory for Systems Biology and Medicine, Research Center for Advanced Science and Technology, The Univ of Tokyo.

Background: Vascular endothelial growth factor-C (VEGF-C) promotes lymphatic angiogenesis associated with renal inflammation and fibrosis in chronic and acute kidney disease (CKD) where glucocorticoids and angiotensin II receptor type 1 (ARB) are widely used as a main remedy. VEGF-C production status and its modification by the two main remedies has remained unclear in human proximal renal tubular cells (HPTCs) under inflammation.

Methods: Confluent HPTECs were treated for 24h with putative VEGF-C inducers in absence or presence of specific kinase inhibitors (SB203580, H89, PD980590), dexamethasone (DXA;10 nM) or Telmisartan (Telm; 1-10μM), an ARB with peroxisome proliferator-activated receptor (PPAR) activity. VEGF-C expression was assessed by RT-PCR and ELISA. Phosphorylation of signalling molecules and PPAR activity were examined by immunoblotting, and PPRE-luc assay and specific inhibitors, respectively.

Results: In HPTECs, TNF-α (1-10 ng/ml) increased glycanation endproducts, and high glucose induced VEGF-C by 2.8-fold, 1.3-fold, and 1.2-fold, respectively, while TGF-β1 (1-5 μg/ml) and hypoxia (1%O2) had no influence on the production. VEGF-C production by TNF-α was mediated via phosphorylation of p38 MAPK/HSP27 pathway but not ERK or NFκB pathway. HSP27 silencing by siRNA reduced VEGF-C expression. DXA reduced TNF-α-induced VEGF-C production at mRNA and protein levels by about 40% via decreasing p38/HSP27 phosphorylation. Like DXA, Telm also decreased basal and TNF-α-induced VEGF-C production by about 30%. Moreover, Telm served as a specific PPAR-β activator, and reduced VEGF-C production which was partially explained by p38/HSP27-dependent suppression of p38 phosphorylation.

Conclusions: Renal parenchymal inflammation may induce VEGF-C production in proximal renal tubular cells, possibly facilitating the surrounding lymphatic vessel formation. Major remedies for CKD may modulate lymphatic angiogenesis as well as fibrotic status.

Funding: Government Support - Non-U.S.

FR-PO176
The Effects of Endothelial Microparticles Induced by Indoxyl Sulfate on TGF-β Signaling in Vascular Smooth Muscle Cells
Jin-Woo Ryu, Shina Lee, Dong-Kyoo Ryu, Duk-Hee Kang, Kyu Bok Chai, Seung-Jung Kim. Dept of Internal Medicine, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea.

Background: Vascular access failure is one of the critical risk factor for the mortality or morbidity in hemodialysis (HD) patients. The venous neointimal hyperplasia (VNH) is the main pathogenesis of access stenosis, and recently it was reported that the proliferation of vascular smooth muscle cells (VSMCs) promoted by activation of TGF-β signaling...
Microvesicles Released by Vascular Endothelial Cells Increase Hypoxia Inducible Factor Expression in Human Proximal Tubular HK-2 Cells

Javier Lucio,1 Ana Valdehi,1 Julia Carracedo,2 Rafael Ramirez,2 Ana Belen Fernandez.1

University Alcala, Spain; 2Hospital Reina Sofia Cordoba, Spain.

Background: Co-culture experiments suggest that vascular endothelial cells may influence transcriptional regulation of HK-2 cells and that several hypoxia-inducible factors (HIF) are upregulated in HK-2 cells. Here we aimed to investigate whether endothelial microvesicles (EMVs) increase the expression of HIF and the production of the putative renal protection factor HIF-regulated VEGF-A (HIF)-dependent genes were upregulated (Am J Physiol 2008, 294:C543–C554). Here we have recently found that the sequential activation of cyclooxygenases (COX), epidermal growth factor receptor (EGFR), mitogen- and stress-activated kinase-1 (MSK-1) and retinoic acid receptor-β (RARβ) up-regulates HIF-1α. This pathway was also involved in EMVs-induced increase in HIF since it was sensitive to diclofenac, AG1478, IBO9 and LE115 (which inhibit respectively COX, EGFR, MSK1 and RARβ). Interestingly, we also found an increased content in EMVs in human urine samples taken from patients with diseases known to induce chronic vascular inflammation, which indicates that tubular cells are exposed to EMVs in vivo.

Results: These results suggest that EMV’s might influence the in vivo expression of HIF, and thereby that of its target genes, in proximal tubular cells.

Funding: Government Support - Non-U.S.

FR-PO180

Kidney Micrvascular Endothelial Cells Exhibit Organ Specific Angiogenic Characteristics in 3D Culture

Nagai,1 Takahide Takanashi,1 Anton Matanovic,2 Hideyuki Ito,1 Dana Zemel,2 Katherine Smarrattiva,2 Rebecca S. Weller,2 Takamune Takahashi.2

Vanderbilt Univ, Nashville, TN.

Background: CD148 is a transmembrane tyrosine phosphatase that is expressed in renal endothelium and tubular cells. CD148 is accumulated at cell-cell contacts. Recent biochemical studies demonstrated that CD148 associates with VE- cadherin/catenin complex, and p120 catenin serves as a substrate. However, the function of CD148 in cadherin adhesion is still unknown. We therefore addressed this issue using a series of stable cells and cell-based assays.

Methods: Wild type (wt) and catalytically inactive (c-s) CD148 was stably introduced into A431D (lacking cadherins), A431D/E-cad (expressing E-cadherin), and A431D/E-cadAAA764 (expressing p120-uncoupled E-cadherin) cells. The effects of CD148 on cadherin cell adhesion were assessed by Ca2+ switch, cell aggregation, and cell density assays. Phosphorylation of E-cadherin/catenin complex and Rho family GTPase activities were examined using WP/BLOT or Rhokin/Pak assays.

Results: CD148wt, but not CD148c-s, extended cadherin contact zone as early as 30 min after cadherin engagement (Ca2+ switch assay) and remarkably strengthened cell-cell adhesion (aggregation assay) in A431D/Ecad cells, although CD148 introduction did not change E-cadherin/catenin levels and complex formation. These effects accompanied p120 and β catenin dephosphorylation and an increase in Rac1, but not RhoA and cdc42, activity. Interestingly, CD148wt increased phosphorylation of p120 Y228 (a Src kinase site) on cell-cell contacts together with an increase in Src activity (well-known CD148 activity). The effects of CD148wt to strengthen cell cell adhesion were abolished by Rac1 inhibition. CD148wt showed no effects in A431D and A431D/EcadAAA764 cells. Notes: β catenin was not dephosphorylated (Am J Physiol 2011 in vitro, suggesting β catenin dephosphorylation in intact cells may be a secondary effect; CD148 showed similar effects in endothelial cells.

Conclusions: CD148 regulates p120 and β catenin phosphorylation upon cell adhesion via the direct and indirect mechanisms, increases Rac1 activity and extends cadherin contacts, strengthening E (and VE-) cadherin adhesion. This CD148 effect requires Ecad-p120 interaction.

Funding: NIDDK Support
**FR-PO181**

The Effect of Angiotensin (1-7) on Glomerular Angiopoietins-Tie-2 and Its Potential Mechanisms

Chengyuan Xu,1 Wei Ding,1 Minmin Zhang,1 Yong Gu.2

1Nephrology, Huaxian Hospital, Fudan Univ, Shanghai, China; 2Nephrology, The Fifth People’s Hospital of Shanghai, Fudan Univ, Shanghai, China.

**Background:** Angiopoietins-Tie-2 is one of the important angiogenesis system in glomeruli. Though Ang (1-7) has been reported inhibiting endothelial cell tube formation in vitro in human umbilical vein endothelial cells, the research regarding its effect in glomerular angiogenesis has not been fully understood. However, these effects are observed in the effects of Ang (1-7) on glomerular angiopoietins-Tie-2 system and its potential mechanisms.

**Methods:** The mouse glomerular endothelial cells (MEGECs) and podocytes were cultured. Under the condition with or without exogenous Ang II, the cells were treated with Ang (1-7)-induced Losartan, A-779 and PD98059 respectively. Real-time PCR was applied to test the gene expression of Ang-II in podocytes and Ang-2 in MEGECs treated with different doses of Ang (1-7) and AngII. The protein expression of Ang-II, Ang-2, Tie-2, phosphorylate eNOS and ERK1/2 was detected by Western blot. The ability of endothelial cells tube formation was observed by Matrigel method.

**Results:** Losartan and Ang (1-7) co-inhibited the expression of angiopoietins-Tie-2 without exogenous Ang II. While under the condition of exogenous AngII, the downregulating effect of Ang (1-7) on angiopoietins-Tie-2 expression was even more significant (P < 0.05). However, the suppressing effect of Ang (1-7) on angiopoietins-Tie-2 could be reversed by Losartan, A-779 and PD98059 (P < 0.05). Furthermore, the eNOS pathway could be activated by Ang (1-7) (P < 0.05). However, under the condition of exogenous Ang II, the phosphorylate eNOS was downregulated whereas the phosphorylated ERK1/2 was upregulated, which could be reversed by L-NAME (P < 0.05).

**Conclusions:** Ang (1-7) inhibited angiogenesis and resisted the effect of AngII by promoting the expression of angiopoietins-Tie-2. With the pretreatment of exogenous AngII, Ang (1-7) inhibited the expression of angiopoietins-Tie-2 more remarkably with downregulating eNOS and activating ERK1/2 pathway, which could be reversed by Losartan.

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

**FR-PO182**

Inhibition of Ca2+ Influx through Reverse-Mode Na+/Ca2+-Exchange (NCX) Preserves Endothelial Barrier Function in Response to Thrombin: Implications for CKD


**Background:** CKD patients exhibit high levels of plasma thrombin activity which could have a direct effect on the endothelium through its major receptor protease activated receptor-1 (PAR-1). This may result in loss of barrier function causing pulmonary and peripheral edema that are hallmarks of CKD and exacerbate the severity of this multifactorial disease. We recently reported that in human endothelial cells (HUCECs), Ca2+ influx through reverse-mode NCX is critical for ERK1/2 activation and angiogenesis by VEGF. Here, we investigated whether NCX activity also plays a role in ERK1/2 activation and endothelial barrier dysfunction by thrombin.

**Methods:** ERK1/2 activation was investigated by western blot, Ca2+ transients were monitored with Fluoro-4NW and permeability was assessed by FITC-dextran accumulation in hepatic cells. However, these effects are overridden by rapamycin, which is an inhibitor of mammalian target of rapamycin (mTOR). This study investigated the role of mTOR pathway in foam cell formation in vascular smooth muscle cells (VSMCs).

**Results:** Rat VSMCs were treated with or without lipopolysaccharide(LPS) in the absence or presence of rapamycin or mTOR siRNA. Lipid accumulation in VSMCs was measured by Oil red O staining. The expression and protein phosphorylation of mTOR pathway, LDLR pathway, and retnoblastoma tumour suppressor protein (pRb) were checked by immunofluorescent staining, real-time PCR, and Western blotting.

**Conclusions:** Inflammation increased lipid accumulation in VSMCs, which were correlated with increased expressions of LDLR, sterol regulatory element-binding protein (SREBP) cholesterol-synthesizing protein (SREBP), and SCAP/SREBP-2 complex from endoplasmic reticulum (ER) to Golgi. Furthermore, inflammation increased both the percentage of cells in the S phase of cell cycle and protein expressions of the phosphorylated forms of pRb, mTOR, eukaryotic initiation factor (EIF)-2 and 4E-BP1, and p70 S6 kinase. After treatment with rapamycin or mTOR siRNA, the activity of mTOR pathway was blocked, and the phosphorylation of pRb was also inhibited. Interestingly, the expression levels of LDLR, SCAP, and SREBP-2 and the translocation of SCAP/SREBP-2 complex from the ER to the Golgi in VSMCs were accordingly decreased in the presence of inflammatory stress.

**Funding:** Inflammation disrupts LDLR feedback regulation through the activation of mTOR pathway. Increased mTOR complex 1-activity was found to upregulate SREBP2-mediated cholesterol uptake through Rb phosphorylation.

**FR-PO185**

Activation of mTOR Modulates SREBP-2 to Induce Foam Cell Formation in Vascular Smooth Muscle Cells through Increased Retinoblastoma Protein Phosphorylation

Kun Ling Ma, Jing Liu, Yang Zhang, Wu Yu, Jie Ni, Bi-Cheng Liu. Institute of Nephrology, Southeast Univ School of Medicine, Nanjing, China.

**Background:** Our previous studies demonstrated that inflammation contributes to foam cell formation through the disruption of low density lipoprotein receptor (LDLR) pathway. However, this effect is overridden by rapamycin, which is an inhibitor of mammalian target of rapamycin (mTOR). This study investigated the role of mTOR pathway in foam cell formation in vascular smooth muscle cells (VSMCs).

**Results:** Rat VSMCs were treated with or without lipopolysaccharide(LPS) in the absence or presence of rapamycin or mTOR siRNA. Lipid accumulation in VSMCs was measured by Oil red O staining. The expression and protein phosphorylation of mTOR pathway, LDLR pathway, and retnoblastoma tumour suppressor protein (pRb) were checked by immunofluorescent staining, real-time PCR, and Western blotting.

**Conclusions:** Inflammation increased lipid accumulation in VSMCs, which were correlated with increased expressions of LDLR, sterol regulatory element-binding protein (SREBP) cholesterol-synthesizing protein (SREBP), and SCAP/SREBP-2 complex from endoplasmic reticulum (ER) to Golgi. Furthermore, inflammation increased both the percentage of cells in the S phase of cell cycle and protein expressions of the phosphorylated forms of pRb, mTOR, eukaryotic initiation factor (EIF)-2 and 4E-BP1, and p70 S6 kinase. After treatment with rapamycin or mTOR siRNA, the activity of mTOR pathway was blocked, and the phosphorylation of pRb was also inhibited. Interestingly, the expression levels of LDLR, SCAP, and SREBP-2 and the translocation of SCAP/SREBP-2 complex from the ER to the Golgi in VSMCs were accordingly decreased in the presence of inflammatory stress.

**Funding:** Inflammation disrupts LDLR feedback regulation through the activation of mTOR pathway. Increased mTOR complex 1-activity was found to upregulate SREBP2-mediated cholesterol uptake through Rb phosphorylation.

**FR-PO186**

Activation of mTOR Modulates LDL Receptor at Transcriptional and Post-Transcriptional Level to Accelerate Lipid Accumulation in Fatty Livers of Apolipoprotein E Knockout Mice

Kun Ling Ma, Jing Liu, Yang Zhang, Wu Yu, Bi-Cheng Liu. Institute of Nephrology, Southeast Univ School of Medicine, Nanjing, China.

**Background:** Our previous studies demonstrated that inflammation exacerbates lipid accumulation in hepatic cells. However, these effects are overridden by rapamycin, which is an inhibitor of mammalian target of rapamycin (mTOR). This study aimed to investigate the role of mTOR pathway in lipid accumulation in fatty livers.

**Methods:** Apolipoprotein E knockout mice were subcutaneously injected with 1H-2H-3H-4H-5H-[ring]L-lysine to induce chronic inflammation. Serum levels of serum amyloid A, tumour necrosis factor-a, and lipid profiles were measured by enzyme-linked immunosorbent assay and clinical biochemistry assay. Lipid accumulation was evaluated by haematoxylin-eosin and filipin staining. The associated protein expression of mTOR and low-density lipoprotein receptor (LDLR) pathways were checked by immunohistochemical staining, immunofluorescent staining, and Western blotting.

**Results:** Inflammation significantly reduced serum levels of lipid profile compared to the controls. However, inflammation increased lipid accumulation in livers, correlated with increased expressions of LDLR, sterol regulatory element-binding protein (SREBP) cleavage-activating protein (SCAP), and SREBP-2, as well as with enhanced translocation of SCAP/SREBP-2 complex from endoplasmic reticulum (ER) to Golgi. Meanwhile, unregulated LDLR gene transcription recruited proprotein convertase subtilisin kexin 9 (PCSK9) with accordingly increased PCSK9 protein expression. Furthermore, inflammation increased the mTOR phosphorylation. After treatment with rapamycin, mTOR activity was inhibited, accompanied with accordingly decreased expression of LDLR, SCAP, and SREBP-2, decreased translocation of SCAP/SREBP-2 complex from the ER to the Golgi, and increased PCSK9 expression in the presence of inflammatory stress.

**Conclusions:** The activation of mTOR pathway caused by inflammation disrupted the regulation of LDLR at transcriptional and post-transcriptional level, resulting in lipid accumulation and exacerbated the progression of fatty liver.

**FR-PO187**

Effect of Cyclosporine Treatment on Akt-FOXO Signaling in C57BL/6 Mouse Cells

Jill Rahmert,1 Bin Zheng,1 Russ Price.1,2 1Dep of Medicine, Emory Univ, Atlanta, GA; 2VA Medical Center, Atlanta, GA.

**Background:** Muscle wasting is a consequence of chronic diseases such as chronic kidney disease (CKD) and type I diabetes (DM). Insulin/IGF-1 deficiency, combined with chronic elevation of glucocorticoids, promotes protein degradation by activating the FOXO pathway.
FR-P0187

Vitamin D Receptor (VDR) Expression Determines p53-Induced Tubular Cell Phenotype

Background: p53 displays a bimodal effect on cellular growth-p53 over expressing cells are prone to apoptosis, whereas, p53 mutant cells display proliferation mode. We hypothesize that vitamin D receptor (VDR) plays a key role in p53-mediated tubular cell growth.

Methods: Human renal proximal tubular cells (HRPTC) were either transfected with siRNA-p53 (siRNA-p53/HRPTC), scrambled siRNA (SCR/HRPTC), or p53 plasmid (p33/HRPTC). Protein blot of CHRPTCs, siRNA-p53/HRPTC, SCR/HRPTC, and p53/HRPTC were probed for VDR, angiostatinogen (Ag1) renin, phospho-p66Sha, and actin. To confirm the activation of the renin angiotensin system (RAS), Ang II content of the cellular lysates was measured by ELISA. To determine the modulation of reactive oxygen species (ROS) generation, cells were co-labeled with Red CC1 and miotracker green in the presence/absence losartan (an Ang II blocker), and a VDR agonist (VDA, EB1089). Cells treated under above mentioned conditions, were also evaluated for occurrence of apoptosis by TUNEL assay/Western blotting for caspase-3 cleavage and for proliferation by labeling for proliferative cell nuclear antigen (PCNA).

Results: p53/HRPTC displayed down regulation of VDR, enhanced expression of renin and Ag1 and elevated levels of Ang II when compared to C/HRPTC and SCR/HRPTC; however, EB1089 inhibited these effects of p53. p33/HRPTC showed enhanced expression of phospho-p66Sha and increased generation of ROS. p53/HRPTC displayed cleavage of caspase-3 and increased number of TUNEL +ve cells. Both siRNA and losartan attenuated down regulation of renin expression as well as apoptosis in p53/HRPTC, it appears that p53 mediated tubular cell apoptotic phenotype through VDR-induced activation of the RAS. On the other hand, siRNA/p53/HRPTC displayed enhanced VDR expression and down regulation of the RAS and attenuated generation of ROS. siRNA/p53/HRPTC not only showed resistance to apoptosis but also enhanced number of PCNA +ve cells.

Conclusions: These findings indicate that VDR expression determines p53-induced tubular cell phenotype.

Funding: NIDDK Support

FR-P0188

Novel Biological Gas H2S Regulates the Length of Primary Cilia of Kidney Tubular Epithelial Cell
Sang Jun Han,1 Jee In Kim,1,2 Kwon Moo Park.1,2

Background: Malformation of primary cilia is associated with various kidney diseases such as polycystic kidney disease and chronic kidney disease (CKD)-induced injury. Others have previously reported that hydrogen sulfide (H2S) attenuated (R)-induced injury in hepatic, myocardial, renal I/R model. Our recent work revealed that length of primary cilia largely depends on oxidative stress and ERK activation. H2S is known to have antioxidative effects. However, the role of H2S in cilogenesis is unknown yet.

Methods: To elucidate the role of H2S in cilogenesis and underlying mechanism, we investigated exogenous H2S donor NaHS and inhibitors of endogenous H2S producing enzymes proprargylglycine (PAG, an inhibitor of CSE), cystathionine gamma lyase and hydroxylation (H2S inhibitor of CBS, cystathionine beta synthase) in the kidney tubular epithelial cells. To determine the primary cilium length, cells were immunofluorescence stained with acetylated tubulin antibody.

Results: NaHS treatment increased expressions of Arl13b and Sec61 which are associated with cilium formation, and elongated primary cilia. Treatment of PAG and HA prevented the elongation of primary cilia. PAG or HA shortened the length of primary cilia. NaHS induced cilia elongation by upregulation of phospho-ERK, Sec10 and Arl13b expressions, whereas PAG and HA suppressed cilia elongation with downregulation of phospho-ERK, Sec10 and Arl13b activity. FR-6087 caused these effects.

Conclusions: Taken together, our results suggest that H2S accelerates primary cilia elongation by ERK activation, and provide a better understanding of molecular mechanism underlying cilia length regulation in the kidney.

Funding: Government Support - Non-U.S.

FR-P0189

The Mammalian Target of Rapamycin (mTOR) Complex Gets Activated during Tight Junction Biogenesis
Laurence Pong, Jean-olivier Defraigne, Joanna Marie H. Krzesinski, Francois Jouret.

Background: The tight junctions (TJ) between renal tubular cells regulate paracellular diffusion and cell differentiation. TJ disruption in acute kidney injury represents one of the earliest events. Still, the signaling network involved in TJ assembly and maintenance remains poorly characterized. The AMP-activated protein kinase (AMPK) has been implicated both in vitro and in vivo in TJ regulation. Several AMPK kinases have been identified, with Liver kinase B1 (LKB1) and Ca2+/calmodulin-dependent protein kinase β (CAMKKβ) being the main ones. In turn, AMPK coordinates various housekeeping mechanisms, including the inhibition of the mammalian target of rapamycin (mTOR) complex. Here, we pharmacologically modulated the AMPK network at the time of a Ca2+ switch in order to further characterize TJ biogenesis.

Methods: The Ca2+ switch, i.e. switching cell culture conditions from low [5 µM] to high [1.8 mM] Ca2+ concentrations, is a widely used model to study TJ assembly in Madin-Darby canine kidney (MDCK) cells.

Results: A Ca2+ switch is not only associated with AMPK phosphorylation (Thr172) and activation, as observed by the phosphorylation (Ser79) of acetyl-CoA carboxylase (ACC), but also with the activation of mTOR, as indicated by an increased phosphorylation (Thr389) of p70 S6 kinase. Incubation of MDCK cells with the AMPK activator, phenformin [10 µM], (in low or high Ca2+ conditions or with LRP5/6 depletion) induced AMPK activation and ACC phosphorylation and mTOR inhibition, as previously reported. Still, phenformin treatment at the time of a Ca2+ switch did not prevent p70 phosphorylation, by contrast, exposure to the mTOR inhibitor, rapamycin [20nM], inhibited p70 phosphorylation, even following a Ca2+ switch.

Conclusions: AMPK and ACC phosphorylation are upstream regulators of mTOR activation, at the time of a Ca2+ switch abrogated AMPK phosphorylation and mTOR activation but did not hamper mTOR activation.

Funding: Private Foundation Support, Clinical Revenue Support, Government Support - Non-U.S.
FR-PO191
Tubular Secretion of Indoxyl Sulfate and Residual Renal Function
Sachin Bhawar,1 Prabhjot Singh,2 Jiri Zavadil,2,3 Jerome Lowenstein.1 1Medicine, NYU Langone Medical Center, New York, NY; 2Medicine, NYU Langone Medical Center, New York, NY; 3WHO International Agency for Research on Cancer, NYU Langone Medical Center, New York, NY.

Background: Residual Renal Function (RRF), persistent urine production in patients with ESRD, is associated with better patient survival, less severe atherosclerotic vascular disease, and lower plasma concentrations of a putative protein-bound, poorly dialyzable uremic toxin, indoxyl sulfate, IS. This solute is normally secreted via Organic Anion Transporters (OATs) in the proximal renal tubule rather than filtered at the glomerulus.

Methods: We devised a reporter system using cultured human renal tubular cells to compare IS expression profiles (using Affymetrix gene chip) in response to incubation with pre- and post-dialysis plasma from subjects with RRF (n=5) and anuric subjects (n=5). Total IS in plasma was measured by HPLC.

Results: Patients with RRF had lower pre- (36.3±18.7 μg/ml) and post-dialysis (19.8±12.8 μg/ml) total IS levels than patients without RRF (pre- 51.2±24.8 μg/ml, post-dialysis 27.3±11.9 μg/ml). We examined the hypothesis that plasma from subjects with RRF might display lower activation of inflammatory pathways than plasma from patients without RRF. Patterns of gene expression in cultured cells revealed a differential response between the two groups. Our tubular cell reporter system detected broad biological differences in the effects of pre- and post-dialysis plasma from patients with RRF as compared to those without RRF, as determined by Gene Set Enrichment Analysis. Plasma from patients without RRF elicited greater activation of the TGF-β pathway and dysregulation of additional pathways that might underlie metabolic changes or vasculopathy.

Conclusions: These findings suggest a role for poorly dialyzable uremic toxins in the pathogenesis of renal scarring and uremic vasculopathy. We suggest that Residual Renal Function may reflect an important component of fluid generated by tubular secretion rather than glomerular filtration. Future, this paradigm would warrant close attention to the avoidance of medications that compete for transport by OATs.

Funding: Private Foundation Support

FR-PO192
The Effect of Farnesyl ThioSalicylic Acid (FTS) on TGFb1 Signaling in Murine Proximal Tubule Epithelial Cells (PTEC) Subash Somalanka,1 Claire C. Sharpe,2 Mysore Keshavmurthy Phanish,1 Mark Edward Dockrell.1,2 SWITRR, St. Helier Hospital, London, United Kingdom; ‘Renal Medicine, Kings College, London, United Kingdom.

Background: Targeting Rats-GTPases has been shown to ameliorate renal disease progression.

Methods: Cells derived from S3 segment of murine proximal tubule of a SV40 transformed brinster transgenic mouse were used for in vitro experiments. Serum starved cells were treated with TGFβ1 [2.5ng/ml], PD98059 [20μM] & FTS [5μM] for 5min & 1h for signaling studies & 24h for CTGF protein expression. Cells were pre-treated for 30min in the presence of the chemical inhibitors where appropriate. Cellular lysates were analysed by western blotting. Bio-Plex Multiplex phosphoproteins assay was used to study activation of Akt, ERK1/2, GSK-3β, histone H3, JNK, MEK1 & p38MAPK.

Results: TGFβ1 induced ‘secreted CTGF’ (1.5 fold, p<0.001) which was inhibited by PD98059 & FTS (p<0.001) at 24h. TGFβ1 induced SMAD activation and phosphorylation of Histone H3 (p<0.001) which was inhibited in the presence of FTS [SMAD (p<0.001), Histone H3 (p<0.01)]. TGFβ1 did not induce P38-kinase activation (p=0.08). The effect of FTS on ERK1/2 activation, p38 MAPK & MEK1 was significant in the presence of TGFβ1 (p<0.03, p=0.03 & p<0.01). There was no significant effect of FTS on JNK at 5mins.

Conclusions: Our results show that TGFβ1-driven induction of CTGF is via the Ras/ERK pathway in murine PTECs. Investigation of intracellular signaling produced unexpected & diverse results. Surprisingly FTS inhibited canonical & non-canonical SMAD pathways including pSMAD2 linker region. Inhibition of pSmad2 linker region by FTS may be due to inhibition of GSK3/β at 1h. We also demonstrate for the first time that TGFβ1 rapidly phosphorylates Histone H3 in an FTS sensitive manner. Some of the effects of FTS may not involve Ras and hence more selective Ras inhibition may require other strategies such as antisense oligonucleotides.

Funding: Government Support - Non-U.S.

FR-PO193
Selective Proximal Tubule Injury Causes Intestinal Fibrosis and Distal Tubule Impairment Koji Takatori,1 Jin Nakamura,1 Tadashi Yamamoto,2 Motoko Yanagita.1 1Nephrology, Kyoto Univ, Kyoto, Japan; 2Structural Pathology, Institute of Nephrology, Nigata Univ, Nigata, Japan.

Background: Recently we clarified that renal fibroblasts including erythropoietin (Epo) producing cells differentiate into myofibroblast and predominantly contribute to fibrosis, with concomitant loss of Epo production in the diseased kidney. It remains unclear, however, what triggers the transdifferentiation of fibroblasts to myofibroblasts and how proximal tubule injury affects other segment of the nephron.

Methods: For in vitro analysis, we utilized co-culture of renal fibroblasts and tubular epithelial cells. For in vivo analysis, we utilized Nmyc downstream-regulated gene (Nrdg)CreERT2 inducible diphtheria toxin receptor (DTX) transgenic mice (NrdgCreERT2:DTX mice) in which Cre-mediated excision of a STOP cassette is achieved after the administration of tamoxifen, and renders proximal tubules sensitive to diphtheria toxin (DT).

Results: First, we confirmed that DTX is expressed in almost all proximal tubules and a part of collecting duct in the kidney of Nrdg1-CreERT2:DTX mice after the administration of tamoxifen. A single DT injection to these mice causes proximal tubule injury and interstitial fibrosis accompanied with the proliferation of proximal tubules and fibroblasts. We also confirmed the induction of collagen expression in fibroblasts when co-cultured with damaged tubular epithelial cells. We further demonstrated the induction of distal tubule injury after the administration of DT to Nrdg1-CreERT2:DTX mice.

Conclusions: Our data provide the new evidence that selective proximal tubule injury induces the transdifferentiation of fibroblast as well as distal tubule impairment. These results indicate the importance of protecting tubule epithelial cells to suppress kidney disease progression. Further understanding of the crosstalk between proximal tubule and fibroblast as well as the crosstalk between proximal tubule and distal tubule will give us new insight into the mechanism of kidney disease progression.

Funding: None

FR-PO194
Biological Properties of Klotho in the Anti-Fibrotic Process and Establishment of Cell Integrity in Coordination with Cell Signaling Pathway/Translocation of Membrane Transporters Ken Tsuchiya,1 Shunji Shiohira,1 Miki Nishida,1 Kazuhiro Okano,1 Hidekazu Sugiyura,1 Kosaku Nitta,1 1Dept of Medicine IV, Tokyo Women’s Medical Univ; 2Dept of Pathology, UT Southwestern Medical Center, Dallas.

Background: Klotho, which exerts anti-aging properties, is known to be acting as an obligate co-receptor of FGFR2 to regulate phosphate homeostasis, and also to be involved in Insulin/IGF1 and WNT signaling, suggesting the Klotho should play important roles in establishing specific cell functions and also maintain primitive cell identity.

Methods: We explored the biological properties of Klotho in cell differentiation and proliferation quantified by using CL-Quant software to analyze time-lapse images in a Nikon Biostation CT combining a high-throughput cell migration assay, and cell polarity by measuring the expression of Na/K ATPase/PKD-2, marker of cell signaling (β-catenine) in 3D culture with collagen mixture. Internal expression of Klotho was modified by siRNA transfection.

Results: Recombinant Klotho suppressed the accelerated migration and expression of fibronectin of cultured renal fibroblasts and renal fibroblast cells (NRK49F cells) in which internal Klotho expression was negligible, stimulated by TGF-β1. In addition, Quercetin, a Wnt/β-catenine inhibitor, attenuated cell migration and up-regulated E-cadherin expression, induced Klotho expression three fold of mRNA and protein in IMCD cells in which Klotho expression has been confirmed. Klotho siRNA reduced the expression of Klotho, resulting in accelerating cell migration. Moreover, addition of recombinant Klotho up-regulated adhesion molecule and Na/K ATPase/PKD-2, translation to the cell membrane not association with the expression of mRNA level, and Klotho siRNA tended to suppress the effect but was not significant.

Conclusions: Taken together, it is likely that Klotho acts anti-fibrotic process in part medicating Wnt/β-catenine pathway and also contribute to establish cell integrity by up-regulation of cell adhesion molecules and one of possible mechanism mediating translocation of membrane transporters.

Funding: Government Support - Non-U.S.

FR-PO195
Severe Proximal Tubular Injury after Kidney-Specific Knockdown of Stanniocalcin-1 Leping Huang, Tatiana Belousova, Jenny S. Pan, David Sheikh-Hamad. Nephrology/Medicine, Baylor College of Medicine, Houston, TX.

Background: Stanniocalcin-1 (STC1) is a paracrine/intracrine protein; it binds to the cell surface, followed by internalization to the mitochondria; it diminishes superoxide generation through induction of uncoupling proteins (UCPs). In vitro, STC1 inhibits mTOR and preserves kidney structure and function; in vivo, mice which overexpress STC1 globally and display high serum levels of STC1 are protected from anti-GBM GN and ischemia/reperfusion (IR) kidney injuries. To determine the phenotype following kidney-specific knockdown of STC1, we employed two novel approaches.

Methods: We generated STC1 shRNA mice expressing STC1 or scrambled shRNA, respectively, upon removal of floxed reporter [phosphoglyceral kinase (PGK)-driven EGFP]; and 2) using ultrasound microbubbles, we delivered to the kidney a plasmid that expresses Cre-recombinase directed by the endothelium specific tyrosine-protein kinase receptor-2 (Tie2) promoter – to achieve kidney endothelium-specific expression of STC1 siRNA or scrambled shRNA.

Results: STC1 mRNA is widely expressed in the kidney. Delivery of Tie2-Cre to STC1 shRNA Tg kidneys diminished the expression of STC1 mRNA and protein throughout the kidney. We observed no change in STC1 mRNA or protein in similarly-treated scrambled shRNA Tg kidneys. Knockdown of STC1 in STC1 shRNA Tg kidneys was associated with severe proximal tubular injury (segments that express AQP1) characterized by vacuolization, decreased UCP2 expression, greater generation of superoxide, activation of the unfolded protein response and initiation of autophagy and apoptosis. There was no
change in Cre protein expression in cultured and Tie2-Cre-transfected proximal tubule cells, suggesting that knockdown of STC1 expression in epithelial cells in vivo is likely related to overexpression of CRE from endothelial cells.

Conclusions: These novel observations suggest a critical role for STC1 in tubular epithelial survival. The above approach provides efficient tool to knockdown the expression of any gene in the kidney – avoiding confounding extra-renal effects that may be associated with global gene knockdown.

Funding: NIDDK Support

FR-PO196

Protein Overload Induces Renal Proximal Tubular Epithelial Cell Apoptosis by Down-Regulating Wnt/β-Catenin Signalling

Dickson W.L. Wong, Wei Han Yiu, Hao-Jia Wu, Ruixi Li, Joseph C.K. Leung, Loretta Y.Y. Chan, Kar Neng Lai, Sydney C.W. Tang. Dept of Medicine, Queen Mary Hospital, The Univ of Hong Kong, Hong Kong.

Background: Numerous studies have demonstrated a tubulotoxic role of excess proteins on renal proximal tubular epithelial cell (PTECs) via various signalling pathways. However, the role of Wnt/β-catenin signalling in PTECs during protein overload remains unknown.

Methods: Wnt/β-catenin expressions were measured in control and human serum albumin (HSA)-treated human kidney 2 (HK-2) cells by real-time PCR and Western blotting. Genetic knockdown of β-catenin was achieved using siRNA transfection. Apoptotic phenotypes were evaluated by real-time PCR and TUNEL assay.

Results: Upon the 4-day HSA stimulation, gene expression of β-catenin, frizzled-7 receptor and Wnt-1 in PTECs declined by 26%±2 (p<0.05, t-test), 65%±2 (p<0.05) and 57%±6 (p<0.05) versus control, respectively. Western blots showed that protein expression of cystosolic and nuclear active β-catenin decreased by 57%±8 (p<0.05) and 66%±8 (p<0.05) after 4-day HSA treatment, respectively. Simultaneously, Bax/Bcl-2 gene expression ratio increased by 31%±8 (p<0.05). Transfection of β-catenin siRNA into HK-2 cells up-regulated Bax/Bcl-2 gene expression ratio by 23%±7 (p<0.05) relative to mock transfection. HAS treatment and β-catenin siRNA transfection increased the number of TUNEL-positive cells by 70%±10 (p<0.05) and 73%±8 (p<0.05), respectively.

Conclusions: Protein-overload promotes tubular cell apoptosis via down-regulation of Wnt/β-catenin signalling in PTECs. Funding: Research Grants Council of Hong Kong (GRF grant number 7782/12M).

FR-PO197

Src Kinase Mediates Renal Interstitial Fibroblast Activation and Renal Fibrogenesis in Obstructive Nephropathy

Shouqiong Zhang, Dept of Medicine, Rhode Island Hospital and Alpert Medical School of Brown Univ, Providence, RI.

Background: Renal interstitial fibroblast activation and proliferation is central to the development and progression of renal fibrosis after various insults, however, the signaling mechanism regulating this process is incompletely clear.

Methods: In this study, we examined the role of Src, a non-receptor tyrosine kinase in renal interstitial fibroblast activation and proliferation in cultured rat renal interstitial fibroblasts and a murine model of obstructive nephropathy induced by unilateral ureteral obstruction.

Results: Exposure of cultured renal interstitial fibroblasts (NRK-49F) to P1, a specific Src inhibitor, resulted in decreased expression of alpha-Smooth muscle actin and fibronectin, two hallmarks of fibroblast activation and type I collagen, a key extracellular matrix protein, in a dose-dependent manner. Silencing Src with siRNA also significantly inhibited the expression of these three proteins. Moreover, inhibition of Src kinase activity with either P1 or siRNA, also blocked cell proliferation, decreased expression of cyclin D1, cyclin B1 and cyclin E and increased expression of p27 and p21. Finally, STAT3, AKT and ERK 1/2 were phosphorylated in cultured NRK-49F cells and presence of P1 or knockdown of Src with siRNA inhibited phosphorylation of all of them. In a murine model of obstructive nephropathy, administration of P1 attenuated abolished the expression of fibronectin, largely suppressed expression of α-SMA and type I collagen, and reduced the deposition of extracellular matrix proteins.

Conclusions: Collectively, our results reveal an important role of Src in mediating activation and proliferation of renal interstitial fibroblasts and renal fibrogenesis, and suggest that Src inhibition might be a potential therapeutic approach for treatment of chronic fibrotic kidney disease.

Funding: NIDDK Support

FR-PO198

20-HETE Monoglyceride Induces ERK1/2 Phosphorylation via a Cannabinoid Receptor-Mediated Signalling Pathway

Kimberly Fisher, Jianchun Chen, Jorge H. Capdevila, Raymond C. Harris. Medicine, Vanderbilt Univ, Nashville, TN.

Background: We have previously shown that glycerol derivatives of epoxyeicosatrienoic acid activate cannabinoid receptors in the kidney. The present study was designed to investigate whether monoglyceride derivatives of the cyclopentadienyl acid metabolite, 20-HETE are present endogenously and activate cannabinoid receptors.

Methods: For measuring distribution of 20-HETE in mouse plasma, we identified pools by resolution of plasma extracts by TLC on SiO2 plates using mixtures of hexane/ether/acetic acid as solvent. Pools with Rf corresponding to triglycerides (TG) diglycerides (DG) and monoglycerides (MG) were collected from the plates and submitted to alkaline hydrolysis, and the released 20-HETE quantified by UPLC/MS/MS by collision induced fragmentation, and searched against reference Compound databases. To analyze the effect of 20-HETE and 20-HETE MG on ERK1/2 phosphorylation, Chinese hamster ovary (CHO) cells were transiently transfected with plasmid vector, CB1 (cannabinoid receptor-1), or CB2 (cannabinoid receptor-2), then stimulated with 20-HETE or 20-HETE MG for 10 minutes. Cannabinoid receptor-specific inhibitors were used to determine the role of CB1 and CB2 in the phosphorylation of ERK1/2 resulting from 20-HETE MG stimulation.

Results: 20-HETE was prevalent in mouse plasma, and 90% of the 20-HETE was found to be esterified. Immunoblot analysis demonstrated that in CHO cells transfected with either CB1 or CB2 cannabinoid receptors, ERK1/2 phosphorylation increased 3.5-fold (p<0.05, N=5) after stimulation with 20-HETE MG, but not when treated with non-esterified 20-HETE. ERK1/2 phosphorylation by 20-HETE MG was blocked by the CB1- and CB2-specific inhibitors, AM251 or AM630, respectively.

Conclusions: In summary, these studies suggest that 20-HETE in plasma circulates predominantly in an esterified form, and 20-HETE monoglyceride might serve as endocannabinoid. Further studies will be required to elucidate the physiologic and/or pathophysiologic role of this novel compound.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO199

Phenybutyric Acid, an ER Chemical Chaperon, Protects against Renal Fibrogenesis In Vivo and In Vitro

Ching-chien Yang,1 Cheng-tien Wu,2 Shing-Fan Liu,3 Chih-Kang Chiang.1,2,3 Institute of Toxicology, National Taiwan Univ, Taipei, Taiwan; 2Dept of Internal Medicine, National Taiwan Univ, Taipei, Taiwan; 3Dept of Integrated Diagnostics & Therapeutics, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Renal tubulointerstitial fibrosis is the common and final pathologic changes of end-stage renal disease (ESRD). Our recent works demonstrated that endoplasmic reticulum (ER) stress contributed to the pathophysiological mechanisms during the development of renal fibrosis. We found that up-regulation of transforming growth factor-β (TGF-β) is associated with the activation of ER stress in the rat unilateral ureteral obstruction (UUO) renal fibrotic model. ER stress-related signals might lead to renal tubulointerstitial fibrosis and fibrosis. However, the detail mechanisms that ER stress involved in the renal disease and fibrosis have not been completely clarified.

Methods: In this study, we applied ER chemical chaperon, sodium 4-phenylbutyrate (4-PBA), in the rat UUO renal fibrosis model and the normal rat kidney epithelial cells (NRK-52E). We explored the modulation of ER-associated signals and profibrotic pathways by 4-PBA.

Results: By using this ER-related chemical chaperon to mimics endogenous ER chaperon, we successfully enhanced the effects of unfolded protein response (UPR) in the UUO model. We found that 4-PBA successfully attenuated UUO-induced ER stress, which associated with the suppression of profibrotic factors, including collagen, fibronectin, plasminogen activator inhibitor-1 and connective tissue growth factor. In addition, we also shown that tubulointerstitial injury, renal apoptosis and fibrosis were attenuated by the administration of 4-PBA in the UUO rats. In vitro model, we also demonstrated that 4-PBA attenuated TGF-β-induced ER stress, tubular apoptosis and profibrotic factors activation in NRK-52E. We successfully demonstrated that the attenuation of ER stress led to lesser renal apoptosis and fibrosis.

Conclusions: These results indicate that 4-PBA may have therapeutic potential in renal fibrosis. It is deserve to explore the potential ER stress targets in preventing renal fibrosis.

Funding: NIDDK Support

FR-PO200

c-Cbl, a Ubiquitin E3 Ligase That Targets Active β-Catenin—A Novel Layer of Wnt Regulation

Sowmya Shivanna, Vipul C. Chitalia. Dept of Medicine/ Renal Section, Boston Univ Medical Center, Boston, MA.

Background: Regulation of transcriptionally active nuclear β-catenin during Wnt-on phase is crucial to ensure controlled induction of Wnt target genes. Several ubiquitin E3 ligases were known to regulate cytosolic β-catenin during Wnt-off phase, but little is known about the fate of active nuclear β-catenin in Wnt-on phase.

Methods: Following methods were employed: Cell culture, transfection, western blotting, immunofluorescence, cellular fractionation, luciferase assay, ELISA etc., as per reference literature.

Results: We now describe ubiquitination of active β-catenin in Wnt-on phase by a RING finger ubiquitin E3 ligase, Casitas B-lineage lymphoma (c-Cbl) in endothelial cells (EC). c-Cbl binds preferentially to nuclear active β-catenin in Wnt-on phase via armadillo repeat region. Wild-type c-Cbl suppresses and E3 ligase-deficient c-Cbl-70Z increases Wnt signaling. Wnt induces nuclear translocation of c-Cbl where it ubiquitinates nuclear β-catenin. Deletion of c-Cbl UBA domain abrogates its dimerization, binding to β-catenin, Wnt-induced c-Cbl nuclear translocation and ubiquitination of nuclear β-catenin. c-Cbl activity inhibits pro-angiogenic Wnt targets IL-8 and VEGF levels and angiogenesis in β-catenin-dependent manner.

Conclusions: This study defines for the first time c-Cbl as an ubiquitin E3 ligase that targets nuclear active β-catenin in Wnt-on phase and uncovers a novel layer of regulation of Wnt signaling.

Funding: NIDDK Support
Cross Talk between p66ShcA and p70S6K Determines Kidney Cell Injury in HIV-Associated Nephropathy


Background: HIV-associated nephropathy (HIVAN) is characterized by both proliferative and apoptotic kidney cell phenotypes. Recently we demonstrated the activation of mTOR pathway leading to proliferative as well as activation of p38 pathway leading on to apoptotic phenotype in HIVAN. Thus, studying cross talk in downstream signaling molecules of mTOR (p70S6K) and downstream signaling of p66ShcA (isoforms 4 and 6) with anti-p66ShcA antibody and probed for p70S6K. To display functional relationship, siRNAs were transfected into cells (MTC) or NL4-3 (HIV/MTC) and transfected with either siRNAp66, siRNAP70S6K, and scrambled siRNA. Subsequently, protein blots were probed for p66ShcA, p70S6K and actin.

Methods: Male 2-, 12-, and 24-month-old C57/BL6 mice were used in this study. To measure molecular binding, EV/MTC and HIV/MTC lysates were immunoprecipitated with anti-p66ShcA antibody and probed for p70S6K. To display functional relationship, siRNAP66-HIV/MTC and siRNAP70S6K-HIV/MTC were assayed after co-labeling with H2AX (for DNA damage) and KU80 (DNA repair).


Conclusions: Cross talk between p66 and p70S6K plays a key role in the induction of tubular cell injury in HIVAN.

Targeting the Ubiquitin-Proteasome System in Complement-Mediated Glomerular Injury

Kapil Sarer-Khanam, Simon S. Wing, Andrey V. Cybulsky. Medicine, McGill Univ, Montreal, Canada.

Background: In experimental membranous nephropathy, complement C5b-9 induces structural damage and epithelial cell injury. MTA1 and C9 activation of serine protease (caspase) promotes complement-dependent cell death. C5b-9 activates pathways to restrict injury. MTA1 is associated with complement-mediated cytoprotective (C5b-9) pathway. MTA1 activates serine protease activity, promotes cell viability, and enhances cell survival. Our work shows that C5b-9 activates epithelial cell injury in HIV AN. Thus, we hypothesize that a cross talk between down-regulated MTA1 and up-regulated C9 promotes cell injury.

Methods: Complement C5b-9, cultured GECs were incubated with antiserum and normal serum. GFP (green fluorescent protein fused with the C1d1, degrons, and Fc) misfolded protein, and CDS5, an Er-associated degradation (ERAD) substrate, were used as reporters of the UPS and ERAD, respectively. Two reporters, as well as human disease-associated nephrin mutants (I171N and S724C), which are misfolded and undergo ERAD, were expressed by transient transfection.

Results: In GECs, GFP and CDS5 reporters undergo time-dependent proteasomal degradation. The USP14-directed inhibitor, IU1, accelerated degradation of GFP and CDS5. IU1 did not modify global ubiquitination of proteins. In 293T cells, IU1 tended to enhance degradation of the I171N and S724C nephrin mutants, but the change was not significant. Incubation of GECs with complement did not affect expression of CDS5 significantly, but accelerated degradation of GFP, and this degradation was further accelerated by IU1. However, IU1 did not alter complement-mediated cytoprotective GECs.

Conclusions: USP14 controls proteasomal degradation of some, but not all, misfolded proteins. CDS5 may be useful in alleviating the proteotoxic effects of misfolded proteins. USP14 inhibition was not effective in reducing cytoprotective GECs.

Funding: Government Support - Non-U.S.

Lack of the Small Ribosomal Protein S6 Phosphorylation Inhibits Compensatory Renal Hypertrophy

Jinhuan Xu, Jianchun Chen, Jian-Kang Chen. Experimental Medicine, Georgia Regents Univ, Augusta, GA; Medicine, Vanderbilt Univ, Nashville, TN.

Background: NEPHRON loss stimulates increases in cell size, with minimal cell proliferation, in the residual nephrons. This phenomenon is known as compensatory renal hypertrophy (CHR). Previous studies have demonstrated that activation of the mammalian target of rapamycin complex 1 (mTORC1)-S6 kinase 1 (S6K1) pathway is a major mechanism underlying CHR. However, the downstream effector of the mTORC1-S6K1 pathway that mediates CHR remains unknown, because multiple potential downstream phosphorylation targets of S6K1 have been reported.

Methods: We backcrossed S6 knock-in mice to the FVB/NJ background for 10 generations and produced congenic mice expressing unphosphorylatable S6 (S6-KO) 6-week-old S6-KO mice, along with their wild type littermates (WT), were subjected to induction of CRH by right uninephrectomy (UNX).

Results: S6-KO mice and WT mice had similar body weight and kidney-to-body weight ratios (K/Bw). Compared with WT mice, UNX-induced CRH in S6-KO mice was blocked by 50-60%, by decreases in K/Bw (41.4±0.4 vs. 18.5±0.5, P< 0.01, n= 7-9), and increased in protein-to-DNA ratios (29.3±1.5 vs. 12.5±2.6, P< 0.01, n= 5-9). UNX markedly induced S6 phosphorylation in the remaining kidney of WT mice, but no S6 phosphorylation was detected in S6-KO mice. However, the phosphorylation of S6K1 and the eukaryotic translation initiation factor (eIF) 4E-binding protein 1 (4E-BP1) was strengthened to equivalent levels in S6-KO mice and WT mice in response to UNX, indicating that mTORC1 is still activated in both S6-KO mice and WT mice. There was no change in

FR-PO201

FR-PO202

FR-PO203

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

Underline represents presenting author/disclosure.

Funding: Other NIH Support - T32 training grant

FR-PO204

FR-PO205
BUN levels in WT mice and S0-/- mice after UNX. K67 staining revealed comparable minimal increases in cell proliferation in the remaining kidney of WT mice and S0-/- mice in response to contralateral nephrectomy.

Conclusions: This study provides the first unequivocal evidence that phosphorylated S6 is the major downstream effector of the mTORC1-S6K1 activation that mediates 50-60% of the hypertrophy seen in wild type mice. Our data also suggest the existence of additional signaling pathways that mediate 40-50% of compensatory renal hypertrophy.

Funding: NIDDK Support

FR-PO206
Role of Retinol Dehydrogenase 9 in Podocyte Injury Xuezu Li,1,2 Yan Dai,1 Peter Y. Chuang,3 John C. He.1 1Div of Nephrology, Mount Sinai School of Medicine; 2Div of Nephrology, Shanghai East Hospital, China; 3Div of Nephrology, Shanghai First People's Hospital, China.

Background: Intracellular concentration of retinoic acid (RA) is determined by two sequential oxidation reactions that convert retinol to retinoic acid. Kidney is a major organ for RA metabolism. Our previous work demonstrated that RA synthesis is significantly less in glomeruli of HIV-1 transgenic mice (Tg26) and the expression of retinol dehydrogenase (RDH)9, which catalyzes the rate-limiting step in RA synthesis, is downregulated. Since it is known that RA has renal protective effects and is able to induce podocyte differentiation, we hypothesize that restoration of RA synthesis could slow the progression of renal disease.

Methods: We compared the expression of podocyte differentiation marker in cultured murine podocytes infected with an HIV-1 provirus with or without RDH9 overexpression. Mice with tetracycline (tet)-inducible, podocyte-specific RDH9 overexpression (POD-RDH9) were generated. We examined the effect of podocyte-specific overexpression of RDH9 on glomerular injury in two murine models of podocyte injury: HIV-associated nephropathy (HIVAN) and Adriamycin (ADR) nephropathy. Podocyte differentiation markers and cell proliferation makers were examined by immunostaining. Proteinuria was measured by urinary albumin ELISA. PAS stained sections were used to assess glomerular histology.

Results: Overexpression of RDH9 in cultured podocytes induced podocyte differentiation. Inducible overexpression of RDH9 in podocyte of Tg26 mice decreased proteinuria, increased podocyte differentiation markers, and reduced glomerular expression of cell proliferation makers. Overexpression of podocyte RDH9 also attenuated ADR-induced proteinuria and glomerulosclerosis.

Conclusions: Our data suggests that restoration of RA synthesis mitigates podocyte injury.

FR-PO207
Telmisartan Activates Endogenous Peroxidase Proliferator-Activated Receptor-δ and May Have Anti-Fibrotic Effects in Human Mesangial Cells Dai Suzuki Mikami,1 Hideki Kimura,2 Kazuko Kamiyama,1 Kunio Torii,2 Seiji Yokoi,1 Yoshinari Yokoyama,1 Nasuki Takahashi,3 Kenji Kasunou,3 Masayuki Iwano.1 1Div of Nephrol, Sch of Med, Univ of Fukui, Fukui, Japan; 2Dept of Clin Nephrol, Univ of Fukui Hosp, Japan.

Background: Telmisartan (Telm), an angiotensin II receptor type 1 blocker (ARB), was recently reported to promote lipolysis in mice by acting as a peroxisome proliferator-activated receptor (PPAR)-δ activator, although in clinical studies, it has also been recognized to activate PPAR-γ as a major cause of its pleiotropic actions. Whether Telm activates endogenous PPAR-δ and thereby exerts anti-fibrotic effects in human mesangial cells (HMC) remains to be investigated.

Methods: Presence of PPAR-δ in human renal tissues was examined by immunohistochemistry. Confluent HMC were treated for 6-24h with Transforming growth factor-β1 (TGF-β1; 10-50pg/ml) in absence or presence of Telm (10-50pg/ml). PPAR-δ expression was measured by immunoblotting for ER chaperones and C/EBP homologous protein (CHOP). Results: Tunicamycin and thapsigargin stimulated production of PGE2 in HMC, and this effect was amplified by overexpressing iPLA2γ. Amplitied PGE2 production was blocked by the iPLA2γ-specific inhibitor, R-bromoenol lactone (R-BEL). Tunicamycin and iPLA2γ independently stimulated ATF6 reporter activity, and iPLA2γ amplified the effect of tunicamycin. Amplified ATF6 activity was inhibited by R-BEL, but not indomethacin, a cyclooxygenase inhibitor. Tunicamycin and thapsigargin increased Grp94 and Grp78. This effect was amplified by overexpression of iPLA2γ, and was reduced by R-BEL, but not indomethacin. Tunicamycin stimulated induction of CHOP, but unlike ER stress inducers, stimulation of CHOP was not modulated by iPLA2γ. Tunicamycin-induced cytotoxicity (lactate dehydrogenase release) was reduced in GEC overexpressing iPLA2γ.

Conclusions: In GEC, induction of ER stress activated iPLA2γ, and overexpression of iPLA2γ amplified the ATF6 pathway of the UPR, resulting in upregulation of ER chaperones and cytoprotection. These effects were dependent on iPLA2γ catalytic activity, but not prostanooids. Thus, iPLA2γ may regulate the UPR via effects on ER membrane lipids. Modulating iPLA2γ activity may provide therapeutic opportunities for glomerular diseases.

Funding: Government Support - Non-U.S.

FR-PO208
Role of Calcium-Independent Phospholipase A2γ in Endoplasmic Reticulum Stress Hanan Elhamim, Tomoko Takano, Andrey V. Cybulsky. Medicine, McGill Univ, Montreal, Canada.

Background: Several glomerular diseases are associated with activation of endoplasmic reticulum (ER) stress and the unfolded protein response (UPR). In the UPR, upregulation of ER chaperones, including Grp94 and Grp78, enhances ER protein folding capacity and may limit cytotoxicity. Recently, we showed that the calcium-independent phospholipase A2γ (iPLA2γ) is localized at the ER, that complement CSB-9 activates iPLA2γ and that the iPLA2γ pathway is cytoprotective. The present study addresses whether the cytoprotective effect of iPLA2γ involves the UPR.

Methods: iPLA2γ was overexpressed in cultured glomerular epithelial cells (GEC) by transient transfection. To activate the UPR, cells were treated with tunicamycin or thapsigargin. iPLA2γ activity was monitored by prostaglandin E2 (PGE2) production. UPR activation was monitored by immunoblotting for ER chaperones and C/EBP homologous protein (CHOP), and by an activating transcrption factor 6 (ATF6) luciferase reporter assay.

Results: Tunicamycin and thapsigargin stimulated production of PGE2 in GEC and this effect was amplified by overexpressing iPLA2γ. Amplified PGE2 production was blocked by the iPLA2γ-specific inhibitor, R-bromoenol lactone (R-BEL). Tunicamycin and iPLA2γ independently stimulated ATF6 reporter activity, and iPLA2γ amplified the effect of tunicamycin. Amplified ATF6 activity was inhibited by R-BEL, but not indomethacin, a cyclooxygenase inhibitor. Tunicamycin and thapsigargin increased Grp94 and Grp78. This effect was amplified by overexpression of iPLA2γ, and was reduced by R-BEL, but not indomethacin. Tunicamycin stimulated induction of CHOP, but unlike ER stress inducers, stimulation of CHOP was not modulated by iPLA2γ. Tunicamycin-induced cytotoxicity (lactate dehydrogenase release) was reduced in GEC overexpressing iPLA2γ.

Conclusions: In GEC, induction of ER stress activated iPLA2γ, and overexpression of iPLA2γ amplified the ATF6 pathway of the UPR, resulting in upregulation of ER chaperones and cytoprotection. These effects were dependent on iPLA2γ catalytic activity, but not prostanooids. Thus, iPLA2γ may regulate the UPR via effects on ER membrane lipids. Modulating iPLA2γ activity may provide therapeutic opportunities for glomerular diseases.

Funding: Government Support - Non-U.S.
Deficiency in Apoptosis Inducing Factor Predisposes to Chronic Kidney Disease Independent of a Decline in Complex I Activity or Assembly
Melinda T. Coughlan,1 Gavin Higgins,1 Sean McGee,2 David Thorburn,3 Mike Ryan,4 Vicki Thallas,1 Mark E. Cooper,1 Josephine Forbes,3 1Baker IDI Heart & Diabetes Institute, Melbourne, Victoria, Australia; 2Metabolic Research Unit, Deakin Univ, Geelong, Victoria, Australia; 3Murdoch Children’s Research Institute, Melboune, Victoria, Australia; 4La Trobe Institute for Molecular Sciences, Melbourne, Victoria, Australia; 5Glycation & Diabetess, Mater-Medica Research Institute, Brisbane, Queensland, Australia.

Background: Deficiency in apoptosis inducing factor (AIF) results in a syndrome likened to disorders of oxidative phosphorylation with a functional loss of complex I activity. Complex I deficiency can also manifest as chronic kidney disease. Here, we have studied Harlequin hemizygous mice (Hq/Hq), which are postulated to have defects in both complex I activity and assembly as a result of reduced AIF expression.

Methods: Eight week old wild type (WT, B6CBA/c-A) and Hq/Hq mice were rendered diabetic with streptozotocin and followed for 10 weeks. Metabolic caging to obtain 24 hour urine collections was performed at week 10, mice were killed and renal cortical mitochondria were freshly isolated and markers of mitochondrial function were assayed.

Results: Hq/Hq mice demonstrated progressive renal dysfunction compared with WT mice, which was worsened by diabetes. The renal phenotype was associated with alterations in mitochondrial ATP synthesis and O2 consumption that were exacerbated by diabetes. However, there was no loss of complex I activity or assembly despite a lower AIF protein content. Human primary proximal tubule epithelial cells (PTECs) exposed to high glucose had loss of AIF expression and impaired cellular respiration, which was rescued by overexpression of AIF. Control and diabetic Hq/Hq and WT diabetic mice demonstrated renal cortical mitochondrial swelling and fragmentation and upregulation of proteins involved in mitochondrial fission.

Conclusions: These studies demonstrate that AIF deficiency is a risk factor for chronic kidney disease. This risk is not dependent on complex I activity or assembly but relates to specific changes in mitochondrial function in the renal cortex.

Funding: Government Support - Non-U.S.

Calcineurin Is Involved in Pathological but Not Adaptive Hypertrophy of the Kidney
Clintoria R. Williams,2 Brandi M. Wyne,3 Jennifer L. Grooth.3 1Dept of Medicine / Renal Div, Emory Univ, Atlanta, GA; 2Atlanta Veterans Affairs Medical Center, Decatur, GA.

Background: Calcineurin is well described as a mediator of hypertrophy of the heart and skeletal muscle. Interestingly, calcineurin’s involvement appears to be specific for pathological forms of cardiac hypertrophy such as aortic banding and not adaptive forms of hypertrophy such as exercise-induced. Previously, our laboratory showed that calcineurin inhibition attenuated whole kidney, glomerular hypertrophy and renal failure in a models of diabetic nephropathy.

More recently, we identified a specific role for the beta isoform of the catalytic subunit of calcineurin (CnAlp) in high glucose-mediated hypertrophy in vitro and in vivo. Activation of CnAlp, in turn, transcriptionally up-regulates Nox4 expression and oxidative stress.

Results: In the current study, we investigated the role of calcineurin in the adaptive hypertrophy of the remaining kidney following uninephrectomy (UNX). UNX kidneys were harvested from sham or UNX WT, CnAlp−/−, and CnAlp−/− mice. Total kidney size, renal function, reactive oxygen species (ROS) production, CnAlp activity and Nox4 expression were examined.

Methods: As expected, UNX induced a significant increase in kidney size in WT mice. Although SHAM kidneys from CnAlp−/− mice are smaller, UNX caused an increase in size consistent with adaptive hypertrophy. SHAM CnAlp−/− kidneys were comparable to WT. UNX also induced hypertrophy in CnAlp−/− mice indicating that neither isoform of calcineurin is required for adaptive renal hypertrophy. Consistent with a calcineurin-independent pathway, analyses of the remaining kidneys showed no increase in CnAlp expression or activity. In addition, ROS generation is not increased and there is no change in Nox4 expression.

Conclusions: Taken together, these data demonstrate that CnAlp−/− mice are selectively involved in pathological renal hypertrophy which is associated with progression to renal disease and renal failure. In contrast, adaptive hypertrophy following UNX involves alternative mechanisms that are not associated with chronic disease. Therefore, signaling mechanisms that mediate adaptive hypertrophy could be novel therapeutic renal targets.

Funding: NIDDK Support, Veterans Affairs Support

FR-P0211

Human and Mouse EGF Ligand and Receptor Expression in Chronic Kidney Disease
Shannon Marie Harlan, Derek D. Yang, Jon Wilson, Matthew D. Breyer, Josef G. Heuer. Biotherapeutic Discovery Research, Eli Lilly and Company, Indianapolis, IN.

Background: The type 1 growth factor receptor (T1GFR) family consists of EGFR, ERBB2, ERBB3, and ERBB4. Accumulating evidence implicates TGFα and other T1GFR ligands in progression of chronic kidney disease (CKD). The purpose of this study was to determine whether renal T1GFR-ligand or receptor levels are altered in human CKD and experimental renal disease.

Methods: Kidney tissue, serum and urine samples were obtained from normals or patients with CKD for mRNA expression by Taqman. Serum creatinine and albuminuria was also measured. TGFα protein levels were obtained by ELISA. Microarray analysis by Affymetrix was done to determine mRNA expression in human podocytes, glomerular endothelial, mesangial and proximal tubule cells which was confirmed by Taqman. Analysis of ligand production from cultured cells was done by specific ELISA assays. The effects of ligands on cultured cells were determined by microarray gene chip analysis as well as cell proliferation and proliferation assays.

Results: mRNA expression of EGF family member ligands including TGFα, Hb-egf and the neuregulins were upregulated in kidneys from CKD patients versus normals. These ligands were also expressed in cultured renal cells. Serum and urine TGFα protein was also significantly elevated in CKD patients and serum TGFα showed a significant positive correlation with serum creatinine. In situ hybridization showed TGFα mRNA was localized to tubules and glomerular podocytes in human and mouse kidneys. Glomerular size, urine TGFα and glomerular EGFR phosphorylation were all significantly elevated in unNx/db/db mice and induced mesangial cell proliferation and podocyte cell migration in vitro and induced the expression of several genes associated with proliferation, inflammation, extracellular matrix and cell migration in podocytes.

Conclusions: TGFα levels are elevated in both clinical and experimental CKD and the activity of TGFα on podocytes and mesangial cells is consistent with a role in disease progression. Other members of this growth factor family are also upregulated in CKD and may also contribute to disease progression.

Funding: Pharmaceutical Company Support - Eli Lilly and Company

FR-P0212

Mizoribine Suppresses Pyroptosis and Ameliorates Renal Inflammation in Aldosterone-Salt Treated Treated Rats
Toshiki Doi, Ayumu Nakashima, Shigehiro Doi, Takao Masaki. Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: It has been reported that aldosterone-salt treatment induces massive inflammation that contributes to fibrosis in the rat kidney. However, the mechanisms underlying renal inflammation remains unclear. Recently, pyroptosis has been recognized as a new type of cell death that is accompanied by activation of inflammatory cytokines. We hypothesized that aldosterone-salt treatment induced pyroptosis and that mizoribine, an effective immunosuppressant, would ameliorate renal inflammation and fibrosis.

Methods: Six-week-old male Sprague-Dawley rats underwent left uninephrectomy under anesthesia. Ten days after recovery from surgery, rats were given 1% NaCl to drink. Rats were divided into three groups (n = 7 per group): (1) vehicle infusion, (2) 0.75 μg/hour aldosterone infusion, or (3) aldosterone infusion plus a three mg/kg/day oral dose of mizoribine. All rats were sacrificed six weeks after the start of treatment. Renal tissues were assessed by terminal deoxynucleotidyl transferase DUTP nick ending (TUNEL) staining and Western blot analysis of caspase-1.

Results: TUNEL-positive cells and expression of active caspase-1 increased in rats with aldosterone-salt treatment, indicating that pyroptosis was induced by aldosterone-salt treatment in vivo. T lymphocyte and macrophage infiltration were also observed in aldosterone-salt treated rats as well as glomerulosclerosis and interstitial fibrosis. Oral administration of mizoribine suppressed both the number of TUNEL-positive cells and expression of active caspase-1 and it ameliorated renal inflammation and fibrosis.

Conclusions: These results suggest that pyroptosis plays an important part in the development of renal injury induced by aldosterone-salt treatment and immunosuppressants could be a rationale therapy.

Funding:

Significant Increase in Podocyte Autophagy in Association with Foot Process Eccentricity in Patients with Minimal Change Nephrotic Syndrome
Ayu Ogawa, Hitoshi Sugiyama, Masashi Kitagawa, Toshio Yamanari, Akifumi Onishi, Hiroshi Morinaga, Yoko Kikumoto, Shinji Kitamura, Yohei Maeshima, Hiromi Makino. Dept of Medicine III, Okayama Univ Graduate School of Medicine, Okayama, Japan.

Background: Autophagy is a cellular process involved in the bulk degradation of proteins and organelle turnover. Recent studies have demonstrated the significance of autophagy of the tubular epithelium in several renal tubulointerstitial disorders using mouse models. However, the role of autophagy in the regulation of human glomerular diseases remains unclear. This study aimed to elucidate the morphological evidence for autophagy and its relation with ultrastructural alterations of podocytes and clinical parameters in patients with minimal change nephrotic syndrome (MCNS).

Methods: The total study population included 103 patients with glomerular diseases (MCNS: 30, IgA nephropathy, IgAN: 21, membranos nephropathy, MN: 21, lupus nephritis, LN: 10 others: 21) who underwent renal biopsies. The study investigated the number of autophagic vacuoles and the degree of foot process effacement (FPE) in podocytes using electron microscopy. The relationships between the expression of autophagic vacuoles, the degree of FPE and the clinical parameters were determined.

Results: Autophagic vacuoles were particularly detected in podocytes. Overall, the number of autophagic vacuoles in podocytes was significantly correlated with age (r = 0.009, n = 103). In the patients with MCNS, the number of autophagic vacuoles in podocytes was significantly correlated with the podocyte FPE score (r = -0.416, p = 0.022), the number of glomerular mesangial matrix (r = 0.367, p = 0.046) and the level of serum albumin (r = -0.428, p = 0.018). The number of autophagic vacuoles in podocytes was significantly increased in the patients with MCNS and MN in comparison to that observed in the patients with IgAN and LN (p = 0.007).

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

Underline represents presenting author/disclosure.

412A
Conclusions: The data indicate that the autophagy of podocytes is associated with FPE and massive proteinuria in patients with MCNS. The mechanisms underlying the activation of autophagy in association with FPE in podocytes should be further determined in order to elucidate the pathophysiology of MCNS.

FR-PO215
Autophagy Protects Kidney from Chronic Metabolic Stress
Tomonori Kimura,1 Atsushi Takahashi,1 Yoshitsugu Takutake,1 Tomoko Nambu,1 Takeshi Yamamoto,2 Jun-Ya Kaimori,2 Jun Matsuda,1 Isao Matsui,1 Hiromi Rakugi,1 Yoshitaka Isaka.1 1Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Advanced Technology for Transplantation, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

Background: Autophagy plays a protective role in several organs including kidney; however, the precise function in pathological metabolic condition is only understood partially. We have demonstrated that autophagy plays a protective role against metabolic stress in vitro. This study aimed to determine the systemic role of autophagy against chronic mitochondrial metabolic stress in vivo.

Methods: Proximal tubule-specific autophagy-deficient mice were treated with cyclosporine A, an inducer of mitochondrial metabolic stress through the blockade of the permeability transition pore of mitochondrial inner membrane, and histological changes and biological profiles were examined. In addition, we exposed kidney for the metabolome analyses.

Results: Autophagy-deficiency exaggerates cyclosporine A-induced kidney injury with significant increase in apoptotic cells. This damage is associated with increase in mitochondria ballooning. Metabolome analyses revealed aberrant metabolism of cysteine and its-related pathways, while corroborating our previous findings.

Conclusions: These observations not only proved our hypothesis that autophagy protects kidney tubular cells against kidney diseases through quality control of mitochondria, but also added a biological significance in the role of autophagy against metabolism-related diseases.

FR-PO216
Cyclosporine A Attenuates Lovastatin-Induced Podocyte Apoptosis
Xue-pia Chen,1 He-ping Ma.1 1Dept of Obstetrics and Gynecology, Ruian Maternity and Child Care Hospital, Ruian, Zhejiang Province, China; 2Dept of Physiology, Emory Univ School of Medicine, Atlanta, GA.

Background: Our recent studies suggest that inhibition of cholesterol synthesis in cortical collecting duct (CCD) cells with a very high concentration of lovastatin causes apoptosis of CCD cells and that cyclosporine A (CsA) attenuates lovastatin-induced apoptosis. We hypothesized thatLovastatin and CsA might also have contradictory effects on podocyte viability.

Methods: We used confocal microscopy and annexin V-propidium iodide double-staining technique to detect podocyte apoptosis.

Results: The data demonstrated that a very high concentration of Lovastatin significantly reduced cholesterol levels in the plasma membrane of podocytes and induced apoptosis. The effects of Lovastatin on cholesterol levels and apoptosis were attenuated by pretreatment of podocytes with either exogenous cholesterol or CsA. However, acute depletion of cholesterol in the outer leaflet of podocyte membrane with methyl-ß-cyclodextrin failed to induce apoptosis, indicating that cholesterol in the inner leaflet of podocyte membrane plays an important role in regulating podocyte apoptosis. Treatment of podocytes with CsA caused significant accumulation of cholesterol in podocytes. These data suggest that CsA attenuates Lovastatin-induced apoptosis via a cholesterol-dependent mechanism.

Conclusions: Since statins have been used as a complement of chemotherapy for cancer patients at a relatively high dose, the present study may provide useful information to management of statin-induced podocyte injury in these patients.

Funding: NIDDK Support

FR-PO217
Tumorigenesis and Organprotection—Two Ends of a Continuum?
Roman-Ulrich Mueller,1,2,3 Puneet Bhardwaj,1,3 Hakam Gharbi,1,2 Torsten Kubacki,1 Marc Johnsen,1 Trippi Mishra,1 Francesca Fabretti,1 Markus M. Rinschen,1 Peter Frommolt,2 Volker Rolf Burst,1 Bernhard Schermer,1,2,3 Thomas Benzinger,1,2 1Dept 2 of Internal Medicine and CMMC, Univ of Cologne, Cologne, Germany; 2CECAD, Univ of Cologne, Germany; 3SyBACol, Univ of Cologne, Germany.

Background: Not only due to its growing incidence acute kidney injury has gained increasing interest during the last decade. On the one hand a growing body of evidence shows its close association with morbidity and mortality. On the other hand no causal treatment exists and preventive measures are limited. However, organ preconditioning has become a potential tool to tackle this problem.

Methods: We employ the nematode Caenorhabditis elegans as a tool to search for keyplayers in the pathways mediating organoprotection. The major signaling pathways mediating increased stress tolerance upon preconditioning are well conserved in the worm and hypotheses generated using this model can be transferred to a mouse model of renal ischemia-reperfusion injury.

Funding: NIDDK Support

FR-PO218
Everolimus Inhibits Invasion and Migration of Human Renal Cancer Cells by Inhibiting Epithelial-to-Mesenchymal Transition and FAK Pathway
In vitro and In vivo
Hong-Rong Chang, Jong-Da Lian. Div of Nephrology, Dept of Medicine, Chung Shan Medical Univ Hospital, Taichung, Taiwan.

Background: Metastasis of kidney cancer, a most important cause of patient death and a multiple and intricate processes, may complicate the clinical management and lead to a poor prognosis for cancer patients and has tremendous physical or economical impact to patients or communities. The epithelial-mesenchymal transition (EMT) is implicated in converting stationary epithelial cancer cells into motile mesenchymal cells during metastasis.

Methods: 786-O cells were treated with everolimus at various concentrations for a defined period and then subjected to gelatin zymography, cascin zymography and Western blot to investigate the impacts of everolimus on invasive, motility, and migratory potential.

Results: An in vivo anti-tumor studies were examined using a nude mice xenograft model and a lung metastasis model.

Conclusions: In the present study, our results showed that everolimus treatment significantly inhibits invasive, motility, and migratory potential of human renal cell carcinoma 786-O cells. Molecular analyses showed that everolimus increases E-cadherin level and decreases vimentin and RhoA expression by Western blot assay, indicating the anti-EMT effect of everolimus in renal cell carcinoma. We performed western blot to find that everolimus inhibits p-Src and p-focal adhesion kinase (p-FAK) that was localized mainly at cellular membrane as evidenced by confocal analyses in 786-O cells, which might be responsible for morphologically observed shift towards epithelial character. In addition, everolimus was found to be effective in reducing the lung metastases formation via tail vein injection as compared to vehicle treated control animals. Everolimus was also evidenced by its inhibition on the growth of 786-O cells in vivo via a cancer cells xenograft nude mice model.

Conclusions: Taken together, our results showing anti-invasive/anti-tumor effects of everolimus and associated mechanisms suggest that everolimus should be tested further in clinically relevant models towards exploiting its potential benefits against metastatic kidney cancer cells.

Funding: NIDDK Support

FR-PO219
DIALOGUE* Phase 2 Program for BAY85-3934 a HIF-PH Inhibitor with Daily Oral Treatment in Anemic Patients Suffering from CKD/ESRD
Iain C. MacDougall,1 Jeffrey S. Berns,2 Tadao Akizawa,3 Steven Fishbane,4 Thomas Bernhardt.5 1Kings College Hospital, London, United Kingdom; 2Hospital of the Univ of Pennsylvania, Philadelphia; 3Showa Univ Hospital, Tokyo, Japan; 4Winthrop Univ Hospital, Mineola; 5Bayer Pharma AG, Berlin, Germany.

Background: Anemia, defined as a deficiency of hemoglobin (Hb), is a frequent and serious complication of severe diseases, including chronic kidney disease (CKD) and cancer.

Methods: The background treatment of anemia due to deficient EPO synthesis has included several forms of recombinant human EPO (rEPO), also known as erythropoiesis-stimulating agents (ESAs). BAY 85-3934, a novel inhibitor of HIF-PH, is developed for the oral treatment of anemia in patients with CKD and end stage renal disease (ESRD). Hypoxia-inducible factor (HIF) is a key transcription factor for the activation of EPO-gene expression. BAY 85-3934, a small molecule inhibitor of HIF-PH, will be evaluated for the induction of endogenous EPO by mimicking hypoxia resulting in an increase of the Hb level.

Results: The BAY 85-3934 Phase 2 program consists of 3 randomized, multicenter parent studies (2 studies in Europe/Asia Pacific and 1 study in US/Japan, each lasting 16 weeks) and 2 safety extension studies (1 study in Europe/Asia Pacific and 1 study in US Japan). Up to 400 patients suffering from anemia due to CKD or ESRD are planned

Poster/Friday
to be enrolled in the 3 parent studies to prove the efficacy and safety of BAY85-3934 in comparison to placebo, Darbepoetin alpha and Epoetin alpha/beta. Eligible patients are either treatment naive with a Hb level below 10 g/dl or on stable ESA dose with a Hb level in the target range per regional ESA label. Different doses of BAY85-3934 will be administered and titrated as indicated. The safety of the treatment is monitored by an independent DMC. An adjudication committee supports the evaluation of reported safety events.

**Conclusions:** In this Phase 2 program BAY 85-3934, a small molecule inhibitor of HIF-PHI, will be developed for the induction of endogenous EPO resulting in an increase in the Hb level. *DIALOGUE = Oral Treatment Increasing Endogenous Erythropoietin.*

**Funding:** Pharmaceutical Company Support - Bayer Pharma AG

---

**FR-PO220**

**Increased Serum Hepcidin Is a Major Contributor to the Anemia of CKD in an Animal Model**

**Joshua Zarisky,1 Victoria Rivka Gabayban,2 Grace Jung,2 Tomas Ganz,1 Isidro B. Salusky,1**

**Background:** Cross-sectional studies have shown that serum concentrations of hepcidin, a key regulator of iron metabolism, are markedly increased in CKD patients. However it remains unknown if these elevations contribute to iron restriction and the anemia of CKD.

**Methods:** We examined changes in hepcidin levels in a mouse model of CKD, avoiding the confounding effects of ESA and iron therapy. Wild-type mice (WT-CKD) and mice with a targeted disruption of the hepcidin gene (HepKO-CKD) were placed on a 20 ppm iron diet containing 0.2% w/w adenine. Corresponding control groups (WT and HepKO-control) were placed on an identical diet without adenine. Serum hepcidin levels were measured by ELISA at diet initiation and at 2 months along with other key biochemical markers (Table). Results: As expected, renal function (assessed by serum BUN) decreased in animals fed adenine. Significantly, at 2 months, Hgb levels were lower in animals fed adenine with lower MCV values consistent with iron restricted erythropoiesis. ANOVA modeling found a significant interaction between diet and genotype indicating that the HepKO-CKD group had a smaller drop in Hgb than the WT-CKD group (p<0.04). Serum hepcidin levels increased only in the WT-CKD group (p<0.001) (Figure).

**Results:**

**Background:** In patients with chronic kidney disease (CKD), the accumulation of uremic toxins promotes renal damage and anemia. During the analysis of uremic solutes on erythropoietin (Epo) production in Epo-producing Hep3B cells, we identified that some of the indole compounds have a potency of enhancing Epo production. So the aim of this study is to identify the mechanism of stimulating Epo production by indole compounds and to identify the new compounds to prevent the CKD progression and anemia.

**Methods:** Forty one indole derivatives were synthesized and analyzed by Epo production, Epo mRNA production, and the Epo promoter assay as well as ATP production in Hep3B cells. Cytoprotective activity against cytotoxic agents (cisplatin, aristolochic acid) in kidney derived HK2 cells was assessed by cytotoxicity assay kit (WST-8). Intracellular ATP contents were measured by ATP kit (TOYO INK). In vivo effect of the compounds were assessed with oral or intraperitoneal administration. Total HIF-1a content was measured by Cell-Based ELISA kit.

**Results:** Indole compound #2, #4, #5 at 10μM enhanced Epo production by 4 fold, Epo mRNA by 60 fold and the Epo promoter activity by 6 fold, while FG4592 at 10μM increased Epo mRNA by 3 fold. Cytotoxic effects of cisplatin (50% reduction) and aristolochic acid (30% reduction) were ameliorated to baseline by 40μM and 3 μM respectively. Administration of the compound #2, #4, #5 at 3μM augmented intracellular ATP contents by 7 fold in Hep3B. These compounds have no cytotoxic effect or ROS generation by itself. The kidney Epo mRNA was increased by 3 fold in mice administered the compound #5 at 50mg/kg intraperitoneally. Total HIF-1a content in Hep3B was increased by compound #2 and #3.5.

**Conclusions:** These data suggest that the indole derivatives promote Epo production. Stabilization of HIF-1a might be the mechanism of enhancement of Epo. These compounds also have cytoprotective effect as well as increased the intracellular ATP contents without increasing oxidative stress.

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

---

**FR-PO221**

**Indole-3-Acetate Inhibits Erythropoietin Receptor Expression and Erythropoietin Signaling In Vitro**

**Yasutoshi Akiyama,1 Hisato Shima,1 Yoichi Takeuchi,1,2 Eikan Mishima,1 Takehiro Suzuki,1 Sadayoshi Ito,2 Takaaki Abe.1 1Tohoku Univ Graduate School of Medicine, Japan; 2Okayama Univ of Science, Japan.**

**Background:** Anemia is one of the major complications of chronic kidney disease (CKD). Although many CKD patients respond to erythropoiesis-stimulating agent (ESA), about 10% of patients have poor responsiveness to ESA. It has been shown that there are several causes of ESA resistance, such as iron deficiency, inflammation, vitamin B12 deficiency and folate deficiency. However, the pathophysiology of ESA-resistant anemia has not been fully elucidated.

**Methods:** To test the hypothesis that uremic toxin(s) decreases the erythropoietin receptor (EPO) expression, we examined the effects of uremic solutes on cell viability, EPO expression and signal transduction through EPO using erythropoietin-dependent human leukemia cell line, UT-7/Epo cells.

**Results:** First, we compared the cell toxicity of various uremic solutes in UT-7/Epo cells with that in kidney-derived ACIN cells by cell viability assay. Many compounds showed the same cell toxicity between the two cell lines. However, the cell toxicity of indole-3-acetate (IAA), one of the uremic toxins, was about 10-fold stronger in UT-7/Epo cells than in ACIN cells, suggesting that IAA may have the toxicity related to EPO signaling as well as the direct cellular injury. To elucidate the mechanism, we examined the effect of IAA on the expression of EPO. As a result, the expression of EPO was dose-dependently decreased by IAA treatment at both mRNA and protein levels. In addition, tyrosine phosphorylation of STAT5 was significantly decreased by IAA treatment, suggesting that IAA inhibited the signal transduction through EPO.

**Conclusions:** IAA may decrease the expression of EPO and cause ESA-resistant anemia in CKD patients.

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

**Underline represents presenting author/disclosure.**

414A
**FR-PO223**

**Chronic Kidney Disease Increases Influx of Bone Marrow Derived Cells into the Heart and Reduces Circulating Endothelial Progenitor Cells Yvonne Riedl,1 Katharina Bibl,2 Karl F. Hilgers,2 Christoph Daniel,1 Kerstin U. Amann.1 1Nephropathology, Univ Erlangen; 2Nephrology and Hypertension, Univ Erlangen.

**Background:** Cardiovascular events are common complications in patients with chronic kidney disease (CKD). CKD leads to cardiovascular functional and structural alterations with impaired angiogenesis playing an important pathophysiological role. Here we investigated if impaired cardiac angiogenesis in a CKD model is due to reduced recruitment of endothelial progenitor cells (EPCs) in the heart.

**Methods:** To evaluate the recruitment of EPCs from the bone marrow into hearts of CKD rats we transplanted bone marrow from human placental alkaline phosphatase (hPAP) transgenic F344 rats into wildtype F344. Ten weeks after lethal irradiation and bone marrow transplantation, the chimeric rats were randomly assigned to two groups, i.e. subtotodial nephrectomy (SNx) or sham operation (sham). 12 weeks after SNx the experiment was terminated and cardiac pathology and bone marrow derived cell (BMDC) recruitment into the myocardium and circulating EPCs were analysed.

**Results:** CKD in SNx rats was accompanied by increased proteinuria as well as structural histological changes in the kidney. Blood pressure and left ventricular weight were significantly higher in rats with CKD. In addition, cardiac capillary density was about 20% lower in SNx animals as assessed by staining for CD31 positive cells (p=0.0493). In the blood EPCs were significantly reduced in CKD rats, as assessed by CD45+CXCR4+ cells (1.7±0.2 vs 3.0±0.9, p=0.03). In contrast, recruitment of BMDC into the heart was about 50% higher in the SNx group. However, in our study neither in sham animals nor in SNx rats BMDC could be identified as an essential source for cardiac endothelial cells. Immunofluorescence double staining proved that the majority of BMDC could be characterized as CD45+ leucocytes (about 50%) and ED1+ macrophages (about 40%) cells.

**Conclusions:** Chronic kidney disease (CKD) reduced the number of circulating EPCs and simultaneously increased influx of BMDC derived inflammatory cells into the heart. However, BMDC seem not to be an important source for cardiac endothelial cells.

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

---

**FR-PO224**

**Altered Macrophage Polarization Promotes Atherosclerosis in a Mouse Model of Chronic Kidney Disease Lixia Zeng, Hye Kyong Kweon, Anna V. Mathew, Pradeep Kayampilly, Philip C. Andrews, Subramaniam Pennathur. Univ of Michigan, Ann Arbor, MI.

**Background:** Atherosclerotic cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD). However, the molecular mechanism underlying this increased risk remain poorly understood. We investigated the role of macrophages in promoting atherosclerosis in a pathophysiologically relevant mouse model of CKD.

**Methods:** Male LDL receptor deficient (LDLr−/−) mice were subjected to sham (Control) or 56 nephrectomy (CKD) surgery. Subsequently, the animals were maintained in low (LDF) or high fat diet (HFD) for 24 weeks. LC/MS analysis of macrophage-derived oxidation markers and the phosphoproteomic profiling of bone marrow-derived macrophages from the two groups were performed. Mouse macrophage cell line RAW 264.7 were used as a stable isotope labeling in cell culture (SILAC). The trypptic peptide digests were subjected to two-step phosphopeptide enrichment and analyzed by on-line nanoLC-MS/MS.

**Results:** The CKD mice had significantly higher plasma creatinine, lower hematocrit, decreased body weight and higher mortality. Quantification of lesion area revealed that both LDF and HFDCKD mice had significantly elevated aortic plaque area fraction, and greater luminal narrowing consistent with accelerated atherosclerosis. Cholesterol content and macrophage infiltration were elevated in the aortic lesions of the CKD animals. LC/MS analysis of macrophage derived myeloperoxidase oxidation markers (nitrotyrosine and dityrosine) showed marked elevation in the aortic lesions and targeted lipidomic analysis revealed inflammatory polarization of macrophages (M1) with increased long-chain fatty acids (COA) accumulation. We identified 1,449 unique phosphopeptides from 434 unique phosphoproteins. Gene Ontology annotations showed selective changes in phosphoproteins involved in cellular component biological processes. 53 hyperphosphorylated and 43 hypophosphorylated domains were identified suggesting distinct phosphorylation signatures underlying inflammatory macrophage polarization.

**Conclusions:** These findings strongly implicate that altered macrophage polarization contributes to CKD-accelerated atherosclerosis.

**Funding:** NIDDK Support

---

**FR-PO225**

**Nuclear Translocation of β-Catenin Mediates Parathyroid Hormone-Induced Endothelial-to-Mesenchymal Transition in Human Aortic Endothelial Cells Min Wu, Hong Liu, Bi-cheng Liu. Institute of Nephrology, Southeast Univ, Nanjing, China.

**Background:** Secondary hyperparathyroidism is a common complication of chronic kidney disease, which is closely correlated with the development of cardiovascular diseases. Our previous have demonstrated that PTH could induce endothelial-to-mesenchymal transition in human aortic endothelial cells (HAECs). However, the potential molecular mechanism has yet to be clarified. Thus, the present study sought to investigate whether nuclear translocation of β-catenin mediates PTH-induced EndMT in HAECs.

**Methods:** Primary HAECs were treated with PTH (10−10 to 10−6mL). DKK1 (500ng/ml) was used to inhibit β-catenin nuclear translocation. The expressions of endothelial markers (CD31 and mesenchymal markers FSP1 and α-SMA) were detected by real-time PCR and western blot. Nuclear and cytoplasmic β-catenin protein levels were examined by western blot and confocal microscopy.

**Results:** PTH treatment significantly down-regulated endothelial marker CD31 expression and up-regulated mesenchymal markers FSP1 and α-SMA expression and up-regulated mesenchymal markers FSP1 and α-SMA were detected by real-time PCR and western blot. Nuclear and cytoplasmic β-catenin protein levels were examined by western blot and confocal microscopy.

**Conclusions:** These data demonstrated that elevated PTH promoted EndMT in HAECs. This effect was partially mediated by nuclear translocation of β-catenin.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only** Underline represents presenting author/disclosure.
Circulating Total Uncharged Matrix Gla-Protein as Biomarker for Vascular Calcification in Chronic Kidney Disease Elke Theeßwissen, Elke Magdeleyns, Heather Pham, Cees Vermeer. Serum levels of t-ucMGP were associated with the burden of vascular calcification. We used and coupled directly to the microtiter plates. A monoclonal antibody against the uncarboxylated MGP sequence was used, and coupled directly to the microtiter plates. We were interested in seeing whether t-ucMGP may serve as biomarker for vascular calcification in CKD patients.

Methods: Circulating t-ucMGP was measured with our lab-developed competitive mono-antibody ELISA. A monoclonal antibody against the uncarboxylated MGP sequence was used, and coupled directly to the microtiter plates. We were interested in seeing whether t-ucMGP may serve as biomarker for vascular calcification in CKD patients.

Results: CKD patients were characterized by extremely low circulating t-ucMGP values, suggesting high affinity for calcium. Nearly all CKD patients had values well below the healthy adult range. Lower circulating t-ucMGP levels were associated with higher calcification scores in these patients.

Conclusions: Circulating t-ucMGP levels are significantly lower in CKD patients than in the healthy population, clearly discriminating CKD patients from controls. Low serum levels of t-ucMGP were associated with the burden of vascular calcification in these patients and hence may serve as biomarker for vascular calcification.

Chest X-Ray May Serve as a Screening Examination for Coronary Artery Calcification in Dialysis Patients Kokyō Watanabe, Hiroki Yoshihda, Yutaka Tanno, Ichiro Ohkido, Keitaro Yokoyama, Takashi Yokoo. Div of Kidney and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan.

Background: Coronary artery calcification (CAC) is highly prevalent among dialysis patients. Moreover, it has been reported that Coronary Artery Calcification Score (CACS) using multi-detector computed tomography (MDCT) is a good predictor of mortality in dialysis patients. However, it is not practical to perform coronary artery examination in every dialysis patient. Therefore, the aim of this study was to clarify which part of the body should be imaged with X-rays for screening of CAC in dialysis patients.

Methods: We examined 163 autopsy cases who had all been on dialysis (age 63.5±16.0 years, 102 male:61 female, 46 diabetic:117 non-diabetic, dialysis duration 4.4±5.3 years). Data were analyzed using the logistic model to determine the correlation between CAC and specific vascular calcification sites (aortic valve, carotid artery, thoracic aorta, and abdominal aorta).

Results: Logistic analyses revealed that thoracic aorta calcification had the strongest correlation with CAC. The table below shows correlation between CAC and specific vascular calcification sites.

<table>
<thead>
<tr>
<th>Site</th>
<th>Odds Ratio</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve</td>
<td>0.790</td>
<td>0.65-1.0</td>
</tr>
<tr>
<td>Carotid arteries</td>
<td>0.724</td>
<td>0.53-0.99</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td>0.54</td>
<td>0.39-0.76</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>0.55</td>
<td>0.36-0.83</td>
</tr>
</tbody>
</table>

Conclusions: The results suggest that a chest X-ray should be performed in dialysis patients to screen for marked thoracic aorta calcification. It is those patients with marked thoracic aortic calcification on chest X-ray who should undergo further cardiovascular assessment. Accordingly, Chest X-ray may serve as a screening examination for CAC in dialysis patients.
Conclusions: This novel study shows that CKD per se causes impaired cardiac functional reserve, thus confirming the presence of cardiomyopathy, which requires further cardiac-renal collaborative research.

FR-PO233
High Sensitivity Troponin T in Chronic Kidney Disease

Background: Chronic kidney disease (CKD) is an independent risk factor for developing coronary heart disease (CHD). The cardiac troponins are structural proteins predictors of CHD. It has been demonstrated that high sensitivity Troponin T (hs-TnT) has greater predictive value than conventional Troponin T in the development of CHD in the general population. However, its usefulness in patients with CKD is unclear.

Methods: We conducted a prospective study including 563 patients: 58% male, 32.5% diabetics, aged 64 ± 17 years, at different stages of CKD. We collected clinical history, routine laboratory parameters and hs-TnT. 20% had CHD history and 9.2% of 32.5% diabetics, aged 64 ± 17 years, at different stages of CKD. We collected clinical history, routine laboratory parameters and hs-TnT. 20% had CHD history and 9.2% of 32.5% diabetics, aged 64 ± 17 years, at different stages of CKD. We collected clinical

Results: The mean hs-TnT was 18.5 ng/ml. Plasma concentrations of as-TnT were directly related to age (r = 0.643, p < 0.001) and inversely with the MDRD 4 (r = -0.674, p < 0.001). The hs-TnT is higher in men than in women (20.4 vs 15.9 ng / ml, p < 0.001), is significantly higher in patients with history of CHD (p = 0.032) and especially in patients with a history of myocardial infarction (p < 0.01). The mean hs-TnT according to stages of CKD was: Stage1: 3.97 ng / ml; Stage 5: 45.56 ng/ml, with a statistically significant difference in the variance analysis (p < 0.01). When we divided the patients with and without history of CHD, the differences remained significant (p < 0.01 and p < 0.001 respectively). 19.1% of patients had left ventricular hypertrophy in this group, the values & D8203; & D8203; & D8203; & D8203; were higher (40.4 vs 13.8 ng / ml, p < 0.001). In a multivariable model, remain as predictors of high hs-TnT values the loss of renal function, history of CHD and LVH.

Conclusions: Hs-TnT levels increased as the severity of CKD, even without evidence of acute myocardial damage, so the value of this marker must be adjust according to the degree of renal function. Hs-TnT concentrations are higher as in men, patients with history of CHD and those with LVH.

FR-PO234
Effect of Adaptive Servo Ventilation Treatment for Chronic Heart Failure in Patients with Chronic Kidney Disease
Akiko Kuma, Masahito Tamura, Emi Hasegawa, Yoko Fujimoto, Kenichiro Bandó, Tetsu Miyamoto, Ryota Serino, Narutoshi Kabashima, Yutaka Otsuji. The Second of Internal Medicine, School of Medicine, Univ of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan.

Background: Many chronic kidney disease (CKD) patients also have cardiovascular diseases, and it is particularly difficult to treat heart failure (HF) accompanied by CKD. Recent studies have shown that adaptive servo ventilation (ASV) is effective for treating and managing HF. We investigated whether ASV has potential for treating HF in CKD patients.

Methods: We registered non-replacement CKD patients (CKD stage II – & D8248; & D8248; & D8248; with chronic HF in our hospital. We then selected patients whose HF was difficult to control using HF medication alone and who were diagnosed with sleep apnea syndrome by the polysomnography test. These patients underwent ASV therapy while sleeping every night. We then analyzed renal and cardiac function 1 and 6 months after initiating therapy.

Results: Patients (n = 23) comprised 16 males and 7 females. Mean age was 66.8 ± 12.2 years. CKD stage II was II (33.3%), III (38.1%), IV (23.8%), and & D8248; & D8248; & D8248; (8.3%). Estimated glomerular filtration rate (eGFR) was 46.5 ± 22.4 mL/min per 1.73m² before ASV therapy (0M), 53.0 ± 21.2 mL/min per 1.73m² 1 month after ASV therapy (1M) (p < 0.01 vs 0M), and 51.4 ± 25.4 mL/min per 1.73m² 6months after ASV therapy (6M) (p < 0.05 vs 0M). Left ventricular ejection fraction (LVEF) was 31.2 ± 15.1 % (0M), 37.4 ± 12.9 % (1M) (p < 0.005 vs 0M), and 39.0 ± 11.9 % (6M) (p < 0.005 vs 0M). No correlation was observed between eGFR (0M) and improvement in LVEF (0M-6M) (r = 0.2192, p = 0.34). Data are expressed as mean ± standard deviation values.

Conclusions: ASV treatment for HF in patients with CKD improved both cardiac and renal functions in the early stage (1M), and functions were maintained for six months. Regardless of renal function, a positive effect of ASV treatment was observed. ASV therapy appeared to be useful for treating HF in CKD patients.

FR-PO235
Risk of Death for Systolic and Diastolic Heart Failure in Patients with Chronic Kidney Disease
Shuling Li, Yan Hu, Charles A. Herzog.1,2 ‘CDRGR/MMRF, U.S. Renal Data System/CVSSC; 2Univ of MN.

Background: Heart failure (HF) is common in elderly pts and its prevalence increased in pts with chronic kidney disease (CKD). Few studies have examined systolic vs diastolic heart failure and their associated risk of death in elderly CKD pts.

Methods: We identified 101,337 CKD pts (age ≥66) prevalent on 12/31/09 and continuously enrolled with Medicare in 2009 using the Medicare 5% sample data. HF was identified from ICD-9 codes 498.91, 428.xx, 402.x1, 404.x1, and 404.x3 in claims during 2009 and included systolic (428.2x), diastolic (428.3x), both systolic and diastolic (428.4x), and unspecified. F/U began on 1/1/2010 and ended at the earlier date of death or 12/31/2011. Unadjusted survival was estimated by Kaplan-Meier method. The risk of death associated with HF types was assessed in a comorbidity-adjusted Cox model.

Results: Of all pts, the percent of pts with systolic, diastolic, both, and unspecified HF was 7%, 6%, 2%, and 16%, respectively. Prevalence of HF increased with age by type, from 6% in 66-69 yrs to 9% in ≥85 yrs for systolic HF, 4% for diastolic HF, 9.1% vs 2% for both HF, and 10% vs 2% for unspecified HF. Prevalence of systolic HF was higher in males than females (9% vs. 6%), but prevalence of diastolic HF was lower in males than females (4% vs. 7%). Two-year survival probability was 54% systolic, 55% both, 59% diastolic, and 64% unspecified HF, and 84% no HF (Fig 1). The adjusted hazards ratio (95% CI) for death was 2.3 (2.2-2.4) and 1.9 (1.8, 2.0) for systolic and diastolic HF, respectively, compared with no HF (Fig 2).

Conclusions: HF of any type in elderly CKD pts is associated with high long-term mortality. Systolic HF has the worst outcome. Future studies targeting this high risk population are warranted.

Funding: NIDDK Support

FR-PO236
Accumulation of Advanced Glycation End-Products Is Associated with Increased Pulse Pressure in Patients with Progressive Chronic Kidney Disease
Khai Ping Ng, Stephanie J. Srininger, Mark David Jesky, Punit Yadav, Mary Dutton, Charles Ferro, Paul Cockwell. Renal Medicine, Queen Elizabeth Hospital, Birmingham, Birmingham, West Midlands, United Kingdom.

Background: Accumulation of advanced glycation end-products (AGEs) and chronic kidney disease (CKD) are both strongly and independently associated with cardiovascular mortality. Emerging evidence indicates that both these processes are associated with an increase in arterial stiffness. We investigated whether AGEs accumulation, as measured by skin autofluorescence (SAF), is independently associated with pulse pressure (PP), a measure of arterial stiffness, in patients with CKD.

Methods: Cross-sectional observation study of the first 500 patients recruited in Renal Impairment in Secondary Care (RIISC) study.

Results: The mean age of participants was 64 ± 16 years with 60% of male gender and 71% of white ethnicity. Forty percent were diabetic and 34% had a previous history of cardiovascular disease (CVD). The median estimated glomerular filtration rate (eGFR) was 25 (interquartile range (IQR), 20-32) mL/min/1.73m². The mean SAF was 3.0 ± 0.8 AU. In univariate analysis, SAF correlated with age (r=0.521, p<0.001), diabetes (r=0.134, p<0.005), CVD (r=0.171, p<0.001), use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (r=−0.167, p<0.001), PP (r=0.286, p<0.001), natural log-transformed (Ln) eGFR (r=−0.243, p<0.001), Ln albumin:creatinine ratio (r=−0.128, p=0.014), uric acid (r=0.149, p=0.002) and Ln high-sensitivity C-reactive protein (r=0.141, p=0.018). SAF did not correlate with gender or smoking status. In multivariate linear regression model, only age (beta=0.406, p<0.001), PP (beta=0.251, p<0.001) and Ln eGFR (beta=0.112, p=0.034) was independently associated with SAF. The model explained 35% of the variance in SAF.

Conclusions: Tissue accumulation of AGEs is independently associated with increased PP in people with CKD. Interventions aimed at preventing the accumulation of AGEs might prevent the development of arterial stiffness in CKD and improve cardiovascular outcomes.
FR-PO237
Skin Perfusion Pressure: An Early Predictor of Peripheral Arterial Disease
Nia J. Jones,1 Ian Mathieson,2 Keith Morris,2 Alod O. Phillips,3 Steve Rile,1
1Institute of Nephrology, Cardiff Univ, Cardiff, United Kingdom; 2Cardiff Metropolitan Univ; 3Cardiff and Vale Univ Health Board.

Background: CKD patients treated with haemodialysis have a high prevalence of peripheral arterial disease (PAD), an increased risk of foot ulceration and mortality. Skin perfusion pressure (SPP) assesses the microcirculation and is superior in the diagnosis of PAD compared to Ankle Brachial Pressure Index (ABPI). SPP value ≤70mm/Hg is an independent risk factor for amputation and survival of haemodialysis patients. This prospective study analysed the risk factors for foot ulceration in CKD stage 4 and measured the progression of PAD.

Methods: 126 CKD patients (53 with Diabetes) and 46 age matched healthy controls were recruited. PAD was investigated using a Doppler and the SensiSafe System (PAD 3000) over a 2 year period.

Results: 33 (26%) CKD cohort had a cumulative history of foot ulceration at end point. 15 (12%) were referred for vascular intervention and three patients had amputation. Analysis demonstrated a highly significant difference in mean SPP and Takey’s pairwise confirmed the significance was associated with the CKD cohort versus the controls (p=0.0005). The right SPP correlated with the left SPP (p=0.018) and no differences were observed among SPP values of the CKD and diabetic cohorts. Mann-Whitney U test confirmed the median SPP was significantly lower in participants that developed foot ulceration (SPP 40mm/Hg v 75mm/Hg; p=0.014). 20 of the CKD patients at baseline had normal biphasic Doppler waveforms despite a reduced SPP ≤50mm/Hg; 10 of this cohort had developed foot ulceration at end point with 7 of these progressing to monophasic pulse waveform by study end.

Conclusions: The micro-circulation is often overlooked during routine foot screening. Risks associated with SPP values ≤70 mm/Hg are not confined to the dialysis population. These findings suggest SPP is an important early predictor of lower limb ischemia when compared to the Doppler and may allow early intervention in this patient group to improve outcome.

FR-PO238
Stroke in CKD Patients: Prevalence, Subtypes and Prognosis
Debashish Banerjee, Hugh Markus. Div of Clinical Sciences, St. Georges, Univ of London, United Kingdom.

Background: Strokes are common in patients with chronic kidney disease (CKD) and associated with poor outcome. Data on prevalence, stroke subtypes and risk factors in CKD patients within large cohorts of stroke patients are lacking. The study aimed to estimate the prevalence of CKD in stroke patients admitted to an inner-city hyper-acute stroke unit; together with associated risk factors, stroke subtypes and outcome.

Methods: Data collected prospectively in 2333 stroke patients were analysed using SPSS 17. Stroke subtypes were reported by clinicians using the “Trial of Org 10172” (TOAST) classification scheme and clinical information. The study was approved as a clinical audit. The GFR was estimated using MDRD equation. CKD was defined as eGFR < 60 ml/min/1.73m2. Short term outcome was estimated with the “Barthel index”; 20 being the best score.

Results: In 2333 stroke patients, 639 (27.4%) had CKD. CKD patients were older (79.11±70.14; p<0.001), less likely of Afro Caribbean or African descent (11.5% vs. 17.3%; p<0.005), with fewer smokers (12% vs. 23%; p<0.001), more diabetes (31% vs. 21%; p<0.001), less hyperlipidaemia (35% vs. 41%; p<0.001), lower cholesterol (4.5±1.4 vs. 4.8±1.1; p<0.001) and lower LDL cholesterol (2.7±1.1 vs. 2.9±1.0; p<0.001), compared to non CKD patients. CKD patients suffered less haemorrhagic strokes (9.2% vs. 14.6%; p<0.001) but more cardioembolic ischaemic strokes (36.8% vs. 23.8%; p<0.001) compared to non CKD patients. Adjusted for age, gender, ethnicity, systolic BP and cholesterol, CKD was associated with more cardioembolic strokes (OR=1.31, 95%CI 1.05 to 1.64; p<0.001) and less haemorrhagic strokes (OR=1.51, 95%CI 1.07 to 2.13; p=0.020).

The Barthel Index at 1 week was lower in CKD patients (11.8±7.84 vs. 13.6±7.38; p<0.001). In multivariable regression age, diabetes, cholesterol, systolic BP and eGFR were all independently related to lower Barthel Index.

Conclusions: Among stroke patients admitted to the hyper-acute stroke unit, CKD was present in 27.4% associated with lower Barthel index at 1 week. The CKD patients were older, more diabetic, with lower cholesterol, similar blood pressure and suffered less haemorrhagic but higher cardioembolic strokes.

FR-PO239
A Novel Model of Advanced Diabetic Kidney Disease in Mice
Jean-Francois Thibodeau,1 Dylan Burger,1 Chet E. Holterman,1 Kevin D. Wu,1 Ara Aslanian,1 Changfu Cheng,1 David J. Turnquist,1 James Shipley,1 George L. Bakris,2 1Div of Nephrology, 2Division of Clinical Sciences, St. George’s, University of London, United Kingdom.

Introduction: Type 1 diabetic OVE26 mice were crossed with a mouse model of angiotensin-dependent hypertension utilizing mice transgenic for active human rennin (TtRhRen) to create the model of type I DN that recapitulates key features of human disease. Such a model may be a new therapeutic target in patients with diabetic nephropathy.

Methods: Type 1 diabetic OVE26 mice were crossed with a mouse model of angiotensin-dependent hypertension utilizing mice transgenic for active human rennin (TtRhRen). TtRhRen mice exhibit angiotensin-dependent hypertension and progressive cardiac hypertrophy beginning at 6 weeks of age.

Results: At 20 weeks of age, OVE26 mice exhibited modest albuminuria as compared to wild-type and TtRhRen mice. However, albuminuria was significantly more pronounced in OVE26/TtRhRen mice. Additionally, OVE26/TtRhRen mice displayed renal and glomerular hypertrophy and evidence of tubulointerstitial fibrosis. Interestingly, beginning at 10 weeks TtRhRen/Ove26 mice were severely hypertensive, significantly exceeding that of TtRhRen littermates.

Conclusions: In summary, our results suggest that TtRhRen/OVE26 mice are a robust model of type I DN that recapitulates key features of human disease. Such a model may be of significant interest in the analysis of DN pathogenesis and in the assessment of putative therapeutics.

FR-PO240
Hyperglycemia Triggered Inflammosomes Activation in Glomerular Cells via Mitochondrial ROS Contributes to Diabetic Nephropathy
Madhusudhan Thal, Khrumur Shahzad, Fabian Bock, Hermann-Josef Groene, Berend Heinrich Iermann. Institute for Clinical Chemistry and Pathobiology, Otto-von-Guericke Univ Magdeburg, Magdeburg, Germany.

Background: Activation of the Nlrp3-Inflammosome has been implicated in many diseases including diabetic nephropathy (dNP). Whether inflammasome activation is causally involved in the pathogenesis of dNP and whether resident or bone marrow derived cells are involved remains to be elucidated.

Methods: Here, we analyzed the processing of caspase-1 and IL-1β in two different diabetic models (type 2 diabetic db/db mice and in STZ induced mice). A cohort of mice was injected with anakinra, an IL-1β inhibitor. In addition we transplanted bone marrow cells from Nlrp3-/- or caspase1-/- mice into db/db or wt control mice to investigate role of hematopoietic cells. Diabetic mice deficient for the mitochondrial RedOx-enzyme flavoenzyme were analyzed. Supplementary in vitro assays were performed in endothelial cells and podocytes.

Results: In renal cortex extracts of diabetic mice an increased expression of Nlrp3 and of mature IL-1β was observed. Nlrp3-/- or caspase1-/- mice as well as anakinra treated mice were protected against dNP. Confocal immunofluorescence analyses revealed that inflammasome activation is enhanced in glomerular cells in mice and humans with dNP. The severity of dNP was unchanged in bone marrow chimeras (Nlrp3-/- or caspase1-/- > db/db, db/db, compared with wt > db/db). Inhibition of mitochondrial ROS prevents inflammasome activation in podocytes in vitro. In diabetic p66-/- mice ROS-makers and inflammasome activation were reduced and these mice were protected against diabetic nephropathy. In vitro studies revealed activation of Nlrp3/caspase-1 pro-IL-1β upon glucose stimulation, while caspase-1 inhibitor/anakinra abolished IL-1β induction. Anakinra had no effect when cells were transduced with mutated Nlrp3 (Q705K) compared with Nlrp3-WT.

Conclusions: Taken together, these results strongly support that activation of the inflammasome in residual glomerular cells contributes to dNP. The inflammasomes may be a new therapeutic target in patients with diabetic nephropathy.

FR-PO241
Baseline Characteristics of Diabetic Kidney Disease Patients Enrolled in a Phase 2 Trial of CTP-499
LuAnn A. Sabounjian,1 Philip B. Graham,1 Lijun Wu,1 Ara Aslanian,1 Changfu Cheng,1 David J. Turnquist,1 James Shipley,1 George L. Bakris,2 1Div of Nephrology, 2Division of Clinical Sciences, St. George’s, University of London, United Kingdom.

Introduction: CTP-499, a novel, deuterium-containing methylxanthine derivative that selectively inhibits PDE subtypes that modulate AMP and GMP hydrolysis, is currently being developed as an additive treatment for delaying the progression of diabetic kidney disease. In preclinical studies, CTP-499 has been shown to suppress inflammatory, oxidative, and fibrotic processes associated with the pathophysiology of diabetic kidney disease. The objective of the double-blind, placebo-controlled, multicenter study (39 centers in the U.S.) is to assess the safety and efficacy of a minimum of 24 weeks of treatment with CTP-499 in patients with macroalbuminuric type 2 diabetic kidney disease who were maintained on a stable ACEi/ARB regimen.

Methods: The study randomized 182 patients 1:1 to either CTP-499 (600 mg BID, oral tablet) or placebo. Key entry criteria were: systolic blood pressure ≤145 mm Hg, diastolic blood pressure ≤90 mm Hg, macroalbuminuria with UACR from 200 for males and 300 for females to a max of 5000 mg/g, and eGFR by MDRD formula between 23 and 89 mL/min 1.73 m2. Additionally, patients were not expected to start dialysis in the next year.

Results: Based on these parameters, the characteristics of the enrolled population are shown below.
FR-PO244

Prevalence of Metabolic Syndrome after Donor Nephrectomy
Pisut Katsavetin, Yingyos Avihingsanon, Kearkit Praditpornsilpa. Div of Nephrology, Dept of Medicine, King Chulalongkorn Memorial Hospital, Thailand.

Background: The association between chronic kidney disease and metabolic syndrome has now been widely appreciated. However, the potential mechanisms for this association are still unclear. Studies mostly focused on how metabolic syndrome cause chronic kidney disease. We, therefore, examined the association in the other way around: Could reduction of nephron mass lead to metabolic syndrome?

Methods: Data of the donors who visited the ‘Donor Clinic’ from 2009-2012 were retrospectively reviewed to examine the prevalence of metabolic syndrome after kidney donation. Data of 494 ‘Donor Clinic’ visits (0.1 to 176.9 months after the kidney donation) from 102 kidney donors were included in the present analysis.

Results: The prevalence of metabolic syndrome was only 6.1% during the first year after kidney donation. The prevalence of metabolic syndrome in the second and the third year after kidney donation was 10.0 and 20.0% respectively. Prevalences of high blood pressure (≥130/85 mmHg) impaired fasting glucose (≥100 mg/dl) and elevated triglycerides (≥150 mg/dl) were also increasing during the first 3 year after donation.

Conclusions: Reduction of nephron mass after kidney donation may increase risk for metabolic syndrome. These findings would explain, at least in part, the association between metabolic syndrome and chronic kidney disease.

FR-PO245

Treatment of Chronic Kidney Disease in Rats Early or Late Post 5/6th Nephrectomy with Multiple Doses of Allogeneic, Narrow StROMAL Cells Is Effective in Arresting the Progressive Loss of Renal Function
Anna Gooch,1 Zhuma Hu,2 Ping Zhang,2 Christo Westenfelder.2 1Medicine, U. of Utah and VA Medical Centers, Salt Lake City, UT; 2Physiology, U of Utah, Salt Lake City, UT.

Background: The NIH reported that from 1980-2009 the prevalence of ESRD increased 600%. Chronic kidney disease (CKD) of all etiologies regularly progresses to ESRD, requiring dialysis or transplantation. Our pre-clinical (AJP Renal 2005) and Phase I Clinical studies (Nat Rev Neph 2010) show that allogeneic rat and human Marrow Stromal Cells (MSCs) effectively protect renal function post IRI Acute Kidney Injury (AKI) and prevent secondary development of CKD. Similar early and late renoprotective responses were observed in on-pump cardiac surgery patients at risk for post-op AKI. The current, preclinical study explores whether administration of MSCs also ameliorates or prevents worsening of CKD.

Methods: Groups of adult, male Sprague-Dawley (SD) rats (n=7/group) underwent 5/6th nephrectomy and were followed for 12 weeks. Animals were treated with 4 i.v. allogeneic MSC injections (1x10⁶ cells/kg.b.w) early (during weeks 2 to 3) or late (during weeks 8 to 11) post nephrectomy. Serum Creatinine (SCr), systolic blood pressure (BP) and urinary albumin (U Alb) excretion were assessed weekly and compared to vehicle treated 5/6th nephrectomized control and sham control groups. Renal histology was performed at end of study to assess glomerular sclerosis, interstitial fibrosis and inflammation.

Results: At end of study animals treated with MSCs either early or late in the course of CKD showed significantly lower SCr levels and U Alb excretion vs. vehicle control animals, as well as lower scores for interstitial and glomerular sclerosis. While BPs were significantly lowered in early MSC treated animals vs. vehicle controls, they were not significantly different in late treated animals vs. their vehicle controls.

Conclusions: Repeated administration of allogeneic MSCs early or late in the course of CKD appears to arrest the progressive loss of renal function and rise in albuminuria in these preclinical studies, supporting the possibility that these cells may be of use clinically in treating CKD.

Funding: Veterans Affairs Support
**FR-PO246**

The Enzymatic Activity of the VEGFR2-Receptor for the Biosynthesis of Dinucleoside Polyphosphates

** Vera Jankowski, 1 Axel Kretschmer, 2 Mirjam Schuchardt, 1 Markus Van der Giet, 1 Joachim Jankowski, 1 1 Med. Klinik IV, Charite, Berlin, Germany; 2 Biomarker, Bayer AG, Wuppertal, Germany.**

**Background:** The group of dinucleoside polyphosphates encompasses a large number of molecules consisting of two nucleosides which are connected by a phosphate chain of variable length. Dinucleoside polyphosphates are uric acids influencing different physiological events. The processes of the receptor tyrosine kinase (RTK) VEGFR2 and dinucleoside polyphosphates as well as their degradation have been studied in detail, its biosynthesis has not been elucidated so far.

**Methods:** Since endothelial cells released the dinucleoside polyphosphate uridine adenosine polyphosphate (Up-A), we tested cytokine-treated human embryonic cells obtained from different cell lines and immortalized cell lines for the expression of VEGFR2 and dinucleoside polyphosphates. Moreover, we used a cell-free assay to determine the enzymatic activity of VEGFR2.

**Results:** The enzymatic activity of VEGFR2 was confirmed in endothelial cells and immortalized cell lines. All of the tested cell lines showed increasing concentrations of Up-A.

**Conclusions:** VEGFR2-receptor is capable of synthesizing dinucleoside polyphosphates. These mediators may modulate the effects of VEGFR2 due to their proliferative effects.

**FR-PO247**

Modulation of NADPH Oxidase Activity by Known Uremic Retention Solutes

**Sera Jankowski, 1 Joachim Jankowski, 1 Gerald Cohen, 2 Med. Klinik IV, Charite, Berlin, Germany; 2 Med. Klinik, Medical Uni of Vienna, Vienna, Austria.**

**Background:** Chronic kidney disease (CKD) and uremia are associated with increased oxidative stress. In addition, a number of diseases like cardiovascular disease are caused by increased concentration of reactive oxygen species (ROS). However, the link between uremia and increased oxidative stress in patients with chronic kidney disease is not well-understood until now.

**NADPH oxidase is one of the keyplayers in genesis of oxidative stress by producing superoxide anion and secondarily derived reactive oxygen species (ROS).** Therefore, to further understand the pathophysiology underlying CKD we investigated the contribution of endothelial SIRT1 deficiency to TbRIIendo+/- mice and its association with reduced MMP-14 expression via Concanavalin A (ConA) treatment to investigate the relationship between endothelial SIRT1 deficiency and attenuated neprilysin activity.

**Methods:** To investigate the contribution of endothelial SIRT1 deficiency per se to SIPS and vasculopathy, we used cre-lox strategy to generate mice with truncated SIRT1 gene in endothelial cell-specific (EKT) and endothelial progenitor cell-specific (EPC) progenitor cells.

**Results:** Studies of SIRT1+/− mice showed impaired endothelial-dependent vasorelaxation and angiogenesis and traces of spontaneous fibrosis already at the early age. In contrast to the mild phenotypes of SIRT1endo−/− mice under basal conditions, induction of nephrotoxic stress (acute and chronic folic acid nephropathy, FAN) resulted in a robust acute renal functional deterioration and exaggerated fibrotic response as examined three months later. To disclose the link between endothelial SIRT1 deficiency and exaggerated renal fibrosis, we examined matrix metalloproteinases-14 (MMP-14), which was suppressed in TbRII+/− EC’s, following TGF-b treatment. Interestingly, ALK1 mediated Smad1/5 phosphorylation in TbRII+/− EC’s following TGF-b treatment phosphorylation of Smad1/5 was not affected. Endoglin S’L mRNA expression ratio was significantly lower in TbRII+/− EC’s with and without TGF-b treatment as compared to TbRII+/− EC’s. An increased L-endoglin mediated Smad1/5 signaling in TbRII+/− EC’s could explain the increased angiogenic potential of these mice observed in vivo.

**Conclusions:** Our data indicate a critical role of endothelial TGF-b signaling in regulating angiogenic and fibrotic response to injury. Funding: NIDDK Support.

**FR-PO249**

Endothelial Sirtuin 1-Deficiency Leads to Down-Regulation of Matrix Metalloproteinase 14 and Exaggerated Kidney Fibrotic Response to Injury: Relevance to Fibrosis of Vascular Sclerosis

**Jun Chen, 1 Radovan Vasko, 1 Sandhya Xavier, 1 Chi Hua Sarah Lin, 1 Brian B. Radliff, 2 May B. Rabadi, 3 Julien Maizel, 1 Fabio Rina, 1 Michael S. Gordon, 1 New York Medical College, Valhalla; 2 State Uni of New York, Stony Brook, NY.**

**Background:** Sirtuin 1 (SIRT1) depletion in vascular endothelial cells mediates endothelial dysfunction and premature senescence. However, the role of endothelial senescent cells and their contribution to organ pathology remain tenuous.

**Methods:** To investigate the contribution of endothelial SIRT1 deficiency per se to SIPS and vasculopathy, we used cre-lox strategy to generate mice with truncated SIRT1 gene in endothelial cell-specific (EKT) and endothelial progenitor cell-specific (EPC) progenitor cells.

**Results:** Studies of SIRT1+/− mice showed impaired endothelial-dependent vasorelaxation and angiogenesis and traces of spontaneous fibrosis already at the early age. In contrast to the mild phenotypes of SIRT1endo−/− mice under basal conditions, induction of nephrotoxic stress (acute and chronic folic acid nephropathy, FAN) resulted in a robust acute renal functional deterioration and exaggerated fibrotic response as examined three months later. To disclose the link between endothelial SIRT1 deficiency and exaggerated renal fibrosis, we examined matrix metalloproteinases-14 (MMP-14), which was suppressed in TbRII+/− EC’s, following TGF-b treatment. Interestingly, ALK1 mediated Smad1/5 phosphorylation in TbRII+/− EC’s following TGF-b treatment phosphorylation of Smad1/5 was not affected. Endoglin S’L mRNA expression ratio was significantly lower in TbRII+/− EC’s with and without TGF-b treatment as compared to TbRII+/− EC’s. An increased L-endoglin mediated Smad1/5 signaling in TbRII+/− EC’s could explain the increased angiogenic potential of these mice observed in vivo.

**Conclusions:** Our data indicate a critical role of endothelial TGF-b signaling in regulating angiogenic and fibrotic response to injury. Funding: NIDDK Support.

**FR-PO250**

Mechanisms of Proteinuria in a Chronic Kidney Disease (CKD) Model following Ischemic Injury

**Silvia B. Campos-bilderback, 1 Monique Desiree Din, 2 Ruben M. Sandoval, 1 Sarah E. Wean, 1 Bruce A. Molitoris, 1 1 Medicine/Nephrology, IU School of Medicine, Indianapolis, IN; 2 Roudabsh VAMC, Indianapolis, IN; 3 Univ of Contestado, Mafra, Santa Catarina, Brazil.**

**Background:** The development and or acceleration of CKD progression following acute kidney injury (AKI) is now well recognized, as is the importance of proteinuria as a risk factor for progression of CKD.

**Methods:** Therefore, to further understand the pathophysiology underlying CKD progression and proteinuria we made Munich Wistar Fronten rats and induced CKD with ischemic injury and a unilateral nephrectomy.

**Results:** Serum creatinine levels increased from 0.3 to 1.5 to 0.3 (P<0.01) and urinary albumin increased from 100 ± 110 to 300mg/24 hr/GFR/100 gm (P<0.01). There was progression of both proteinuria and loss of GFR in this CKD model. Histologic evaluation revealed tubular atrophy with an interstitial mononuclear infiltrate and edema, peri-glomerular fibrosis, hyaline drop formation and generalized fibrosis. Two-photon microscopy demonstrated albumin glomerular sieving coefficients (GSC) increased from 0.41 ± 0.03 to 0.74 ± 0.03 with intra-glomerular deposits within a single glomerulus. In PTs uptake of fluorescently labeled albumin was reduced from 2.911.3 ± 1.815.4 AU/um2 to 1.763.3 ± 932.5 AU/um2 (p=0.05), the most noticeable difference occurred in the area devoid of albumin uptake among Pt’s. Untreated rats had only 18.2 ± 7.2% of PT area with no albumin uptake while CKD rats had 42.9 ± 21.1% of the PT area devoid of albumin uptake (p=0.05).

**Conclusions:** These data demonstrate albuminuria in rats with ischemic CKD resulted from a combination of increased GSC, and reduced albumin uptake by PT. The model offers a reproducible model of proteinuria and progression, or other study glomerular, tubular and interstitial interactions, and to utilize in developing therapeutic strategies to minimize CKD and AKI-CKD interactions.
Abnormal Circadian Rhythm of Blood Pressure Related to Kidney Damage in IgA Nephropathy

**Background:** Abnormal circadian rhythm of blood pressure is a risk factor of cardiovascular and cerebrovascular lesions in the patients with primary hypertension, also it is closely related with diabetic nephropathy progression and cardiovascular events in hemodialysis patients. The purpose of this study is to investigate the role of abnormal BP rhythm in IgAN.

**Methods:** 341 IgAN patients were recruited in the study. Renal biopsy and 24 hour ambulatory blood pressure monitoring were performed. The pathological scores were evaluated according to the IgAN Oxford criterion. Influencing factors were determined by Spearman and Pearson correlation analysis and logistic regression analysis.

**Results:** (1) Incidence of abnormal BP rhythm is 73.0% (294/41) in IgAN patients, 73.8% (93/126) in IgAN patients with hypertension, 72.6% (156/215) in IgAN patients without hypertension. (2) Cystatin C, urinary PCi, uric acid, renal histological score, TIF, hyaline degeneration of small arteries were closely associated with abnormal blood pressure rhythm in IgAN patients with or without hypertension. The decline of nocturnal BP was negatively related with cystatin C, uric acid, renal histological score. (3) EGF levels was closely associated with abnormal blood pressure rhythm in IgAN patients with hypertension. The decline of nocturnal BP was positively related with eGFR. (4) Uricary PCi and night-day ratio of urinary sodium excretion (RN/UNa) were closely associated with abnormal blood pressure rhythm in IgAN patients without hypertension, and the decline of nocturnal BP was positively related with urinary PCi, RN/UNa.

**Conclusions:** Abnormal blood pressure rhythm is closely related with kidney glomerulonephritis, renal tubulointerstitial and arteriolar lesions in IgAN patients, indicating that abnormal blood pressure rhythm is a potential risk factor for IgAN progression. Abnormal blood pressure rhythm in IgAN patients is directly related with RN/UNa and blood uric acid level, implying the ion transport dysfunction caused by renal tubular interstitial lesions in IgAN may be an important cause of abnormal blood pressure rhythm. Abnormal blood pressure rhythm can increase the risk for the progression to ESRD in hypertensive IgAN patients.

**Funding:** Clinical Revenue Support

---

**FR-PO254**

**Association of Systolic Blood Pressure with Progression to Chronic Dialysis in Patients with Advanced Kidney Disease**

**Background:** The mean eGFR was 18 ± 7 ml/min. 615 patients (56%) initiated dialysis after mean follow-up time of 2.9 years. After adjustment for age, gender and race there was an association between HDL-C levels and kidney disease progression (HR 0.99, 95% CI 0.99 to 1.004). After further adjustment for age, race, gender, diabetes, hypertension, cardiovascular disease, smoking, body mass index, eGFR, systolic blood pressure, low-density lipoprotein cholesterol and triglycerides, HDL-C levels did not predict progression of kidney disease (HR 1.03, 95% CI 0.99 to 1.07, p=0.30). There was no increase in risk of kidney disease progression in patients in the lowest quartile of HDL-C levels compared to the highest quartile (HR 1.2, 95% CI 0.96 to 1.51, p=0.12).

**Conclusions:** Low HDL-C levels are not associated with progression to chronic dialysis in patients with advanced kidney disease. Further studies are needed to elucidate the role of HDL-C in kidney disease progression.

**Funding:** NIDDK Support

---

**FR-PO255**

**Role of PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) in the Pathogenesis of Hypercholesterolemia in Nephrotic Syndrome**

**Background:** Nephrotic syndrome (NS) is associated with impaired LDL clearance and elevated serum total and LDL cholesterol levels. LDL receptor (LDLR) plays a key role in cholesterol metabolism by mediating endocytosis and lysosomal degradation of LDL. In a series of earlier studies we found marked reduction in LDLR despite normal LDLR mRNA expression in the liver of nephritic rats, denoting a post-transcriptional or post-translational phenomenon. LDR is, in part, regulated by PCSK9 which is secreted in the blood by the liver.

**Methods:** We performed an analysis on 1,099 patients with advanced kidney disease not yet on dialysis, who participated in the Homocysteine in Kidney and End Stage Renal Disease study. The study population was divided into quartiles based on serum HDL-C levels. We used Cox proportional hazard models to examine the association between HDL-C levels and time to initiation of chronic dialysis.

**Results:** The mean age and eGFR were 69 ± 11 years and 18 ± 7 ml/min/1.73m², respectively. After a median follow-up time of 2.9 years, 615 patients (56%) initiated chronic dialysis. After adjustment for age, gender and race there was no association between HDL-C levels and kidney disease progression (HR 0.99, 95% CI 0.99 to 1.004). After further adjustment for age, race, gender, diabetes, hypertension, cardiovascular disease, smoking, body mass index, eGFR, systolic blood pressure, low-density lipoprotein cholesterol and triglycerides, HDL-C levels did not predict progression of kidney disease (HR 1.03, 95% CI 0.99 to 1.07, p=0.30). There was no increase in risk of kidney disease progression in patients in the lowest quartile of HDL-C levels compared to the highest quartile (HR 1.2, 95% CI 0.96 to 1.51, p=0.12).

**Conclusions:** Low HDL-C levels are not associated with progression to chronic dialysis in patients with advanced kidney disease. Further studies are needed to elucidate the role of HDL-C in kidney disease progression.

**Funding:** NIDDK Support

---

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

*Underline represents presenting author/disclosure.*

421A
liver where it binds, internalizes, and facilitates degradation of LDLR. Thus by preventing recycling of LDLR, upregulation of PCSK9 causes LDLR deficiency. Loss-of-function mutation of PCSK9 is associated with reduced LDL cholesterol and diminished risk of coronary disease. This has led to emergence of PCSK9 as a novel target for treatment of hypercholesterolemia. The mechanism(s) by which NS causes LDLR deficiency is not known. This study was undertaken to test the hypothesis that impaired LDLR clearance in NS is mediated to increased PCSK9.


**Results:** Elevated serum total and LDL cholesterol in the nephrotic group was associated with significant increase in plasma PCSK9 level. Plasma PCSK9 was directly related to serum total and LDL cholesterol concentrations and urinary protein excretion and inversely related with serum albumin concentration.

**Conclusions:** NS results in elevation of the circulating PCSK9 which can contribute to elevation of LDL by promoting LDLR deficiency.

**Funding:** Private Foundation Support

**FR-PO256**

Is ENPP1 Gene SNP Associated With Lower Pyrophosphate Levels in ESRD

**Methods:** PBMCs and analyzed using the Illumina iScan and tissue proteins, and provide new evidences for the involvement of CDPs and especially 25(OH)D, which not uncommonly is reduced in the serum of patients with CKD, directly induces expression of the antimicrobial peptide, cathelicidin (LL-37), which, if low, could explain the severity of CP frequently seen in CKD. The aim of this study was to examine the relationship among CP, 25(OH)D and IL-6 in patients with CKD.

**Results:** In the present study, 15 patients with CKD were enrolled and staged and 25(OH)D are presented in the table. Patients with CKD and CP presented a worse CP, which, if low, could explain the severity of CP frequently seen in CKD.

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

**FR-PO257**

Akt-Pathway-Selective Insulin Resistance Contributes to Decreased Angiogenic Function of Bone Marrow-Derived Mesenchymal Stem Cells under Uremic Conditions

**Background:** Chronic kidney disease (CKD) is associated with increased risk for cardiovascular disease (CVD). We recently reported a significant functional incompetence in bone marrow (BM)-derived mesenchymal stem cells (MSCs) under uremic conditions, which may contribute to the high risk for CVD in patients with CKD. To study the mechanisms of dysfunctional MSCs induced by uremia, we characterized insulin signaling in these cells.

**Methods:** BM-derived MSCs were generated from control and subtotal nephrectomized CKD mice. MSCs’ multipotency was confirmed by positive differentiation into adipocytes and osteocytes.

**Results:** In mice model of hindlimb ischemia, we confirmed that CKD MSCs show functional incompetence. Blood flow recovery, capillary density, and local production of angiogenic factors in the ischemic limb treated with CKD MSCs were significantly inferior to those promoted by control MSCs. In cultured cells, insulin induced HIF-1α, VEGF, and SDF-1α expressions via phosphatidylinositol 3-kinase (PI3K)/Akt-dependent pathway. CKD MSCs could not induce angiogenesis in a selective manner for the activation of IRS-1/PI3K/Akt pathway, whereas the activation of ERK pathway remained active. Insulin-induced tyrosine phosphorylation of IRS-1, p85 association with IRS-1, and IRS-1-associated PI3K activity were significantly reduced by p-cresol. In parallel, p-cresol treatment was associated with basal elevation in inhibitory phosphorylation of IRS-1 at Ser307. Modifying the basal expression of IRS-1 by SDF-1α and HIF-1α restored the impaired blood flow recovery, capillary density, and local production of angiogenic growth factors induced by CKD MSCs in the hindlimb ischemic model.

**Conclusions:** The present study shows that insulin signaling and actions in MSCs are significantly inhibited in a selective manner for the activation of IRS-1/PI3K/Akt pathway under uremia. We suggest that this might be a biological explanation for the functional incompetence of CKD MSCs.

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

**FR-PO258**

Carbamylated Tissue Proteins: A Risk Factor for Complications during Chronic Kidney Disease

**Background:** Chronic kidney disease (CKD) independently increases the risk of any type of cardiovascular events and generates many other complications. Among other processes, carbamylation of proteins has been recently suggested as a novel risk factor for CKD complications. Carbamylation corresponds to the nonenzymatic binding of isocyanic acid, a urea by-product, to free amino groups of proteins. This reaction leads to the formation of carbamylation-derived products (CDPs). In vitro and clinical studies have suggested the potential involvement of CDPs in CKD complications, but their metabolic fate in vivo is still unknown, without evidences of CDPs accumulation in tissues.

**Methods:** To address this issue, we have submitted C57Bl/6 mice to sham surgery or 75% nephrectomy. Animals were sacrificed 5, 10 or 20 weeks later. Then we quantified HcIt, a CDP resulting from lysine residue carbamylation, in plasma and tissues (aorta, kidney, bone, skin, liver, heart) by LC-MS/MS.

**Results:** We showed that carbamylation was a general biological process since plasma and tissue contents of HcIt were evidenced in control mice. Carbamylated proteins accumulated to a higher extent in studied tissues after 20 weeks of CKD with a 2-fold increase of HcIt content. Carbamylation rate was especially remarkable in type II collagen, a long-lived extracellular matrix protein. Carbamylated collagen accumulated progressively in CKD mice to reach a 5-fold increase after 20 weeks.

**Conclusions:** These results show that CKD increases carbamylation rate of plasma and tissue proteins, and provide new evidences for the involvement of CDPs and especially carbamylated collagen in CKD complications. These data reinforce the hypotheses raised by the in vivo demonstrations of the deleterious effects of CDPs and by the recently evidenced relationship between plasma CDP concentrations and cardiovascular risk or mortality in CKD patients.

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

**FR-PO259**

Associations among Chronic Periodontitis, Vitamin D and Cathelicidin in Patients with Chronic Kidney Disease

**Background:** The occurrence of chronic periodontitis(CP) in patients with chronic kidney disease (CKD) has been associated with adverse outcomes. Vitamin D (25(OH) D), which not uncommonly is reduced in the serum of patients with CKD, directly induces expression of the antimicrobial peptide, cathelicidin (LL-37), which, if low, could explain the severity of CP frequently seen in CKD.

**Methods:** A case-control study was conducted. Case and controls were defined as patients with CKD and CP (CKD+CP; n= 15), CKD without CP (CKD-CP, n= 14), CP without systemic disease (SD-CP; n= 14), and participants without both systemic disease and CP (-SD-CP; n= 15). Demographic, clinical and laboratory data were obtained when the patients were seen at the outpatient clinic. CKD was defined and staged according to the National Kidney Foundation KDOQI (2002). Serum 25(OH)D was measured by chemiluminescence immunoassay when evaluating the CP (defined according to the American Academy of Periodontology). LL-37 and interleukin-6 (IL-6) were measured by ELISA.

**Results:** The data regarding the CP (clinical attachment level or CAL), IL-6, LL-37 and 25(OH)D are presented in the table. Patients with CKD+CP presented a worse CP, were more inflamed, presented lower levels of 25(OH)D and LL-37.

**Conclusions:** CKD patients have a worse CP, probably due to lower levels of LL-37 secondary to inadequate levels of vitamin D.

**Funding:** Private Foundation Support

**Note:** Table. Clinical and lab results of the 4 study groups.
FR-PO260  
**Albumin-to-Creatinine Ratio versus Protein-to-Creatinine Ratio and Complications of CKD**  
Herrick Nadine Fisher, Chi-juan Hsu, Eric Vittinghoff, Feng Lin, Nisha Bansal. UCSF.

**Background:** Urine albumin-to-creatinine ratio (ACR) and protein-to-creatinine ratio (PCR) are important markers of kidney damage and are utilized for prognosis in persons with chronic kidney disease (CKD). However, due to the discordance between these measurements, the present study’s main objective was to identify factors associated with lower bicarbonate. The purpose of this study was to identify factors associated with lower bicarbonate and higher PTH.

**Methods:** We performed a cross-sectional study of 3,481 participants in the Chronic Renal Insufficiency Cohort (CRIC). We examined the association between ACR and PCR with measures of common CKD complications: serum hemoglobin, bicarbonate, parathyroid hormone (PTH), phosphorus, potassium and albumin. Restricted cubic spline analyses adjusted for eGFR were performed to study the continuous association with our predictors with each outcome.

**Results:** Mean eGFR 43 ± 13 ml/min/1.73 m² and median levels of PCR and ACR were 140 mg and 46 mg/l, respectively. In continuous analyses adjusted for eGFR, higher ACR and PCR were comparable and both associated with lower serum hemoglobin, lower bicarbonate concentration, higher PTH, higher phosphorus, higher potassium and lower albumin (Figure). Across all outcomes, the associations of ACR and PCR were comparable and only small, absolute differences in the outcome measure. Similar associations were seen in patients with and without diabetes mellitus.

**Conclusions:** In persons with CKD, ACR and PCR are relatively comparable in their associations with common complications of CKD. Thus, routine measurement of PCR may provide similar information as ACR in managing immediate complications of CKD.

**Funding:** NIDDK Support

FR-PO261  
**Factors Associated with Lower Serum Bicarbonate in Chronic Kidney Disease**  
Kalani L. Raphael,1,2 Y. Zhang,1 Jian Ying,2 Tom Greene.2 Salt Lake City VA Health Care System, UT; 2Univ of Utah.

**Background:** Acidosis is common in CKD, yet most with moderate-severe CKD do not have acidosis. The purpose of this study is to identify factors associated with lower serum bicarbonate in CKD.

**Methods:** This is a cross-sectional study using baseline data from the Chronic Renal Insufficiency Cohort (CRIC) Study. A base multivariable linear regression model included eGFR, UACR, age, gender, race, protein intake, diuretic use, and alkali use. Cause of renal insufficiency, waist circumference, CVD, CRP, smoking, blood pressure, use of ACE-I or ARB, anemia, hyperkalemia, iron, and education were individually added to the base model.

**Results:** The prevalence of acidosis was 17%. Lower eGFR had the strongest relationship with lower bicarbonate in CKD. Other factors associated with lower bicarbonate were anemia (Figure). Across all outcomes, the associations of ACR and PCR were comparable and only small, absolute differences in the outcome measure. Similar associations were seen in patients with and without diabetes mellitus.

**Conclusions:** In persons with CKD, ACR and PCR are relatively comparable in their associations with common complications of CKD. Thus, routine measurement of PCR may provide similar information as ACR in managing immediate complications of CKD.

FR-PO262  
**Dose-Relativity of Calcium Acetate and Lanthanum Carbonate in the Treatment of Hyperphosphatemia**  
Rosamund J. Wilson,1 Brian Copley,2 Michael S. Keith,3 Peter Preston.2 Spicis Consultants, Marlborough, United Kingdom; 3Shire Pharmaceuticals, Wayne, PA.

**Background:** Hyperphosphatemia can be managed with phosphate (P) binders such as lanthanum carbonate (LC) and calcium acetate (CA). Our aim was to evaluate the dose-relativity between CA and LC monotherapy and assess elemental calcium (Ca) intake.

**Methods:** We completed a post hoc analysis from the phase 4 study of patients with end stage renal disease (ESRD) and hyperphosphatemia. The study included a 1-week observation period in which patients remained on their existing P binder, a 12-week LC monotherapy titration phase and a 4-week LC maintenance period. Serum P and daily P binder dose were assessed at baseline for patients treated with CA and at weeks 12 and 16 after switching to LC.

**Results:** At baseline 707 patients received a prior recorded dose of CA monotherapy, 551 of whom were receiving LC at 16 weeks post-baseline. Mean dose, daily P relativity, P level and elemental Ca intake overall and by prior CA dose are shown below. The recommended maximum intake of Ca from Ca-based P binders is 1.5g; ~50% of patients exceeded this. The recommended daily intake of 2.0g was exceeded in ~25% of patients based on Ca content of their P binder alone.

**Conclusions:** The overall CA:LC dose relativity was 2.0. The lower tablet burden with LC may improve adherence for patients with ESRD. The recommended elemental Ca intake was exceeded by ~50% of patients which may have vascular calcification implications.

**Funding:** Pharmaceutical Company Support - Shire Pharmaceuticals

FR-PO263  
**Statin Use and Lipid Profiles in a Predialysis Clinic**  
Mathilde Laferrère, Sarah Bezzaoucha, Vincent Pichette, Jean-Philippe Lafrance, Robert Zoël Bell, Michel Vallerie. Nephrology Dept, Hôpital Maisonneuve-Rosemont, Montreal, Canada.

**Background:** Dyslipidemia and chronic kidney disease are well-recognized independent risk factors for cardiovascular disease. Large randomized-controlled studies had previously demonstrated that the treatment of dyslipidemia resulted in a substantial reduction in cardiovascular events and mortality. The SHARP trial was the first study to demonstrate that treatment of dyslipidemia resulted in a significant cardiovascular risk reduction in an advanced chronic kidney disease population. The objective of our study was to assess the lipid profile and statin use in our predialysis population, in order to determine the proportion of patients reaching target values.

**Methods:** We have retrospectively collected statin use and the lipid profile in patients at our predialysis clinic between 2010 and 2011. Demographic data as well as other risk factors for cardiovascular disease were also collected. At baseline, lipid profiles were available for 289 predialysis patients. Average age was 68.8 years, 40.8% were women and BMI 31 (SD ±7). Mean glomerular filtration rate was 19.7 mL/min/1.73m² (SD ±7). Mean lipids levels were: 12.4 mmol/L ±0.9 (85mg/dl ±33), with 76% patients already taking a statin and 5.4% taking ezetimibe. Despite being on atorvastatin, the most frequently prescribed statin, a subgroup exceeded this. The recommended daily intake of 2.0g was exceeded in ~25% of patients based on Ca content of their P binder alone.

**Conclusions:** The overall CA:LC dose relativity was 2.0. The lower tablet burden with LC may improve adherence for patients with ESRD. The recommended elemental Ca intake was exceeded by ~50% of patients which may have vascular calcification implications.

**Funding:** Veterans Affairs Support, Private Foundation Support.

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

Underline represents presenting author/disclosure.

423A
Warfarin Dose Requirements in Patients with Kidney Dysfunction
Sami Sakka,1 Joanna Hudson,1,2 Carrie Oliphant,1,3 Carolyn Cummings,1,2 Numan Alabdan,1 Tim Self,1,2 The Univ of Tennessee; 3Methodist Univ Hospital, Memphis, TN.

Background: The effect of chronic kidney disease (CKD) on warfarin response remains largely unstudied despite increased risk of thromboembolism and bleeding in this population. Data suggest that patients with reduced kidney function require lower warfarin doses; however, relatively few patients with end stage renal disease (ESRD) were included in previous studies. The purpose of this study is to evaluate warfarin dosing requirements in patients with stage 3 and higher CKD compared to patients with normal kidney function.

Methods: A retrospective review was conducted to evaluate warfarin response in hospitalized patients with “normal” kidney function (glomerular filtration rate > 60 mL/min/1.73 m²) and in patients with CKD stage 3, stage 4 or 5 or ESRD initiated or maintained on warfarin for ≥4 consecutive days. The average daily dose to maintain a therapeutic INR, time to achieve this INR in patients newly initiated on warfarin, and adverse effects were compared among groups.

Results: Of the 225 patients studied, the average daily dose to maintain a therapeutic INR was statistically lower in CKD/ESRD patients compared to patients with normal kidney function (p=0.0014). The median time to reach a therapeutic INR did not differ among groups (p=0.931). Significantly more bleeding episodes during hospitalization or within 30 days of discharge were observed in patients with CKD stage 3 or higher compared to patients with normal kidney function (p = 0.0258).

Conclusions: Our findings suggest that CKD and ESRD patients require 20% lower warfarin doses to maintain a therapeutic INR and warrant more monitoring for bleeding compared to patients with normal kidney function.

Academic Achievement in Pediatric Chronic Kidney Disease
Lyndsay Harshman,1 Douglas Russo,1 Sheila Barron,1 Natalie L. Denburg,2 Patrick D. Brophy.1 1Pediatrics, Univ of Iowa Children’s Hospital, Iowa City, IA; 2Neurology, Univ of Iowa Hospitals and Clinics, Iowa City, IA; 3Education, Univ of Iowa, Iowa City, IA.

Background: Children with chronic kidney disease (CKD) are at risk for neurocognitive impairment. Interest in neurocognition has increased as medical management of underachievement.

Methods: The Iowa Tests of Basic Skills and Iowa Tests of Educational Development were used to examine the association of %GMV with each score of three cognitive tests. Volume of brain tissue was calculated from T1-weighted MRI images and modulated to adjust for variations in head size. Univariate and multivariate linear regression analyses were matched with each group. Blood samples were collected in PaxGene RNA collection tubes at the entry of this study. Sleep and awakening related gene expression in CKD patients, and brain tissue and electroencephalographic analysis in a mouse CKD model.

Results: Of the 225 patients studied, the average daily dose to maintain a therapeutic INR was statistically lower in CKD/ESRD patients compared to patients with normal kidney function (p=0.0014). The median time to reach a therapeutic INR did not differ among groups (p=0.931). Significantly more bleeding episodes during hospitalization or within 30 days of discharge were observed in patients with CKD stage 3 or higher compared to patients with normal kidney function (p = 0.0258).

Conclusions: Our findings suggest that CKD and ESRD patients require 20% lower warfarin doses to maintain a therapeutic INR and warrant more monitoring for bleeding compared to patients with normal kidney function.
hazards regression with mortality as a competing risk was used to analyze the associations between sex and incident CKD after adjustment for demographics (age, race/ethnicity, marital status, education, smoking), traditional CKD risk factors (BMI, hypertension, low-density lipoprotein (LDL), body mass index (BMI), hemoglobin A1c), and behavioral risk factors for CKD (depression and adherence to diet, exercise, glucose monitoring, and self-foot exam). Multiple imputation was used for covariates with missing values.

Results: Of the 1,468 total subjects, 766 were women (52.2%). Women were younger, less likely to be married, had lower education levels, and higher LDL, BMI and baseline eGFR compared to men. Taking into account pre-CKD death as a competing risk, women had a higher cumulative risk of incident CKD at 10 years (sub-hazard ratio (SHR) 1.33, 95% CI 1.10-1.62). This association persisted after adjustment for demographics (SHR 1.44, 95% CI 1.21-1.72), traditional risk factors (SHR 1.48, 95% CI 1.23-1.77), and behavioral risk factors for CKD (SHR 1.48, 95% CI 1.23-1.77).

Conclusions: Compared to men, women with diabetes had an increased 10-year risk of incident CKD which was not attenuated after adjustment for traditional and behavioral risk factors for CKD. Diabetic women may represent a high risk group for the development of CKD.

FR-P0269
Incidence of Chronic Kidney Disease in Cancer Survivors Exposed to Cisplatin Swati Mehta, Sujata Patil, Carlos D. Flombaum, Ilya Glezerman, Sheron Latcha. Nephrology, Memorial Sloan Kettering Cancer Center, NY.

Background: Cisplatin, an important antineoplastic agent, is notoriously nephrotoxic. Reports in the literature on long term nephrotoxicity of cisplatin are sparse and have focused on pediatric population. We present data on long term (5 to 12 year follow up) renal effects of cisplatin in cohort of 859 adult patients.

Methods: Retrospective analysis was performed after obtaining approval from the Institutional Review Board. We collected data for 859 adult patients treated with cisplatin from 1st Jan 2000 till 20th Sept 2011. Data included age, gender, race, ethnicity, primary malignancy, serum creatinine level prior to cisplatin therapy and subsequent serum creatinine values. We calculated the estimated glomerular filtration rate (eGFR) using the 3-variable MDRD equation. Inclusion criteria for the study was age at diagnosis of malignancy ≥18y and patients who survived at least 5 years after their initial dose of cisplatin. Patients who received ifosfamide concomitant or subsequent to cisplatin or in whom baseline creatinine was unavailable were excluded.

Results: 859 patients met the inclusion criteria. 63.3% were Male and 85.6% Caucasian. Most patients were between the age of 25 and 65 when exposed to cisplatin. Head & Neck, testicular and gastrointestinal malignancies accounted for 62% cases. Most patients received a cumulative cisplatin dose from 100 to 400 mg/m2 (77%). 742 patients (90%) had eGFR more than 60ml/min per 1.73 m2 at baseline, 95% patients maintained an eGFR >60ml/min per 1.73 m2 in 5 years post cisplatin exposure and per the data available, none of the patients had eGFR<15ml/min per m2 or developed ESRD.

Conclusions: Cisplatin is an important chemotherapeutic agent with well known acute nephrotoxic effects. Long term renal effects of cisplatin in adults has not been studied well. Our study of 859 adult patients has limitations in being a retrospective chart review. Its strengths are the sheer sample size of 859 adult patients and a first of a kind study to show that cisplatin is notorious for causing acute renal failure; its long term effects on renal function are not as severe with no patients developing ESRD in our study.

FR-P0270
Carotid Plaque Predict Rate of Renal Function Decline in Patients with Chronic Kidney Disease Inva-kyung Kim, Sung Jin Moon, Sun Ryong Choi, Jong-woo Yoon, Jung-woo Noh, Sung Gun Kim. 1. Internal Medicine, Hallym Univ Sacred Heart Hospital, Kidney Research Institute, Korea; 2. Internal Medicine, Myongji Hospital, Kwandong Univ College of Medicine, Korea.

Background: Carotid plaque is a surrogate marker of systemic atherosclerosis and closely associated with adverse cardiovascular outcomes. However, prospective data regarding the predictive role of carotid plaque for renal progression are limited in chronic kidney disease (CKD) patients.

Methods: As a prospective design, a total of 411 Stage 3 and 4 CKD patients were enrolled, and all patients underwent carotid ultrasonography at the time of CKD diagnosis. A carotid plaque was defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding carotid intima-media thickness (cIMT) or a thickness ≥1.5mm as measured from the media- adventitia interface to the intima-lumen interface. Renal function decline was measured by estimated glomerular filtration (eGFR) slope and the renal endpoint was defined as the start of dialysis.

Results: Baseline eGFR was 44.5±11.6 mL/min/1.73m2 and eGFR slope was −2.8±3.76 ml/min/1.73m2/yr. A carotid plaque was found in 282 (68.6%) patients, and these patients had significantly faster rates of renal function decline than those without plaque (-3.6±4.38 ml/min/1.73m2/yr vs. −1.20±2.85 mL/min/1.73m2/yr, p<0.001). According to multivariate analysis, statistically significant variables determining eGFR slope were diabetes (β=−0.77, p=0.033), increased pulse pressure (β=−0.02, p=0.015), elevated proteinuria (β=−0.50, p=0.001), increased cIMT (β=−4.36, p=0.001) and the presence of a carotid plaque (β=−1.48, p=0.001). During the 2.5-year follow-up, 47 (11.4%) of patients started dialysis. Patients with carotid plaque had a poorer dialysis-free survival rate than those without carotid plaque (hazard ratio 3.3: 95% confidence interval 1.01, 10.77).

Conclusions: Carotid plaque was closely associated with rapid decline of renal function and progression to dialysis in stage 3 and 4 CKD patients. Detecting carotid plaque may help identify patients at high-risk for progression of renal dysfunction.

FR-P0271
Association of Fluid Overload, Diabetes and Renal Disease Progression in Chronic Kidney Disease Yi-chun Tsai, Mei-Chuan Kuo, Hung-Chun Chen. Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

Background: Fluid overload is one of major presentation in patients with late stage of chronic kidney disease (CKD). Diabetes is the leading cause of renal failure and progression of diabetic nephropathy has been associated with changes in extracellular fluid volume. The aim of the study was to assess the association of the severity of fluid status, diabetes and diabetic renal progression in a late CKD cohort.

Methods: This study analyzed the association of the severity of fluid overload measured by bioimpedance spectroscopy method, Body Composition Monitor, with maintenance dialysis and rapid renal progression (estimated GFR slope < −3ml/min/1.73 m2/yr) in 472 patients with stage 4-5 CKD.

Results: During a median 13.7-month follow-up, there were 71 (15.0%) subjects commencing maintenance dialysis, and 187 (39.6%) subjects presenting rapid renal progression. The adjusted risks of commencing dialysis increased near 3-fold (HR: 2.96, 95% CI: 1.13-7.72, P= 0.03) for non-diabetic patients with fluid overload compared with those without fluid overload. The adjusted risks of maintenance dialysis increased near 4.5-fold (HR: 4.48, 95% CI: 1.69-11.93, P= 0.003) for diabetic patients with fluid overload compared with non-diabetic patients without fluid overload. The adjusted OR for non-diabetic patients with fluid overload compared with those without fluid overload in renal function progression analysis were 4.26 (95% CI: 2.08-8.73, P<0.001). The adjusted risks of renal function progression increased more than 2.8 fold (OR: 2.82, 95% CI: 1.27-6.26, P= 0.01) for diabetic patients with fluid overload compared with non-diabetic patients without fluid overload. However, there was no significant increased risk for renal disease progression between diabetic and non-diabetic patients without fluid overload.

Conclusions: Fluid overload is an independent risk factor associated with maintenance dialysis and rapid renal progression. Fluid overload has a higher predictive value for an elevated risk for kidney disease progression than diabetes in late CKD.

FR-P0272

Background: Patients with chronic kidney disease (CKD) are frequently advised to modify sodium (Na) and potassium (K) intake, but supporting evidence is limited.

Methods: We studied 28,800 participants at high cardiovascular risk, 90.6% on renin-angiotensin system blockade, followed for a mean of 4.5y in the ONTARGET & TRANSCEND trials. We used the Kawasaki formula to estimate 24hr Na and K from morning fasting urine. The primary outcome was eGFR decline ≥30% or chronic dialysis (CD); secondary outcomes were eGFR decline ≥40% or CD, doubling of creatinine or CD, ≥5%/yr loss of GFR, progression of albuminuria and hyperkalemia. We used multimodal logit regression with multivariable fractional polynomials, adjusted for known predictors, to determine the association between Na & K and outcomes, with death as a competing risk. We also analysed Na & K in thirds.

Results: At baseline, 9.8% had eGFR<45 and 22.6% eGFR 45-60 mL/min/1.73m2; 3.5% had macro- and 12.5% micro-albuminuria. The primary outcome occurred in 7.0% (p=0.03). There was no significant association between Na excretion and any renal outcomes [A-C, fig] [primary outcome OR 0.97; 95% CI 0.87-1.08 for highest (median 2.7g/d) vs. lowest third (median 1.7g/d), except doubling of creatinine or CD (no relationship) and hyperkalemia (increased risk)]D-F,fig].
FR-PO273

Uremic Toxins as Risk Factors for Progression in Chronic Kidney Disease
Jan A.J.G. Van den Brand,1 Henricus A.M. Mutsaers,2 Arjan D. Van Zuilen,3 Peter J. Blanksteijn,2 Rosalinde Masereeuw;1 Jack F. Wetzels.

Nephrology, Radboud Univ Medical Centre, Nijmegen, Netherlands; 2Toxicology and Pharmacology, Radboud Univ Medical Centre, Nijmegen, Netherlands; 3Nephrology, Univ Medical Centre Utrecht, for the MASTERPLAN Study, Netherland.

Background: The concentration of uremic toxins is increased in patients with kidney failure. We questioned if uremic toxins may influence the rate of eGFR decrease in CKD patients.

Methods: Baseline serum samples of patients that participated in the MASTERPLAN trial were used (Van Zuilen et al. Kidney Int. 2012). Cases were rapid progressors, i.e. patients with decline of eGFR > -4.5 ml/min/1.73m²/year. Controls with lower rate of progression were selected and matched for baseline eGFR. Concentrations of uremic toxins (hippuric acid, indole-3-acetic acid, indoxyl sulphate, kynurenic acid, pyrrolidone, p-cresyl glucuronide, p-cresyl sulphate) were measured using in-tandem mass spectrometry and high pressure liquid chromatography.

Results: In total, 27 cases and 65 controls were included. Concentration of all uremic toxins was above control values. Correlations with eGFR ranged between -0.58 to 0.07. Uremic toxins correlated poorly with other known risk factors. Rapid progressors were more likely to be male, younger and have polycystic kidney disease; had higher blood pressure and proteinuria, and lower serum albumin and bicarbonate. None of the uremic toxins was statistically significantly associated to eGFR decline in univariate nor multivariate linear regression analysis. The figure shows regression coefficients and 95% confidence intervals for the association between uremic toxins and the rate of eGFR decline adjusted for proteinuria and polycystic kidney disease.

Conclusions: Baseline serum uremic toxin concentrations are not associated with eGFR decline in CKD patients.

Funding: Private Foundation Support

FR-PO274

Uriney Trofile Factor 3 Significantly Predicts the Renal Outcomes in Patients with Chronic Kidney Disease
Toshio Yamanari,1 Hitoshi Sugiyama,1 Hiroshi Morinaga,2 Masashi Kitagawa,2 Akifumi Onishi,1 Ayu Ogawa,1 Yoko Kikumoto,1 Shinji Kitamura,1 Yohei Maeshima,1 Daisuke Ogawa,1,2 Toshio Yamanari,1 Hitoshi Sugiyama,1 Yoko Kikumoto,1 Shinji Kitamura,1 Yohei Maeshima,1 Daisuke Ogawa,1,2 Toshio Yamanari,1 Hitoshi Sugiyama,1 Yoko Kikumoto,1 Shinji Kitamura,1 Yohei Maeshima,1 Daisuke Ogawa,1,2 Toshio Yamanari,1 Hitoshi Sugiyama,1 Yoko Kikumoto,1 Shinji Kitamura,1 Yohei Maeshima,1 Daisuke Ogawa,1,2 Toshio Yamanari,1 Hitoshi Sugiyama,1 Yoko Kikumoto,1 Shinji Kitamura,1 Yohei Maeshima,1 Daisuke Ogawa,1,2

Background: TFF3 plays essential roles in mucosal surface maintenance and reconstituent. A decrease in the urinary levels of TFF3 is associated with acute kidney injury in animals. However, whether the urinary levels of TFF3 are associated with renal dysfunction in patients with chronic kidney disease (CKD) is unclear.

Methods: We analyzed the urinary TFF (uTFF) levels in spot urine samples from 216 patients with CKD, and assessed the relationships among the uTFF, proteinuria and kidney function. Patients were prospectively followed for three years for doubling of the baseline serum creatinine concentration and the initiation of renal replacement therapy.

Results: The excretion of uTFF3 significantly increased with the extent of albuminuria, urinary a1 and β2-microglobulin and the decline in the eGFR. A multivariate logistic regression analysis showed that the patients with higher levels of uTFF3 were more likely to have CKD stage ≥ G3b (P < 0.01). A longitudinal analysis demonstrated that patients with a higher uTFF3, in combination with microalbuminuria, had a significantly worse renal prognosis (Log rank, P < 0.0001). The levels of urinary TFF3 in the renal end-point group were significantly higher than those in the renal survival group (P < 0.01). The AUROC of uTFF3 for predicting the progression of CKD (0.879) was significantly higher than that of albuminuria (0.692) (P < 0.0001). The levels of uTFF1 and uTFF2 did not correlate with albuminuria.

Conclusions: The excretion of uTFF3 is therefore significantly associated with albuminuria and decline in the renal function. Moreover, the uTFF3 level can be used as a biomarker to predict the renal outcomes in CKD patients.

FR-PO275

Uriney Biomarkers as Risk Factors of End-Stage Renal Disease in the General Population: CKD Biomarkers Consortium
Meredith C. Foster,1 Josef C. Feldman,2 Vasant S. Ramachandran,3 Kathleen S. Waikar,4 S. Waikar, Kathleen D. Liu.

Background: We determined the association of 3 urinary markers of tubular injury, liver fatty acid binding protein (L-FABP), kidney injury molecule 1 (KIM-1), and N-acetyl-β-D-glucosaminidase (NAG), with incident end-stage renal disease (ESRD) in the Atherosclerosis Risk in Communities Study, a community-based sample of middle-aged adults.

Methods: We performed a nested case-control study with Visit 4 (1996-98) as the baseline. ESRD cases were ascertained through 2008 with 2 controls frequency matched to each case on estimated glomerular filtration rate (eGFR), urinary albumin to creatinine ratio (ACR), diabetes, sex, and race. L-FABP, KIM-1, and NAG were measured and standardized to urinary creatinine. We estimated the incidence odds ratio (OR) for ESRD for an interquartile range increase in each biomarker and for an elevation (highest quintile) in any biomarker using conditional logistic regression. Results: 138 cases were matched to 192 controls with urine available (mean age 64.9 vs. 64.7 years, 43.5% vs. 43.2% women). ESRD occurred a median of 6.0 years after Visit 4. L-FABP and KIM-1 were associated with an increased odds of ESRD, but associations were attenuated with adjustment (Table). NAG was not associated with ESRD. In multi-marker analyses, elevated levels for any marker (cases: 59%; controls: 34%) were independently associated with ESRD (Table).

Conclusions: L-FABP and KIM-1 were associated with risk of ESRD before but not after adjustment for other risk factors. Combinations of markers may have independent risk information.

Funding: NIDDK Support, Other NIH Support - The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).

FR-PO276

Uriney Uromodulin Excretion Predicts Progression of Chronic Kidney Disease Resulting from IgA Nephropathy
Yuqing Chen,1 Jingjing Zhou,2 Xueying Li,3 Hong Zhang,4 1Peking Univ First Hospital; 2Peking Univ First Hospital; 3Peking Univ First Hospital.

Background: Uromodulin, or Tamm-Horsfall protein, is the most abundant urinary protein in healthy individuals. Recent studies have suggested that uromodulin may play a role in chronic kidney diseases. We examined an IgA nephropathy cohort to determine whether uromodulin plays a role in the progression of IgA nephropathy.

Methods: A total of 340 IgA nephropathy patients were involved in this study. Morphological changes were evaluated with the Oxford classification of IgA nephropathy. Enzyme Linked Immunosorbent Assay (ELISA) measured the urinary uromodulin level at renal biopsy day. Follow up was done regularly on 185 patients. Time-average blood pressure, time-average proteinuria, estimated glomerular filtration rate (eGFR) and eGFR decline rate were calculated. Association between the urinary uromodulin level and the eGFR decline rate was analyzed with SPSS 13.0.

Results: We found that lower baseline urinary uromodulin level (P<0.03) and higher time-average proteinuria (P<0.04) were risk factors for rapid eGFR decline in a follow-up subgroup of the IgA nephropathy cohort. Urinary uromodulin level was correlated with tubulointerstitial lesions (P<0.016). Patients with that had more tubular atrophy/intertstitial fibrosis on the surface had lower urinary uromodulin levels (P<0.02).

Conclusions: Urinary uromodulin excretion predicts progression of IgA nephropathy.

FR-PO277

Urine Complement C3 Cleavage Fragments Are Associated with Abnormal Kidney Function and CKD
Erwin P. Bottinger,1,2 Avelino Teixeira,1,2 Girish N. Nadkarni,1,2 Ilese S. Daehn,1,2 Joseph V. Bonventre,1 Kathleen D. Liu,1,2 Chiyuan Hsu,2 Brad H. Rovin,2 Robert G. Nelson,2 Paul L. Kimmel,2 Harold I. Feldman,2 Vasan S. Ramachandran.1,2 Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York City, NY; The CKD Biomarker Consortium, NIDDK.

Background: Urine complement C3 fragments have been associated with kidney diseases, yet little is known about urinary C3a (anaphylotoxic), C3b-9 (cytotoxic), and iC3b (opsonic) fragments in individuals with abnormal kidney function.

Methods: We measured urine complement C3-derived fragments C3a, C3b-9, and iC3b in urine samples obtained from patients as part of routine ambulatory or inpatient clinical care using modified ELISA kits (Quidel® Corp., San Diego, CA).
Results: Patient groups included 96 controls, suspected abnormal kidney function without documented CKD (eGFR 90 to 90 ml/min/1.73m2) and/or proteinuria (N=230), CKD+HFrEx with loss of eGFR ≤3 (N=160), or >3 to ≤1 (72m1/7cm2) per year for at least 3 years (N=81). Fractions (%) of samples with detectable urinary C3a, C5b-9, or iC3b were significantly increased in all kidney dysfunction groups compared with controls. In multivariable logistic regression models C3a, C5b-9, or iC3b were significantly associated with kidney dysfunction. We quantified using adjusting stratification by proteinuria (U/pro) of >0.5 mg/ml but not at lower levels.

<table>
<thead>
<tr>
<th>Table 1. Multivariable logistic regression for suspected abnormal kidney function, CKD III or higher</th>
<th><strong>P</strong> value</th>
<th><strong>OR (95% CI)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.00</td>
<td>1.00 (0.74-1.39)</td>
</tr>
<tr>
<td>Suspected abnormal kidney function</td>
<td>1.21 (1.15-1.27)</td>
<td></td>
</tr>
<tr>
<td>CKD III or higher</td>
<td>1.54 (1.06-2.23)</td>
<td></td>
</tr>
<tr>
<td>eGFR loss &lt;15</td>
<td>1.83 (1.20-2.81)</td>
<td></td>
</tr>
<tr>
<td>eGFR loss &gt;15</td>
<td>2.27 (1.39-3.70)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Urine complement fragments C3a, C5b-9, and iC3b were associated with kidney dysfunction. Associations were strongest between C5b-9 or iC3b and CKD with eGFR loss. We are planning validation studies in prospective CKD cohorts accessible in the CKD Biomarker Consortium. Funding: NIDDK Support

FR-PO280

Serum Lipoproteins and Progression of Chronic Kidney Disease (CKD)—A Report from the CRIC Study

Mahboob Rahman,1 Wei Yang,2 Sanjeev Akkina,3 Arnold B. Alper,4 Amanda Hyre Anderson,2 Lawrence J. Appel,5 Jiang He,6 Dominic S. Raj,7 Jeffrey R. Scilling,1 Valerie L. Teal,3 ‘Case Western Reserve Univ; 2Univ of Pennsylvania; 3Univ of Illinois; Tulane Univ; Johns Hopkins Univ; George Washington Univ.

Background: It is unclear whether lipoprotein measurements independently predict kidney disease progression in patients with established CKD.

Methods: Adults (n=3939) with CKD were followed in a prospective cohort study for a median of 4.1 years. The predictors for these analyses were baseline total cholesterol, triglycerides, very-low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-1 (apoA-I), apolipoprotein B (apoB), and lipoprotein (a) [Lp(a)]. The outcomes were a composite of end stage renal disease (ESRD) or 50% decline in estimated glomerular filtration rate (GFR) from baseline, and rate of change of GFR.

Results: Mean age of the study population was 52 years, and mean GFR was 44.9 ml/ min/m2; 48% had diabetes, and 55% were prescribed statin therapy. None of the lipoprotein measurements was independently associated with the risk of the composite renal endpoint, or with rate of change of GFR. However, there were significant (p<0.01) interactions by level of proteinuria. In participants with low levels of proteinuria (<0.2 g total protein/day) one standard deviation higher total cholesterol (LDL-C) was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02). In participants with levels of proteinuria (>0.2 g total protein/day) one standard deviation higher LDL-C was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02). In participants with levels of proteinuria (>0.2 g total protein/day) one standard deviation higher total cholesterol was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02). In participants with levels of proteinuria (>0.2 g total protein/day) one standard deviation higher total cholesterol was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02).

Conclusions: In this large cohort of patients with CKD, total cholesterol, triglycerides, VLDL-C, LDL-C, HDL-C, apoA-I, apoB, and Lp (a) were not independently associated with progression of kidney disease. However, there was an inverse relationship between LDL-C and total cholesterol levels and kidney disease outcomes in patients with low levels of proteinuria. Funding: NIDDK Support

FR-PO278

Association of Urinary LFABP, KIM-1, and NAG with Incident End-Stage Renal Disease and Mortality in Type 2 Diabetes

Gudeta D. Fufaa,1 Theodore E. Mifli,1 Jennifer E. Kline,2 Ben Caplin,1 Markus Ketteler,2 Kathleen D. Liu, Wei Yang,2 Sanjeev Akkina,3 Amanda Hyre Anderson,2 Lawrence J. Appel,5 Jiang He,6 Dominic S. Raj,7 Jeffrey R. Scilling,1 Valerie L. Teal,3 ‘Case Western Reserve Univ; 2Univ of Pennsylvania; 3Univ of Illinois; Tulane Univ; Johns Hopkins Univ; George Washington Univ.

Background: Patients with chronic kidney disease (CKD), identified in the Kidney and Bone Outcomes study cohort.

Methods: Serum Fetuin was measured in baseline serum samples. Serum Fetuin is independently associated with protection from the development of ESRD.

Results: Serum Fetuin was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02). In participants with low levels of proteinuria (<0.2 g total protein/day) one standard deviation higher LDL-C was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02). In participants with levels of proteinuria (>0.2 g total protein/day) one standard deviation higher total cholesterol was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02). In participants with levels of proteinuria (>0.2 g total protein/day) one standard deviation higher total cholesterol was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02). In participants with levels of proteinuria (>0.2 g total protein/day) one standard deviation higher total cholesterol was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02).

Conclusions: Serum Fetuin is independently associated with protection from the progression of chronic kidney disease. Funding: NIDDK Support

FR-PO279

Urine NGAL and the Risk of Cardiovascular Disease and Death in CKD: Results from the CRIC Study

Kathleen D. Liu,1 Wei Yang,2 Sanjeev Akkina,3 Amanda Hyre Anderson,2 Harold I. Feldman,1 Michael J. Fischer, Jiang He,6 Dominic S. Raj,7 Jeffrey R. Scilling,1 Valerie L. Teal,3 ‘Case Western Reserve Univ; 2Univ of Pennsylvania; 3Univ of Illinois; Tulane Univ; Johns Hopkins Univ; George Washington Univ.

Background: Patients with chronic kidney disease (CKD), identified in the Kidney and Bone Outcomes study cohort.

Methods: Serum Fetuin was measured in baseline serum samples. Serum Fetuin is independently associated with protection from the development of ESRD.

Results: Serum Fetuin was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02). In participants with low levels of proteinuria (<0.2 g total protein/day) one standard deviation higher LDL-C was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02). In participants with levels of proteinuria (>0.2 g total protein/day) one standard deviation higher total cholesterol was associated with a 26% lower risk of the renal endpoint (HR 0.74, p=0.01), and one standard deviation higher total cholesterol was associated with a 23% lower risk of the renal endpoint (HR 0.77, p=0.02).

Conclusions: Serum Fetuin is independently associated with protection from the progression of chronic kidney disease. Funding: NIDDK Support

FR-PO281

Serum Fetuin Is Independently Associated with Protection from the Progression of Chronic Kidney Disease

Ben Caplin,1 Markus Ketteler,2 Willi Jahnchen-dechert,3 John Cunningham,1 David C. Wheeler,1 ‘UCL Medical School, United Kingdom; 2Klinikum Coburg, Germany; 3Aachen Univ, Germany.

Background: Decline in kidney function is associated with worsening bone-mineral disorder in CKD patients. The relationship between biomarkers linked to arterial calcification and progression of CKD was investigated in the London Arterial Calcification, Kidney and Bone Outcomes study cohort.

Methods: 288 patients with stage 2-5 CKD were recruited. Biomarkers including fibroblast growth factor-23 (FGF23) and fetuin were measured in baseline serum samples. Follow-up data were obtained from hospital records after a median of 40 months and eGFR values over 3 years. A co-proportional hazards method was used to examine predictors of dialysis (censored at death) and a hierarchical model of eGFR over time (censored at dialysis start) used to examine whether similar factors associated with biochemical decline in kidney function.

Results: In the whole cohort, baseline median MDRD eGFR was 39.7 ml/min/1.73m2, IQR:26.8-51.1 median and median fetuin 0.40g/L, IQR:0.35-0.43. Follow-up data, fetuin, FGF and urinary protein levels were available on 189 subjects (159 with eGFR data). After adjustment for baseline eGFR, proteinuria, age, sex, ethnicity and FGF23, fetuin was associated with a reduced risk of requiring dialysis (HR=0.03 per 1 log unit fetuin; 95% CI:0.00-0.33; Figure).
In the eGFR model adjusting for the same potential confounders, fetuin was associated with a 6.3mL/min/1.73m²/year slower decline in eGFR per unit log fetuin (95% CI: 0.03-12.5). In neither model was the association confounded by a measure of inflammation (hsCRP).

Conclusions: Using two independent approaches, need for dialysis and eGFR change, serum fetuin was independently associated with preservation of kidney function. Whether this association is causal and is worth exploring from a therapeutic perspective requires further study.

Funding: Private Foundation Support

FR-PO282

Associations between Osteoprotegerin, Mortality and Progression of CKD
Helen Alderson, James Ritchie, Philip A. Kaira. Salford Royal Hospital.

Background: Elevated levels of osteoprotegerin (OPG) are observed in CKD and have been associated with vascular calcification and mortality. The relationship with cause specific mortality and rate of change in renal function is less well described.

Methods: Patients were selected from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS), a prospective observational study of outcome in CKD 3-5. OPG was measured in stored sera from 493 patients. Levels were analysed in continuous and categorical forms (quartiles of OPG) in relation to all-cause and cardiovascular mortality and progression of CKD.

Results: At time of OPG measurement mean eGFR was 31±12mL/min/1.73m², age 64±14 years. Over a median follow up of 5.4 (3.9-7.2) years 23% of patients reached dialysis, 40% died. Median OPG level was 7.3 (5.7-9.6) pmol/L, with higher levels significantly correlated with increasing age and lower eGFR (r=0.54 and -0.26 respectively, both p<0.001). OPG levels significantly correlated with rate of change in GFR (r=-0.11 p=0.009) but did not associate with increased risk for dialysis (HR 1, p=0.5). When divided by quartile of OPG there was a trend towards most rapid eGFR loss in the highest quartile, with a statistically significant difference observed between lowest and highest quartiles (+0.3±3.5 vs. -1.2±3.4 mL/min/1.73m²/year p=0.04) In multivariate Cox regression (adjusted for age, eGFR, blood pressure, diabetes, smoking history and previous macrovascular events) OPG level was associated with all cause mortality, (HR 1.1 [1.04-1.1] p<0.001). The greatest risk was observed in patients in the highest quartile of OPG (HR 2.2 [1.14-4.1] p=0.03). No significant association between OPG and risk for cardiovascular mortality was observed.

Conclusions: OPG levels are independently associated with all-cause but not cardiovascular mortality. Patients with the highest OPG levels have a greater annual loss of eGFR but do not have increased risk for dialysis. This is most likely due to the excess mortality observed in this group. With elevated risk clustered in patients in the upper quartile of OPG, our data suggest a threshold value of clinical importance may exist.

FR-PO283

The Relationship of Parathyroid Hormone Levels with Cardiovascular Disease Is Stronger When Urine Fractional Excretion of Phosphorus Is Low
Joachim H. Ix,1 Cassianne Robinson-Cohen,2 Michael Shlipak,3 Andrew N. Hoofngale,4 Kenneth J. Mukamal,4 Ian H. de Boer,2 Ravi I. Thadhani,1,5 S. Ananth Karumanchi,4 Mary Wholey,1 Bryan R. Kestenbaum.2 1UCSD; 2U. Washington; 3UCSF; 4Harvard.

Background: The association of FGF23 with CVD is stronger when accompanied by a high PTH/Low FePi group. However, whether renal resistance to other hormones identified with a high PTH/Low FePi group was at highest risk for CVD. Trends were similar for mortality. In SKS, 75 deaths occurred in 3 yrs. Neither PTH nor FePi were associated with mortality. The p-interaction was 0.09. Again, the high PTH/low FePi groups was at highest risk.

Conclusions: High PTH/Low FePi identifies risk for CVD independent eGFR and urine ACR, and may represent kidney tubule resistance to PTH's phosphaturic actions.

Funding: Other NIH Support - NHLBI, Private Foundation Support

FR-PO284

Unresolved Subclinical Hypothyroidism Is Independently Associated with Progression of Chronic Kidney Disease
Sangju Lee,1 Inhsuk Lee,2 Yoon-Kyung Chang1 Hy-Eun Yoon,3 Chul Woo Yang,1 Suk Young Kim,1 Hyeon Seok Hwang,1 1Div of Nephrology, Depts of Internal Medicine, The Catholic Univ of Korea, Daejeon, Korea; 2Div of Endocrinology, Depts of Internal Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: Patients with chronic kidney disease (CKD) often have subclinical hypothyroidism. However, few reports have investigated changes in the status of subclinical hypothyroidism in CKD patients and its clinical significance in CKD progression.

Methods: We included 168 patients with nondialysis-dependent CKD stages 2-4. The normalization of subclinical hypothyroidism during follow-up was assessed, and the association between transitions in subclinical hypothyroid status and the rate of decline of the estimated glomerular filtration rate (eGFR) was investigated.

Results: At baseline, 127 patients were euthyroid and 41 (24.4%) patients were diagnosed with subclinical hypothyroidism. Of these 41 patients, 21 (51.2%) spontaneously resolved to euthyroid during follow-up. The rate of eGFR decline of patients with resolved subclinical hypothyroidism was similar to that of euthyroid patients. The patients with unresolved subclinical hypothyroidism showed a steeper renal function decline than patients with euthyroidism or resolved subclinical hypothyroidism (all p < 0.05). The proportion of CKD patients progressing to end-stage renal disease was significantly greater in those with unresolved subclinical hypothyroidism than in those who were euthyroid (p = 0.006). In multivariate linear regression for rate of eGFR decrease, unresolved subclinical hypothyroidism (β = -0.23, p = 0.001), baseline renal function (β = -0.34, p = 0.001) were independently associated with the rate of renal function decline.

Conclusions: Half of the CKD patients with subclinical hypothyroidism did not resolve to euthyroid, and this lack of resolution was independently associated with rapid renal function decline.

FR-PO285

Comparison of CKD with Modifiable Traditional Cardiovascular Risk Factors in Their Contributions to Mortality in the US
Kunihiro Matsushita, Yingying Sang, Shoshana Ballew, M. Grams, Josef Coresh. Dept of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Background: The aim of this study was to compare chronic kidney disease (CKD) with modifiable traditional cardiovascular risk factors regarding their contributions to all-cause and cardiovascular mortality among the participants in the Third National Health and Nutrition Examination Survey (NHANES III).

Methods: CKD was defined as eGFR with CKD-EPI creatinine equation <60 mL/min/1.73m² or urinary albumin-creatinine ratio (ACR) ≥30 mg/g. Modifiable traditional risk factors included hypertension (blood pressure ≥140/90 mmHg or treatment), diabetes (fasting glucose ≥126 mg/dL or treatment), hypercholesterolemia (total cholesterol ≥240 mg/dL), low high-density lipoprotein cholesterol (HDL-C) <40 mg/dL for men and <50 for women), and current smoking (yes vs. no). Prevalence, hazard ratio for mortality, and % population attributable risk (%PAR) were obtained for each risk factor.

Results: Among 15933 participants, the prevalence was highest for low HDL-C followed by smoking, hypertension, hypercholesterolemia, CKD, and diabetes (Table).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
During a median follow-up of 8.7 years, there were 2259 deaths (987 due to cardiovascular disease). When all predictors were incorporated into Cox models accounting for sampling probability weights and the inclusion of all-cause, age, sex, and race, only CKD, diabetes, and smoking remained significant for both total and cardiovascular mortality (Table). %PAR of mortality outcomes for CKD was 11-14% and higher than that for hypertension, diabetes, or dyslipidemia.

**Results:**

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (HR)</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CKD, No MSPD</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>CKD, No MSPD</td>
<td>2.32 (1.09-5.19)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>CKD, MSPD</td>
<td>3.79 (1.58-9.29)</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

When analyses were restricted to individuals with CKD, MSPD was associated with higher all-cause mortality (HR 1.57, 95% CI 1.15-2.12, P < 0.01) and cardiovascular mortality (HR 1.72, 95% CI 1.10-2.69, P < 0.01). In a sensitivity analysis that additionally adjusted for smoking, the effect of MSPD remained significant (HR 1.52, 95% CI 1.06-2.17, P < 0.05). These results are similar to those found in other studies, suggesting that MSPD may be an important risk factor for both all-cause and cardiovascular mortality.

**Conclusions:**

MSPD is associated with higher all-cause and cardiovascular mortality in individuals with CKD. Future work is needed to evaluate mechanisms for these associations.

**Funding:** Private Foundation Support

FR-PO286

Periodontal Disease as a Predictor of Survival in Chronic Kidney Disease: Results from the Third National Health and Nutrition Examination Survey

**Methods:**

We studied adult members with CKD (glomerular filtration rate [eGFR] <60 mL/min/1.73 m² by the CKD-EPI equation) enrolled in Kaiser Permanente Northern California who were identified between 2002-2010 and did not have previous AF. Incident AF was identified using primary hospital discharge diagnoses and/or two or more outpatient visits for AF. Death was ascertained from health plan administrative databases, Social Security Administration vital status files, and California state death certificate registry. We used validated algorithms to identify demographics, comorbidity, blood pressure, eGFR, hemoglobin, proteinuria and cardiovascular medication use from health plan databases.

**Results:**

Among 81,088 adults with documented CKD, a total of 6,269 (7.7%) patients developed incident AF during a mean follow-up of 4.8 ± 2.7 years. Patients who developed incident AF were more likely to have higher blood pressure and lower eGFR at cohort entry. There were 2,388 deaths that occurred after development of incident AF (145 per 1000 person-years) compared with 18,865 deaths during periods without AF (51 per 1000 person-years, P < 0.001). After adjustment for potential confounders, incident AF was associated with a 63% increase in rate of death.

**Conclusions:**

Incident AF is independently associated with increased risk of death in adults with CKD. Further study is needed to identify modifiable risk factors to decrease the burden of AF and subsequent risk of death in this high-risk population.

**Funding:** NIDDK Support

FR-PO287

Fibroblast Growth Factor-23 Resistance, in Addition to Fibroblast Growth Factor-23, is Associated with Clinical Outcome in CKD Patients

**Background:**

FGF23 has emerged as an independent predictor with a high hazard ratio for clinical outcome in CKD patients. Whether FGF23 per se or tubular resistance to the actions of FGF23 is responsible for this increased risk is debated. We aimed to evaluate the effect of fractional excretion of phosphate (FePi) or TmP/GFR on the association of FGF23 with clinical in patients with moderate CKD.

**Methods:**

We retrieved baseline data and available urine samples of 166 patients from the Masterplan randomized controlled trial, in two participating centers, which allowed measurement of urine calcium, phosphorus, and creatinine, and calculation of FePi and TmP/GFR. Four categories were compared, based on relative median values of FGF23 and FePi or TmP/GFR.

**Results:**

Median eGFR was 36 mL/min/1.73m² (IQR 27-44), serum phosphate 1.04 mmol/L (IQR 0.92-1.20), FGF23 140 RU/mL (IQR 81-236) FePi 0.32 (IQR 0.25-0.44) and TmP/GFR 0.21 (IQR 0.19-0.23). Of the four groups, FGF23 and FePi or TmP/GFR confirmed to be a significant, independent predictor for the combined outcome of death, renal survival and cardiovascular events (HR 1.84, p<0.01). HR for the primary outcome gradually increased for the four categories of FGF23 and TmP/GFR.

**Conclusions:**

FGF23 predicts outcome in patients with CKD. FGF23 resistance as defined by indices of efficacy of phosphate excretion is an additional risk factor. The tubular abnormality that causes FGF23 resistance may be local klotho deficiency and may be causally related to clinical outcome.

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

FR-PO288

Incident Atrial Fibrillation and Risk of Death in Adults with Chronic Kidney Disease

**Methods:**

We studied adult members with CKD (glomerular filtration rate [eGFR] <60 mL/min/1.73 m² by the CKD-EPI equation) enrolled in Kaiser Permanente Northern California who were identified between 2002-2010 and did not have previous AF. Incident AF was identified using primary hospital discharge diagnoses and/or two or more outpatient visits for AF. Death was ascertained from health plan administrative databases, Social Security Administration vital status files, and California state death certificate registry. We used validated algorithms to identify demographics, comorbidity, blood pressure, eGFR, hemoglobin, proteinuria and cardiovascular medication use from health plan databases.

**Results:**

Among 81,088 adults with documented CKD, a total of 6,269 (7.7%) patients developed incident AF during a mean follow-up of 4.8 ± 2.7 years. Patients who developed incident AF were more likely to be older, male, white, have other cardiovascular conditions, have higher blood pressure and lower eGFR at cohort entry. There were 2,388 deaths that occurred after development of incident AF (145 per 1000 person-years) compared with 18,865 deaths during periods without AF (51 per 1000 person-years, P < 0.001). After adjustment for potential confounders, incident AF was associated with a 63% increase in rate of death.

**Conclusions:**

Incident AF is independently associated with increased risk of death in adults with CKD. Further study is needed to identify modifiable risk factors to decrease the burden of AF and subsequent risk of death in this high-risk population.

**Funding:** NIDDK Support

FR-PO289

Chronic Kidney Disease and Long-Term Risk of Cardiovascular Events following CABG for Acute Coronary Syndromes

**Background:**

Renal dysfunction is related to cardiovascular events after elective coronary artery bypass grafting (CABG). We aimed to investigate the impact of renal dysfunction on long-term risk of cardiovascular events after CABG for acute coronary syndromes.

**Methods:**

From the SWEDHEART registry we included all 12,956 patients who underwent a first, isolated, non-emergent, CABG for acute coronary syndromes in Sweden between 2000 and 2008. We calculated hazard ratios with 95% confidence intervals (CI) for renal dysfunction for heart failure, stroke or myocardial infarction in relation to glomerular filtration rates (eGFR) estimated by the MDRD study equation.

**Results:**

During a mean follow-up of 5 years there were 2,844 events. Patients with eGFR 15-45 mL/min/1.73m² had a 24% increase in risk of an adverse event compared with patients with eGFR > 60 mL/min/1.73m², even after adjustment for confounders including postoperative acute kidney injury. The hazard ratios with 95% CI were 1.08 (0.98-1.19) and 1.24 (1.08-1.43), in patients with eGFR 45-60 and 15-45 mL/min/1.73m², respectively, after adjustment for age, sex, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, left ventricular ejection fraction, atrial fibrillation, prior myocardial infarction, heart failure, stroke or perioperative acute kidney injury.

**Conclusions:**

Renal dysfunction is related to rehospitalization for cardiovascular disease in patients undergoing CABG for acute coronary syndromes.
FR-PO290

Biomarkers of Inflammation Are Associated with Cardiovascular Disease in Chronic Kidney Disease (CKD)—Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study
Jayaanta Gupta,1 Elizabeth Dominic,2 Tulsi K. Mehta,3 Alan S. Go,4 Marshall M. Joffe,5 Melanie Glenn,6 Valerie L. Teal,1 Dawei Xie,1 John W. Kusek,3 Harold I. Feldman,1 Dominic S. Raj.7 1U of Pennsylvania; 2George Washington Univ; 3U of California, San Francisco; 4NIDDK.

Background: We hypothesized that inflammatory pathways are important in the development of cardiovascular disease (CVD) in the setting of CKD and that inflammatory cytokines would be associated with CVD even after adjustment for traditional risk factors.

Methods: Plasma concentrations of IL-1β, IL-1 receptor antagonist (IL-1RA), IL-6, TNF-α, TGF-β, hs-CRP, fibrinogen and serum albumin were measured at baseline in a sub-group of 2613 CRIC study participants without any history of cardiovascular disease at enrollment. Cox proportional hazards regression was used to examine the association between biomarkers of inflammation and the risk of atherothrombotic vascular disease events (myocardial infarction, stroke, or peripheral arterial disease) (ASVD) and congestive heart failure (CHF) events. Analyses were adjusted for age, sex, race/ethnicity, diabetic status, current smoking status, estimated glomerular filtration rate, proteinuria, systolic blood pressure, body mass index, total cholesterol as well as use of ACEI/ARB and lipid lowering agents.

Results: During a 4 year follow-up 130 participants developed ASVD and 139 developed CHF.

Conclusions: hs-CRP and IL-6 were associated with increased risks of ASVD and CHF respectively in patients with CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO291

Newer Biomarkers Slightly Improve Prediction of Progression to Renal Replacement Therapy in CKD Patients–Can Predict Study Outcomes Adeera Levin,1 Ognjenka Djurdjev,2 Claudio Rigatto,3 Francois Madore,4 Brendan J. Barrett,5 Norman Muirhead,6 Myles S. Wolf.7 1Univ of British Columbia; 2BC Renal Agency; 3Univ of Manitoba; 4Univ de Montréal; 5Memorial Univ of Newfoundland; 6Western Univ; 7Univ of Miami Miller School of Medicine.

Background: Patients with chronic kidney disease (CKD) experience variable progression of kidney disease (KD). Better prediction models are needed. To assess if newer biomarkers (NBM), alone or as a panel, improve risk prediction of renal replacement therapy (RRT), over and above conventional clinical, demographic and laboratory predictors.

Methods: Pan-Canadian prospective cohort study of 2544 referred CKD patients, from 25 centres. NBM tests at baseline included asymmetric dimethylarginine (ADMA), high sensitivity C-reactive protein (hsCRP), interleukin 6, pro-brain natriuretic peptide (NTproBNP), troponin I, transforming growth factor β1, cystatin C and fibroblast growth factor (FGF23). Outcome: dialysis or transplantation (RRT) within 3 years. We compared discrimination (C statistic) and classification (net reclassification index (NRI)) of proportional hazards models based on conventional vs. combination of conventional and NBM predictors.

Results: Mean age of the cohort is 68yrs; median eGFR was 28ml/min/1.73m2; 62% were male. 15.5% patients died during 3-year follow-up. Models based on base, base+NBM and ‘best’ predictors are presented in the following figure:

Conclusions: Inclusion of NBM in risk prediction models significantly improves precision of death prediction in the cohort of CKD patients but needs to be validated in similar cohorts.

Funding: Pharmaceutical Company Support - Ortho Janssen

FR-PO293

Cystatin C Independently Predicts Change in Left Ventricular Mass Index (LVMI) in Children with Chronic Kidney Disease (CKD)
Tamy M. Brady, Kelly C. McDermott, Michael F. Schnieder, Christopher Cox, Bradley A. Warady, Susan L. Furt, Mark Mitsnefes. CKD Study Group.

Background: In the Chronic Kidney Disease in Childhood (CKiD) longitudinal cohort study of children 1-16 yrs with CKD, indexed GFR (GFR) is not associated with LVMI. In adults, cystatin C is more associated with cardiovascular (CV) risk factors than GFR. We investigated whether cystatin C had an independent association with LVMI over time among CKD participants.

Methods: The longitudinal association of cystatin C with change in log(LVMI) was assessed using a linear mixed model adjusting for confounders and visit with random subject effects to account for repeated measurements. Log(LVMI) was converted to %change LVMI.

Results: 475 children (median age 11.5yrs (Interquartile range (IQR):8.3, 15.2), 39% females, median GFR 50.2 ml/min/1.73m2 (IQR:38.3, 64.2)) were followed in the CKiD study. During a mean follow-up of 2.5 years (IQR:1.7, 4.1) 261 participants (54.7%) were excluded due to progression to ESRD. In this cohort, cystatin C was independently associated with change in LVMI (β = -0.026, p = 0.001) at 1 of 766 CKD visits with complete data. Median follow up time was 3.1 yrs (IQR:1.1, 5.0). Over time and after adjustment, each mg/L increase in cystatin C was associated with a 0.7% increase in LVMI. In addition, younger age, lower HB and height z-scores, greater BMI and SBP z-scores and African American (AA) race were independently associated with a significant percentage increase in LVMI.

Conclusions: This is the first analysis of CKD cohort progression that includes NBM as a panel. Although NBM are independent predictors of RRT progression, addition of the panel of NBM to models based on conventional clinical, demographic and laboratory predictors results in only modest improvement of RRT risk prediction.

Funding: Pharmaceutical Company Support - Ortho Biotech
Conclusions: Higher cystatin C levels are independently associated with increased in LVM in CKD patients. This study provides novel information about modifiable risk factors for increased LVM. It is the first study investigating the association of body mass index (BMI) and waist circumference (WC) with LVM in hypertensive predialysis CKD patients.

Methods: In 2004 and 2005, 206 incident adult patients from the outpatient CKD clinics of two hospitals in Greece, were included. Inclusion criteria were the presence of CKD and with LVM in the cross sectional data, BMI (β=4.7; 95%ci:2.0;7.4) and WC (β=1.2; 95%ci:0.14;2.3) were significantly associated with LVMI all-cause mortality in early CKD stages, but not in CKD stage 4-5. In these later stages the relationship may affected by uremia and peripheral muscle wasting. Longitudinal analysis showed that an increase in BMI and WC was associated with an increase in LVM. These results suggest that in the early CKD stages, overweight and obese patients should be advised to lose weight to prevent cardiovascular events.

FR-PO295
Impaired Kidney Function after Myocardial Infarction Is a Risk Factor for 40 Months All-Cause Mortality

Elleen K. Hoogeveen,
Johanna M. Geleijser,
Sabita Soedamah-muthu,
Janette De Goede,
Daan Kromhout,
Erik Giltay,
Nephrology, Jeroen Bosch Hospital, Den Bosch, Noord-Brabant, Netherlands;
Human Nutrition, Wageningen Univ, Wageningen, Gelderland, Netherlands;
Psychiatry, Leiden Univ Medical Center, Leiden, Zuid Holland, Netherlands.

Background: Post-myocardial infarction patients have an increased risk for all-cause mortality. Chronic kidney disease (CKD) 3-5 (eGFR<60 ml/min/1.73 m²) is an important risk factor for mortality. Little is known whether CKD 2 is also a risk factor for mortality.

Methods: We explored the relation between kidney function at baseline and all-cause mortality during 40-months follow-up in an observational study of 4650 post-myocardial infarction patients of the Alpha Omega Trial, receiving state-of-the-art cardiovascular treatment. Creatinine-cystatin C-based eGFR was assessed with the CKD-EPI equation.

Results: We accrued 14,957 person-years of follow-up. Of all patients 350 (7.5%) deceased. Mean (SD) age was 69.5 (5.7), 78.5% were men, 21% had diabetes, 60% hypertension, 85% used statins, and 17% were current smokers. At baseline the median (interquartile range) eGFRmeasured was 79 (66-91) ml/min/1.73 m². Patients were divided into three categories on the basis of their baseline kidney function: CKD 0-1: ≥90 (27%); CKD 2: ≥60 to <90 (55%), and CKD 3-5: <60 (18%) ml/min/1.73 m². Using a Cox proportional hazards model the HRs (95%CI) for death by CKD level, after adjustment for the interaction between 3 factors: age, sex, diabetes including chronic kidney disease stage, hypertension, and C-reactive protein were: 1 (reference), 1.51 (1.06 to 2.14) and 3.51 (2.41 to 5.12).

Conclusions: We conclude that there is a dose response relation between kidney function and all-cause mortality in post-myocardial infarction patients. Independent of classic risk factors, CKD 2 is a 1.5-fold and CKD 3-5 is a 3.5-fold stronger risk factor for death compared with CKD 0-1 in post-myocardial infarction patients.

Funding: Other NIH Support - Dutch Kidney Foundation, Dutch Heart Foundation, US National Institutes of Health (NIH) and Unilever R&D

FR-PO296
Cardiovascular Events and Mortality in a Prospective Cohort of CKD Patients in Japan: Effects of Underlying Kidney Diseases
Hirovuki Tanaka,
Soichiro Iimori, Shotoru Nakate, Tomokazu Okado, Tatsunori Kajiwara, Shincare Uchida, Sei Sasaki.
Nephrology, Tokyo Medical and Dental Univ, Bunkyo-ku, Tokyo, Japan.

Background: Individuals with CKD were more likely to die than to reach renal replacement therapy (RRT) in Western countries. We analyzed the risk of cardiovascular (CV) events, CV-related death and initiation of RRT stratified by underlying kidney diseases.

Methods: New patients from 16 nephrology centers who were older than 20 years of age and who visited or were referred for the treatment of CKD stage 2-5 were recruited in this study. 1138 patients were registered and classified by underlying kidney diseases: diabetes nephropathy (DN) (n=287), nephrosclerosis (NS) (n=451), glomerulonephritis (GN) (n=216), other nephropathies (ON) (n=173). The association between underlying kidney diseases and cardiovascular events, initiation of dialysis and mortality were analyzed using Cox proportional hazards models.

Results: 1. During 12 months follow-up, all groups showed decreased blood pressure (p<0.001) and decreased LDL-cholesterol (p<0.001), and no change in proteinuria. Body mass index and hemoglobin decreased in DN (p<0.05) but did not change in other groups. 14 of 44 patients died (including 19 patients of CV-related death), 103 patients reached RRT, and 62 patients were suffered from CV events (ischemic heart disease (n=9), peripheral arterial disease (n=7), stroke (n=10), congestive heart disease (n=36)).

2. The mortality and RRT rates (per 100 patient-years) in the three groups (DN, NS, GN) were as follows: mortality, 9.51, 3.06, 3.28; RRT, 34.1, 5.81, 8.49, respectively, indicating that participants were more likely to reach RRT than to die.

3. Compared to those with GN, patients with DN had significantly higher risks for CV events (HR 3.4; 95%CI 1.3-8.9) and initiation of RRT (HR 5.0; 95%CI 2.5-9.8), but not for all-cause death or CV-related death. NS group did not show significant difference in those events and mortality compared to GN group.

Conclusion: This prospective cohort study suggests that new CKD patients in Japan are likely to reach RRT than to die within 12 months observation. Risks of CV events and mortality differ according to underlying kidney diseases.

FR-PO297
Differences in Augmentation Index Between Different Etiologies of Chronic Kidney Disease
Thilini Nishani Abeysingunate, Darren Green, James Ritchie, Diana Chiu, Philip A. Kalra. Salford Vascular Research Group, Univ of Manchester, Manchester, United Kingdom.

Background: Chronic kidney disease (CKD) is associated with increased vascular stiffness. This is independently associated with all cause mortality and cardiovascular mortality. This study aims to consider if AIX varies by cause of CKD.

Methods: 360 patients with AIX measured by pulse wave analysis were selected from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS) study, a prospective study of outcome in patients with CKD 3-5. Primary cause of CKD was assigned by notes review. Heart rate adjusted AIX was assessed against primary disease as a binary variable (above/below median) using the Chi-squared test and as a continuous variable using student’s t-test.

Results: At the time of AIX measurement mean±SD age was 66±12 years, eGFR 30±14 ml/min/1.73 m², 65% of patients were male. 27% had diabetic nephropathy, 13% IgA nephropathy, 14% autosomal dominant polycystic kidney disease (ADPKD) and 46% renovascular/hypertensive renal disease. Median AIX was 24.

For each primary disease a different proportion of patients had a measured AIX above the median - diabetes 36%, IgA 55%, APKD 65% and vascular 53%, p between groups = 0.004.

When individual primary diseases were compared to the other primary disease in combination the most significant differences was observed using diabetic nephropathy as the referent (36% vs. 52% above median AIX p=0.003). This difference persisted when AIX was considered as a continuous variable (21±8 vs. 24±9 p=0.001). Patients with diabetic nephropathy were generally comparable to the remainder of the study population: age 54±7 years, p=0.57, systolic blood pressure, 134 ±22mmHg vs. 135±21 mmHg p=0.6; diastolic blood pressure 86±9 mmHg vs. 71±11 mmHg p=0.02, despite having a lower eGFR 26±11 ml/min/1.73 m² vs. 33±16 ml/min/1.73 m₃, p<0.001.

Conclusions: The study suggests primary disease may confound measurements ofvascular stiffness in CKD. This is defined by Pulse wave velocity and augmentation index (AIX), which is independently associated with all-cause mortality and cardiovascular mortality. This study aims to consider if AIX varies by cause of CKD.
FR-PO298
Prognostic Value of Pulse Pressure in Patients with Chronic Kidney Disease: A Report from the Gonryo Study
Tae Yamamoto,1 Mariko Miyazaki,1 Massaki Nakayama,2 Hiroshi Sato,3 Toshinobu Sato,2 Sadayoshi Ito,1 Tohoku Univ, Sendai, Miyagi, Japan; 2Fukushima Medical Univ, Fukushima, Japan; 3Sendai Shakaihoken Hospital, Sendai, Miyagi, Japan.

Background: Cardiovascular disease is high prevalent in chronic kidney disease (CKD) due to decreased kidney function. Studies suggest that pulse pressure (PP) may be a better predictor of outcome, but information on PP and the risk for cardiovascular events (CVE) or renal failure in CKD is limited.

Methods: 2,656 CKD patients, the mean age 60 ± 16 years and males 53%, recruited from 11 outpatient nephrology hospitals, and evaluated prospectively the effects of PP on CVE, including ischemic heart disease, congestive heart failure, strokes and death, and on progression of end-stage kidney disease (ESKD).

Results: During a median follow-up of 1096 (645 - 1101) days, 124 patients experienced cardiac disease or strokes, 64 died and 225 patients started renal replacement therapy (RRT). PP correlated positively with age (r=0.378, P<0.001) and systolic blood pressure (SBP) (r=0.735, P<0.001), and negatively with eGFR (r=-0.203, P<0.001). When patients were divided by PP level of 60 mmHg, patients with high PP were older, and had higher SBP, higher prevalence of hypertensive renal disease and diabetic nephropathy as the underlying renal disease and a higher eGFR. CVE rate increased linearly in patients with higher PP levels than 60 mmHg. The effect of renal function on CVE modified in patients group with high PP, but did not in patients group with low PP. High PP level modified the CVE risk predicted by renal function at baseline, but did not low PP level. Such modification of high PP level was not observed for the risk of ESKD.

Conclusions: We concluded that PP > 60 mmHg increased a risk for CVE in Japanese CKD population, and was a modifier of CVE predicted by decreased renal function.

FR-PO299
Stage 4 to 5 Chronic Kidney Disease Is Associated with Coronary Artery Calcification in Patients with Atypical Chest Pain
Jung-woon Noh,1 Jong-woo Yoon, Seungyeon Son, Jwa-kyung Kim, Soo Jin Kim, Sung Gyun Kim, Jieun Oh, Youngki Lee. Dept of Internal Medicine, Hallym Kidney Research Institute, Hallym Univ College of Medicine, Seoul, Republic of Korea.

Background: Coronary artery calcification (CAC) screening can predict the risk of cardiovascular event in individuals with atypical chest pain. It is well known that CAC occurs in patients on maintenance dialysis commonly and severely. The increased risk of cardiovascular event in individuals with atypical chest pain. It is well known that CAC occurs in patients on maintenance dialysis commonly and severely. It is well known that CAC occurs in patients on maintenance dialysis commonly and severely. It is well known that CAC occurs in patients on maintenance dialysis commonly and severely. It is well known that CAC occurs in patients on maintenance dialysis commonly and severely. It is well known that CAC occurs in patients on maintenance dialysis commonly and severely.

Methods: To address this question, 2562 participants with atypical chest pain underwent coronary CT from March 2006 to September 2011. CAC score was quantified using the method described by Agatston. Renal function was categorized by estimated GFR (eGFR) (eGFR). Decreased kidney function was defined as an eGFR <60 mL/min/1.73 m2 and staging of CKD was done according to GFR (G stage).

Results: Fifty-two percent of subjects had CAC, mean eGFR was 76.44 mL/min/1.73 m2 and 15.5% had an eGFR 60 mL/min/1.73 m2. The median CAC scores by CKD stage 3a, 3b, 4 and 5 were 25.6, 55.5, 197 and 119.5, respectively. In unadjusted analysis, eGFR was strongly associated with CAC score (r=0.203, P<0.001). Logistic regression showed the association between reduced renal function and CAC scores >100, and >400 versus scores <10. Compared with no CKD, stage 4 to 5 CKD was associated with CAC scores >100, (odds ratio(OR), 2.64; 95% confidence interval(CI), 2.03-3.45) and >400 (OR, 2.79; 95% CI, 2.11-3.71) after adjustment for covariates. However, no valuable association was noted between stage 3a to 3b and CAC scores >100.<400. In diabetic patients, stage 4 to 5 CKD had a more than five-fold increased odds of CAC scores >400.

Conclusions: Stage 4 to 5 CKD is associated with increased CAC scores, and this association is more intense in diabetic populations. In future, we need further evaluations in prospective study in patients with CKD.

FR-PO300
Association Between Variability in eGFR and Risk of Cardiovascular Events
Tanvir Chowdhury Turin,1 Min Jun,1 Marcello Tonelli,2 Braden J. Manns,1 1Univ of Calgary; 2Univ of Alberta, Canada; 3Univ of Sydney, Australia; 4Univ of Groningen, the Netherlands.

Background: Relationship between dynamic changes in kidney function, specifically variability in eGFR, and risk of CVE has not been defined. We studied association between eGFR variability and risk of congestive heart failure(CHF), acute myocardial infarction(AMI), and stroke among a community-based population.

Methods: We studied 529,954 adults who had at least 3 outpatient eGFR measurements over 4-year period (the accrual period) in Alberta during 2002-2008. Variability in eGFR was defined using the coefficient-of-variation(CV) from regression measurements for each participant during the accrual period. Variability was categorized by quintile, with the lowest quintile representing patients with the least variability(referent) and increasing quintiles reflecting greater degrees of variability. Cox models (adjusting for baseline covariates, kidney function, proteinuria, and rate of change in eGFR) were used to estimate the HRs for outcomes during the subsequent follow up period, associated with increasing quintiles of eGFR variability, with follow-up to March 2009.

Conclusions: Among the participants(mean age 55y, 42% male) there were 5255(1%) CHF, 4795(0.9%) AMI, and 4014(0.8%) stroke events over a median follow-up of 2.5 y. Increased eGFR variability was associated with an increased risk of CVE events, including CHF(trend p<0.01), AMI(p<0.13) and stroke(p<0.01). Compared with the lowest quintile, patients in the highest quintile had more than two-fold increased risk of CHF, 13% increased AMI risk, and 24% increased risk of stroke.

FR-PO301
Soluble Urokinase Receptor (suPAR) Predicts Mortality and Cardiovascular Disease in Patients with Mild-to-Moderate Chronic Kidney Disease
Bjorn Meijers,1 Ruben Poensen,2 Markus Stoor,2 Kathleen Claes,1 Dirk R. Kuypers,2 Pieter Evenepoel.1 1Nephrology, Univ Hospitals Leuven, Belgium; 2Gambro dialysatoren GmbH, Hechingen, Germany.

Background: suPAR is linked to mortality and cardiovascular disease in patients without chronic kidney disease (CKD). Studies evaluating the role of suPAR as FSGS biomarker observed an inverse association between eGFR and suPAR. Whether suPAR accumulates in patients with CKD and whether accumulation of suPAR is associated with mortality in CKD has not been studied to date.

Methods: We measured suPAR concentrations in 486 patients with known non-FSGS CKD patients who were recruited in the Leuven mild-to-moderate CKD study (Clinical trials protocol NCT00441623) using the human uPAR enzyme-linked immune sorbent assay (R&D systems™). Associations with overall mortality and cardiovascular disease were explored using Kaplan-Meier estimates and multivariate Cox proportional hazards analyses.

Results: We determined suPAR concentrations in 486 patients with known non-FSGS CKD patients. eGFR was the strongest determinant of suPAR concentrations (P<0.0001) and suPAR accumulated in patients at low eGFR. suPAR concentrations were associated with overall mortality (P<0.0001) and cardiovascular events (P<0.0001). These associations persisted after correction for age, sex, eGFR and C-reactive protein concentration, but for mortality was lost after correction for serum albumin. suPAR remained associated with cardiovascular disease in multivariate analysis.

Conclusions: suPAR accumulates in patients with CKD and is directly and gradually associated with overall mortality and cardiovascular events, independent of kidney function. Given the versatile roles of suPAR as signaling orchestrator, accumulation of suPAR in patients at lower eGFR may be in the causal chain of extrarenal manifestations of CKD.

Key: TH- Thursday; FR- Friday; SA- Saturday; OR- Oral; PO - Poster; PUB- Publication Only
Underline represents presenting author/disclosure.
FR-PO302
Atrial Fibrillation Independently Predicts Mortality in Patients with Chronic Kidney Disease after Myocardial Infarction Hyeon Seok Hwang, Hye Eun Yoon, Sangju Lee, Yoon-Kyung Chang, Chul Woo Yang, Suk Young Kim.

1Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea; 2Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: Chronic kidney disease (CKD) is an important predictor for mortality after acute myocardial infarction (AMI), and atrial fibrillation (AF) often coexists with CKD and AMI. However, the impact of AF on mortality and morbidity in patients with CKD is not well understood after AMI.

Methods: This study was based on a retrospective cohort, the COREA-AMI registry. A total of 4744 patients with AMI were enrolled, and CKD was defined as estimated glomerular filtration rate <60 mL/min/1.73 m². Patients were divided into CKD (n = 2181) or non-CKD (n = 2563) groups, and were analyzed to investigate the association of AF with mortality and morbidity risk.

Results: Of CKD patients with AMI, 123 (5.6%) had AF and it was significantly more prevalent than those of patients without CKD (2.9%, P< 0.001). The CKD patients with AF were associated with worse in-hospital outcomes than CKD patients without AF; more need of vasopressor and renal replacement therapy and development of resuscitation (all P < 0.05). The all-cause mortality and ischemic stroke during a median follow-up of 3.53 years was significantly higher in CKD patients with AF than in CKD patients without AF (P < 0.001 and P = 0.026, respectively). However, AF had no impact on in-hospital outcomes and all-cause mortality in patients without CKD. The adjusted hazard ratio for all-cause mortality and ischemic stroke including all other risk factors was 1.74 and 2.62 for AF in patients with CKD, respectively.

Conclusions: AF was more prevalent in patients with CKD, and only the association of CKD and AF increased hazard for in-hospital events and long-term mortality after AMI.

FR-PO303
C-Reactive Protein Mediates the Association between Low Socioeconomic Status and Status of Pressure Pulse in Japanese CKD Cohort (CKD-JAC) Naohiko Fujii, Takayuki Hamano, Yoshitaka Isaka, Tsuyoshi Watanabe, Kosaku Nitta, Tadao Akizawa, Seichi Matsuo, Enyu Imai, Hirofumi Makino.

1Dept of Biostatistics and Epidemiology, Univ of Pennsylvania, Philadelphia, PA; 2Dept of Public Health, School of Public Health, Osaka, Japan; 3CKD-JAC Steering Committee, Shinjuku, Tokyo, Japan.

Background: High brachial pressure pulse (PP) independently associates with faster decline in renal function and worse outcome. Low socioeconomic status (SES) has been recognized as a key environmental factor of hypertension. While dietary salt intake might contribute to abnormal PP, the role of other SES risk factors is not yet elucidated. Here we explored the association between PP, SES, and CRP.

Methods: We performed a cross-sectional observational study with the baseline data of the Japanese CKD cohort study (CKD-JAC, N=2,977). SES was assessed by self-administered questionnaire followed by classification into four income groups (Q1-4). Multivariate linear regression analyses adjusting for demographic factors, renal function, comorbidities, medication, nutritional parameters, and facilities were performed to test the relationships between PP, SES, and CRP.

Results: 1,854 (62%) patients answered the questionnaire. The prevalence of diabetes and prior cardiovascular disease (CVD) was significantly higher in the lowest income group (Q1). Significant step-wise decrease in eGFR and increases in PP, age, urinary Na/K ratio (uNa/K), and CRP along with the decrease in income were observed. The association between PP and SES was robust after adjustment for age, sex, eGFR, diabetes, prior CVD, ABCK, hypertensive medications, and animal protein intake (Coefficients [95% CI] vs Q4: Q1: 0.3 [1.3, 4.8], Q2: 1.6 [0.2, 3.3], Q3: 1.3 [0.4, 3.0]). Although addition of uNa/K to the model did not attenuate the coefficients, introduction of CRP dramatically reduced the magnitude of correlation coefficients and even cancelled out the statistical significance of SES (Q1: 0.3 [0.3, 3.6], Q2: 0.7 [1.2, 2.5], Q3: 0.4 [1.6, 2.3]).

Conclusions: There was a significant negative correlation between SES and PP in CKD patients, where CRP plays a crucial role.

Funding: Pharmaceutical Company Support - Kyowa Hakko Kirin

FR-PO304

1Salford Royal Hospital, 2FYU Meds Centre, 3Univ of Alberta.

Background: The novel Artery Brain, Cardiac and Kidneys (ABCK) framework is a novel, cardiac vascular staging system based upon the severity of target organ damage (TOD) in an individual. This differs from traditional scoring systems that consider risk factors, not existing/incipient vascular damage. In a low-risk cohort, ABCK added predictive value to the SCORE and Framingham systems. Here we assess the utility of the ABCK framework in a higher-risk CKD population.

Methods: Patients were selected from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS), a prospective study of outcome in CKD 3-5. Patients were scored using ABCK, SCORE and Framingham (all cause mortality). ABCK scores remained independently associated with increased risk for death.

Conclusions: The ABCK framework combined with risk factors seems to reflect susceptibility for risk and predict mortality better than risk factor based methods alone.

FR-PO305
Relationship of Oxidized to Non-Oxidized PTH in Children with Chronic Renal Failure, Adult Patients on Hemodialysis and Kidney Transplant Recipients Berthold Hochs1, Christoph Reicheltzeder, Torsten Slowinski, Ulrike Luger, Anke Dreyer, Heinz Jürgen Roth, Franz Paul Armbruster.

1Center for Cardiovascular Research, Charité, Berlin, Germany; 2Dept of Pediatric Nephrology, Univ of Heidelberg, Heidelberg, Germany; 3Odense Univ Hospital, Dept of Nephrology and Institute of Clinical Research, Univ of Southern Denmark, Odense, Denmark; 4Limbach Laboratory, Heidelberg, Germany; 5Immundiagnostik AG, Bensheim, Germany.

Background: Oxidized PTH (oPTH) loses its PTH receptor stimulating properties, whereas non-oxidized PTH (n-PTH) is a full agonist of the receptor. This was described in more than 20 studies in the 70ies and 80ies of the last transpant recipient.

Methods: We recently developed a new assay to differentiate between oPTH and n-PTH. We established normal values for this assay system. Furthermore, we compared the ratio of oPTH to n-PTH in different populations with chronic renal failure: 620 children with renal failure stage 2-4 of the 4C study, 342 adult patients on dialysis, and 602 kidney transplant recipients.

Results: Children had the highest mean as well as maximum n-oPTH concentrations as compared to adult patients (both patients on dialysis as well as kidney transplant recipients).

Conclusions: The relationship between oPTH and n-oPTH of individual patients varied substantially in all three populations. The analysis of n-oPTH in 89 healthy control subjects revealed that n-oPTH concentrations in patients with renal failure were higher as compared to healthy adults (2.5-fold in children with renal failure, 1.53-fold in adult dialysis patients, and 1.56-fold in kidney transplant recipients, respectively).

FR-PO306
Improvements in Control of Blood Pressure and A1c among Adults with Chronic Kidney Disease, Diabetes, and Hypertension: U.S. 1999-2010 Sharon Saydah, Edward Gregg, Meda E. Pavkov, Neil R. Powe, Rajiv Saran, Nilka Rios Burrows, Yi Li, Desmond Williams. 1CDC; 2UCSF; 3UMich.

Background: Prevention of chronic kidney disease (CKD) progression includes control of blood pressure and glycemia among adults with hypertension and diabetes. Whether control of these conditions has improved among adults with CKD in the past decade is unknown.

Methods: NHANES from 1999-2010 was analyzed in 4 year periods to examine trends among adults ≥ 18 years with CKD and treatment for diabetes (DM) (n = 1,405), or treatment of hypertension (HTYN) (n = 2,817) or treatment for both (n = 985). We report percent uncontrolled blood pressure (BP ≥ 140/90 mmHg) and uncontrolled A1c (A1c ≥ 9.0%). CKD was defined as eGFR < 60 mL/min/1.73 m² or elevated urinary albumin/creatinine ratio (ACR ≥ 30 mg/g).

Results: Trends in uncontrolled BP and high A1c are reported.

Funding: The National Institutes of Health.
Conclusions: While significant declines were observed, 2 out of 5 adults with CKD and treated HTN have uncontrolled BP and 4 out of 25 adults with CKD and treated DM have high a1c levels. These results indicate that among adults with CKD, there is a need for health care professionals to continue to work to reduce uncontrolled blood pressure and diabetes to prevent progression of CKD.

FR-PO307
A New Model for CKD Care: Home Telehealth by an Interprofessional Team Areef Ishani,1 Julieen Christopher,1 Sara Otterness,1 Deirdre A. Palmer,1 Mark E. Rosenberg.2 1Minneapolis VAHCS; 2Univ of Minnesota.

Background: Chronic kidney disease (CKD) is common and is associated with poor patient outcomes. Multidisciplinary care management with or without telementoring has been demonstrated to improve outcomes in non-CKD populations. The purpose of our study was to determine if a multidisciplinary case management with remote video monitoring of patients with CKD (eGFR <60mL/min) reduces a composite outcome (death, hospitalization, ER visits, admission to a skilled nursing facility) compared to usual care.

Methods: We recruited 601 veterans from the state of Minnesota with a last eGFR <60mL/min. At baseline all patients completed a home visit including surveys, a brief exam, and collection of blood and urine. 450 patients were randomized to the intervention consisting of a remote monitoring device (touch screen computer, BP cuff, scale, webcam, and glucometer). Patients were also provided with broadband if required. Patients in the intervention group were cared for by a multidisciplinary team of nurses, nurse practitioners, pharmD, dietician, social worker, psychologist, and a nephrologist following CKD guidelines and the chronic disease model of care. The overall goals of care were to optimize chronic conditions and to rapidly identify and resolve acute issues. Patients in the usual care group were informed of their kidney disease and invited to attend CKD education classes. The overall study duration is 12 months, with an anticipated primary event rate of 50% in the usual care group and 35% in the intervention group.

Results: Over an 8-month recruitment period 601 patients were enrolled in the study. Baseline characteristics of the overall study group are: age 78 years, male 98.7%, Caucasian 98.7%, eGFR 38mL/min. Patients lived on average 98 miles from the Minneapolis VA hospital, with 147 (24%) patients greater than 200 miles away. 292 (65%) patients had existing broadband, and the study provided broadband to the remaining patients.

Conclusions: This is a novel multifacetted intervention aimed at reduce adverse outcomes in CKD patients. The approach is feasible, connectivity can be established, and multidisciplinary care can be delivered using telehealth.

Funding: Veterans Affairs Support

FR-PO308
Implementation of CKD Care Coordinators Is Associated with Better Outcomes When Starting Dialysis Dugan Maddux,1 Daniel Defalco,1 Kevin Chan,1 Len A. Usvyat,1 Monet M. Carnahan,1 Koshy O. Abraham,2 Franklin W. Maddux.1 1FMCNA, Waltham, MA; 2Columbia Nephrology Assosciates, Columbia, SC.

Background: The Renal Care Coordinator (RCC) Program places CKD case managers and analytical tools in the Nephrology Practice to co-manage late stage CKD patients. We compared outcomes in patients starting dialysis who were previously enrolled in the RCC program to CKD patients who were cared for in the Nephrology practice for 4 months or more (Timely Referral), but were not in the RCC program.

Methods: All CKD 5 patients who transitioned to ESRD between 1/2009 and 12/2012 in 10 nephrology practices who adopted the RCC program were included. Within this cohort, we compared outcomes in those patients who were enrolled into the RCC program (RCC) versus those who were considered to have a timely referral for dialysis but were not in the RCC interaction. For each patient, we noted access type, albumin, neutrophil to lymphocyte ratio [NLR] (as marker of inflammation), hgb, and EPO dose at the first 30 days of dialysis.

Results: 4768 CKD 5 patients were identified for the study where 15% of the population was enrolled in the RCC program. Patients who were in the RCC program had a lower % of patients with catheters, higher albumin, lower NLR, non-significantly different Hgb, and lower EPO dose on the first in-center HD treatment compared to patients with no RCC care. Hospital days were 41% lower and mortality rate was 24% lower in the RCC program compared to patients with Timely Referral alone in the first 120 days.

Conclusions: This analysis demonstrates that placement of CKD coordinators in Nephrology Practices is associated with better outcomes, including mortality and hospitalizations, in the first 120 days of dialysis.

Table 1. Comparison of parameters at the first in-center HD treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RCC</th>
<th>Timely Referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access type (%)</td>
<td>48.5</td>
<td>50.5</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Neutrophil to lymphocyte ratio</td>
<td>12.7</td>
<td>14.2</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>10.5</td>
<td>10.3</td>
</tr>
<tr>
<td>EPO dose (units/kg)</td>
<td>21.6</td>
<td>22.1</td>
</tr>
</tbody>
</table>

FR-PO309
Healthcare Resource Utilization and Costs Associated with the Treatment of Autosomal Dominant Polycystic Kidney Disease Christopher M. Blanche,1 Serban R. Iorga,1 Aylin A. Riedel,1 Jerry G. Sear,1 Ying Fan,1 Sandro Rossetti,1 Ben Gutierrez,1 1Otsuka America Pharmaceuticals, Inc., Princeton, NJ; 2Univ of North Carolina, Charlotte, NC.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disease associated with cyst growth and loss of renal function that leads to renal failure. Symptoms of ADPKD can lead to multiple complications, including most commonly hypertension, urinary tract infections, renal cyst infections, hematuria, kidney stones, rupture of intracranial aneurisms, and chronic pain. Real-world data on healthcare costs and resource utilization for ADPKD is lacking; therefore we assessed healthcare cost in a sample of commercially insured (COM) and Medicare Advantage (MAPD) patients.

Methods: Patients diagnosed with ADPKD (≥2 claims) with ≥30 days of continuous medical and pharmacy benefits, and no evidence of autosomal recessive polycystic kidney disease were selected from a large health plan claims dataset (1/1/06-8/31/12). Plan and patient paid costs and utilization per patient per month (PPPM) were described in total and by payer type, and estimated using generalized linear models by chronic kidney disease (CKD) stage (defined by ICD-9 or serum creatinine).

Results: Of 36,253,096 patients in the database during the observation period 5,051 (0.014%) were identified with ADPKD. After applying exclusion criteria, 4,356 COM and 468 MAPD remained. Patients had an average length of time-in-study of 1,299 days. Post-index complications included hypertension (88%), anemia (47%), urinary tract infections (41%), kidney stones (19%), liver disorders (35%), and kidney transplants (20%).

Conclusions: Total healthcare cost and resource utilization associated with ADPKD was high, which was driven mostly by end-stage renal disease and was similar for COM or MAPD patients.

Funding: Pharmaceutical Company Support - Otsuka America Pharmaceuticals, Inc.
Cross-Sectional and Longitudinal Associations with Creatinine Generation Rate (CGR) in the Chronic Renal Insufficiency Cohort (CRIC) Francis P. Wilson,1 Wei Yang,1 Amanda Hyre Anderson,1 Peter P. Reese,1 Radhakrishna Reddy Kallem,1 Sankar D. Navaneethan,1 Akinolu O. Ojo,1 James H. Sondheimer,2 Raymond R. Townsend,1 Mary B. Leonard,1 Harold I. Feldman,1 1Pereleman School of Medicine at the Univ of Pennsylvania; 2Tulane Univ; 3Children’s Hospital of Philadelphia; 4Cleveland Clinic; 5Univ of Michigan; 6Wayne State Univ.

Background: Muscle mass may be lower in patients with more severe CKD. We examined factors associated with muscle mass and muscle loss as measured by CGR in a large national chronic kidney disease population.

Methods: We used data from 3725 participants in the CRIC study, a national, prospective study of chronic kidney disease and assessed their CGR, a proxy for muscle mass, from 24-hr urine collections yearly for a median of 4 yrs. We examined associations between CGR and factors assessed at study entry using mixed-effects models.

Results: Mean (SD) age was 58 (11) years, 55% were male, and 42% reported black race. Mean (SD) baseline CGR was 1333 (591) mg/day, and declined by 13.8 mg/year (p<0.001). At study entry, participants in the highest tertile of baseline CGR were more likely to be black, male, and younger (all p<0.001). They also had higher BMI, larger waist circumference, larger fat mass, and lower high-density lipoprotein (all p<0.001), but lower rates of diabetes (p=0.02) and lower hemorrhagic AIF (p=0.001). Participants with the highest CGR had lower serum creatinine and cystatin levels (p<0.001), greater urine urea appearance (p<0.001), but similar urinary protein excretion (p=0.42) compared to those in the lowest CGR tertile. Longitudinally, higher cystatin C levels (p<0.001), female sex (p<0.001), older age (p<0.001), more proteinuria (p<0.001), non-black race (p=0.002), smoking (p=0.01), and higher C-reactive protein (p<0.02) were independently associated with loss of CGR over time.

Conclusions: Greater protein intake is associated with greater muscle mass as measured by CGR in CKD. As well, proteinuria, anemia, and smoking are potentially modifiable factors associated with progressive muscle wasting in CKD.

Funding: NIDDK Support

FR-PO311

Association of Creatinine Generation Rate (CGR) with Death and End-Stage Renal Disease (ESRD) in Patients with Chronic Kidney Disease (CKD) in the Chronic Renal Insufficiency Cohort (CRIC) Francis P. Wilson,1 Wei Yang,1 Amanda Hyre Anderson,1 Peter P. Reese,1 Radhakrishna Reddy Kallem,1 Sankar D. Navaneethan,1 Akinolu O. Ojo,1 James H. Sondheimer,2 Raymond R. Townsend,1 Harold I. Feldman.1 1Pereleman School of Medicine at the Univ of Pennsylvania; 2Tulane Univ; 3Children’s Hospital of Philadelphia; 4Cleveland Clinic; 5Univ of Michigan; 6Wayne State Univ.

Background: Greater severity of CKD may be associated with lower muscle mass, but the association of muscle mass to clinical outcomes in CKD is undefined.

Methods: We used data from 3725 participants in the CRIC study, a national prospective study of CKD and assessed their CGR, a proxy for muscle mass, from 24-hr urine collections at study entry. Proportional hazards analysis was used to assess the association between CGR and factors associated with progressive muscle wasting in CKD.

Results: Higher CGR was associated with a lower rate of all-cause mortality in unadjusted models with hazard ratio for death 0.68 (0.61 - 0.75, p<0.001) for each standard deviation increase in CGR. After adjustment for age, sex, race, ethnicity, serum cystatin, urine protein, hemorrhagic, diabetes, cardiovascular disease, smoking status, height, weight, waist circumference, and urine urea appearance, CGR remained independently associated with death - aHR 0.86 (0.76 - 0.98, p=0.02). CGR was associated with the development of ESRD in unadjusted - HR 0.72 (0.60 - 0.80, p=0.001) and fully adjusted models - aHR 0.79 (0.70 - 0.89, p<0.001). Accounting for death as a competing risk showed similar results; aHR 0.81 (0.69 - 0.94, p=0.006).

Conclusions: Lower CGR, a proxy for low muscle mass, is independently associated with death and ESRD in patients with CKD.

Funding: NIDDK Support

FR-PO312

Low Compliance with Protein Intake Recommendations and Outcomes in Patients with Chronic Kidney Disease Benedicte Stengel,1 Wenlun Yuan,1 Martin Flamant,2 Pascal Houillier,3,5 Francois Vrtovska.3,5 InsERM U1018, Univ Paris Sud, Villejuif; 4APHP, Paris; 5Univ Paris Descartes, France; 6The NephroTest Study Group.

Background: Little is known about real compliance with dietary protein intake recommendations and its outcomes in patients with chronic kidney disease.

Methods: We measured glomerular filtration rate (mGFR) and assessed protein intake in g/kg/day based on both 24-hr urinary urea nitrogen (UUN) and 7-day food record in 1,018 men and 502 women with nondialysis CKD stages 1 to 5. Cox models were used to assess hazard ratios (HR) for end-stage renal disease (ESRD) and death before ESRD over a mean follow-up of 3.5 yrs.

Results: Mean age was 60 (15) yrs in men vs women, and mean body mass index, 26.6±4.4 vs 26.2±6.0 kg/m². Baseline mean UUN-based protein intake did not significantly differ between men and women, 1.35±0.33 g/kg/d vs 1.32±0.39 g/kg/d; estimates based on 7-day food record were 0.27±0.44 g/kg/d lower on average in both genders. 24-h UUN significantly decreased from 1.48 to 1.14 g/kg/d with decreasing mGFR from ≥10 to <15 mL/min/1.73 m² in men and from 1.45 to 1.10 g/kg/d in women. Similar decrease was observed with food record, from 1.50 to 1.15 g/kg/d in men and from 1.54 to 1.29 in women. Fifty-two percent of men and 47% of women had protein intake above the 2012 KDOQI upper limit of 1.30 g/kg/d recommended for CKD patients. Adjusted HR of ESRD associated with 1 g/kg/d UUN increase was 1.54 [0.98-2.43] and for mortality before ESRD, 0.95 [0.52-1.75]. These HR were 3.51 [2.02-6.12] and 1.84 [0.77-4.38] for the association with 7-day record-based protein intake, respectively.

Conclusions: Despite lower protein intake and lower mGFR levels, compliance with recommendations remains low in patients with chronic kidney disease. High protein intake appeared to be associated with increased risk for ESRD, but not for mortality. It is worth noting that the decrease in 24-h UUN associated with kidney function decline may not be attributed to increased extrarrenal urea elimination, since similar results were found for 7-day record-based protein intake.

Funding: NIDDK Support
Results: TNFR1 as well as TNFR2 were correlated with measured GFR(r=−0.63 and r=−0.67). Median values of TNFR1 and TNFR2 according to GFR were as follows: 59.4±13.4 for GFR<30, 92±121.25 for 90-GFR, 169±341.10 for 60-GFR, 292.5±6994 for 30-GFR, 2267.4±4414 for GFR<15. TNF receptors had similar diagnostic power in patients with GFR less than 60 when compared to SCR through ROC curve. The levels of TNF receptors in CKD1 and 2 patients(n=60) were higher than healthy volunteers. Compared with stable renal function participants, TNF receptors values were elevated in individuals with renal function decline. Multivariate analysis revealed that highest quartile of TNF receptors were associated with renal function impairment compared to the other quartiles.

Conclusions: Our study identified that TNF receptors were correlated with measured GFR. TNF receptors showed similar increment pattern and diagnostic power compared with SCR. Even mild renal impairment was associated with higher levels of TNF receptors in comparison to healthy controls. TNF receptors were associated with progression of renal function.

FR-P0315
Concentration of Serum Tumor Necrosis Factor Receptors and Progression of Chronic Kidney Disease in Patients with Moderate to Severe Renal Dysfunction
Su Mi Lee1, Ran-hui Cha1, Hajoong Lee1, Sunwha Lee1, Seung Hee Yang1, Jung Pyo Lee3, Dong Ki Kim1, Yon Su Kim1

Background: The prevalence of chronic kidney disease (CKD) has been increased steadily, and it’s one of public health problems. However, there is a paucity of biomarkers for the prediction of CKD progression other than high serum creatinin (SCr), reduced glomerular filtration rate (GFR), and proteinuria. Chronic inflammation may contribute to kidney damage and interaction between tumor necrosis factor alpha (TNFα/TNF) and its receptors (TNF receptor 1 and 2) has essential role in the inflammation signaling. We aimed to evaluate the clinical significance of TNF receptors as a biomarker of CKD progression.

Methods: We recruited 473 patients with CKD stage 3 (n = 148) and 4 (n = 321). Primary outcome was defined as composite of SCr increase more than 2 times, GFR decrease more than 50 percent, or initiation of renal replacement therapy. We measured serum concentration of TNF receptors by ELISA (DRT100 and DRT200; R&D Systems, Minneapolis, MN).

Results: A total of 205 patients reached primary outcomes during 3 years of follow-up. Patients with primary outcomes showed higher baseline level of SCr, glomerular filtration rate (GFR), proteinuria, and TNF receptor 1/2 than patients without primary outcomes. When the levels of TNF receptors were categorized as tertiles, there was a significant association between tertiles of TNFR 1 and primary outcome after adjustment for age, gender, GFR, and proteinuria (OR (C.I.) ; 1 (reference), T2: 1.357 (0.718-2.563), T3: 3.096 (1.618-5.926)). In addition, there was a trend to increased adjusted odds ratio of primary outcome according to increasing TNFR2 tertiles after adjusted with age, gender, GFR, and proteinuria (OR (C.I.) ; 1 (reference), T2: 1.357 (0.718-2.563), T3: 3.096 (1.618-5.926)).

Conclusions: Our study identified that higher serum level of TNF receptors (TNF receptor 1 and 2) are associated with progression of CKD in patients with moderate to severe renal dysfunction (CKD stage 3 to 4).

FR-P0316
Time Trend of Body Mass Index in Maintenance Dialysis Patients
Elani Streja1, Connie Rhee1, Lilia R. Lukowsky1, Allen R. Nissenson2, Csaba P. Elvira Fernandez, Maria Jose Soler1

Background: Among dialysis patients, lower body mass index (BMI) has been associated with increased mortality, RRT (dialysis or kidney transplant) or Dec 2012. The risk of mortality or RRT increases with increasing BMI. We compared the trend of BMI over time, after excluding the first quarter there was a trend decrease more than 50 percent, or initiation of renal replacement therapy. We measured serum concentration of TNF receptors by ELISA (DRT100 and DRT200; R&D Systems, Minneapolis, MN).

Methods: We analyzed all CKD 3-5 patients in China Medical University Hospital from 2003 to 2012. The types, frequency and duration of exercise were recorded on the initiation of CKD program and all patients were followed to the date of incident dialysis patients. This study reported the effect of frequency, duration and types of exercise in CKD 3-5 patients. We measured BMI and TNF receptors in patients with elevated BMI, muscle mass and survival in dialysis patients.

Funding: NIDDK Support, Private Foundation Support

FR-P0317
Circulating Angiotensin Converting Enzyme 2 in Patients with Chronic Kidney Disease without History of Cardiovascular Disease
Lidia Anguiano1, Marta Riera1, Julio Pascual1, Clara Barrios1, Angels Betriu2, Jose M. Valdivielso2, Elvira Fernandez3, Maria Jose Soler1

Background: Circulating ACE2 activity is increased in cardiovascular disease(CVD) and in experimental models of diabetes(DM). It has not been studied in Chronic Kidney Disease(CKD)without history of CVD.

Methods: Analysis of 2572 patients without history of CVD from NEFRONA study. Groups:non-dialysis CKD stage 3-5 (n=1458) and dialysis(CKD5D,n=514). 568 patients without CKD were controls. Variables analyzed:gender,age,DM,dyslipidemia,by pertension and ACEi or ARBs.ACE2 activity was measured by fluorimetry.

Results: Patients on CKD3-5 had higher levels of ACE2 activity compared to CKD5D(45.2±2.8RFU/µl h vs 38.5±1.6 p<0.05). Control patients had higher levels of ACE2 activity(52.9±1.5)compared to CKD3-5 and CKD5D(p<0.05). In CKD3-5 ACE2 activity was increased in men compared to women(50.4±1.6 vs 36.6±1.5 and in DM(49.9±2.0 vs 43.3±1.4 p<0.05). In CKD5D, ACE2 activity was increased in men(45.6±2.5 vs 27.7±1.4),in dyslipidemias(42.6±2.8 vs 33.9±1.3 p<0.05) and in ARBs (40.3±1.9 vs 37.6±2.2 p<0.05). Direct correlation between both ACE2 activity and in experimental models of diabetes(DM).

Conclusions: In patients without history of CVD, old age and DM were independent predictors of ACE2 activity in CKD3-5. Predictors in CKD5D were male gender, age and ARBs. When all patients included, male gender, older age, ARBs and CKD5-3 were predictors of elevated ACE2.

FR-P0318
Stroll Saves Lives and Delays Renal Replacement Therapy
J-RU Chen, Che-yi Chou, Hsin Hung Lin, I-kuan Wang, Shih-yi Lin, Yao-Lung Liu, Jiung-hsun Lui, Chih-chia Liang, Yafei Yang, Huey-Liang Kuo, Chiu-Ching Huang.

Dept of Internal Medicine, Kidney Institute and Div of Nephrology, China Medical Univ Hospital, Taichung, Taiwan.

Background: There is increasing evidence of the benefit of increasing physical activity in chronic kidney disease (CKD) patients receiving renal replacement therapy (RRT). Increasing physical activity may improve quality of life and clinical outcomes. There is little evidence for the benefit of increasing physical activity in CKD 3-5 patients. This study reported the effect of frequency, duration and types of exercise in CKD 3-5 patients on clinical outcomes.

Methods: We analyzed all CKD 3-5 patients in China Medical University Hospital CKD program from 2003 to 2012. The types, frequency and duration of exercise were recorded on the initiation of CKD program and all patients were followed to the date of mortality, RRT (dialysis or kidney transplant) or Dec 2012. The risk of mortality or RRT was analyzed using Cox regression with adjustments for age and CKD stage (3a,3b,4,5).

Conclusions: Incident dialysis patients were observed to have a significant increase in serum creatinine level following dialysis initiation irrespective of survival or death status, while BMI increased over time only among patients who survived. Our findings also corroborate prior reports whereby lower creatinine levels and lower BMI is associated with increased mortality. These results offer further insight into the obesity paradox and relationship between BMI, muscle mass and survival in dialysis patients.

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

436A
Results: A total of 4832 CKD 3-5 patients (stage 3a 720, stage 3b 818, stage 4 996 and stage 5 2596) including 2525 female and 2777 male with mean age of 69.1 ± 13.6 years old were analyzed. Out of 357 patients (7.4%) patients were diagnosed with CKD 5 (33.7%) and the average 1.7 ± 1.6 years follow-up. Diabetes and hypertension was not significantly associated with the outcomes while types, frequency, and duration of exercise were taken into consideration. The increasing frequency of exercise was linked to a decrease of overall mortality (p<0.001). The increasing duration of exercise was linked to a decrease of RRT risk (p<0.001). Stroll, independent of frequency and duration of exercise, was linked to a decreased mortality risk (p=0.05) and RRT risk (p=0.04).

Conclusions: Stroll is a common and easy physical activity in chronic kidney disease patients. Stroll may decrease the risk for mortality and RRT, the benefit of stroll is independent of it’s frequency and duration. More studies are needed to determine if behavior instructions can increase physical activity to improve clinical outcomes in CKD patients.

FR-PO319
Predictors of Renal Outcome in Nephrotic Idiopathic Membranous Nephropathy with Declined Renal Function
Xiang-Mei Chen, Yizhi Chen, Li Zhang, Guangyan Cai. Div of Nephrology, State Key Discipline and State Key Laboratory of Kidney Diseases, Chinese People’s Liberation Army (PLA) General Hospital.

Background: The outcome of patients with idiopathic membranous nephropathy (IMN) who presented with nephrotic-range proteinuria and declined renal function was seldom described. The value of pathologic and clinical features in predicting the outcome has long been debated. The aim of this study was to identify factors associated with persistent renal decline and progression to end-stage renal disease (ESRD).

Methods: A retrospective study was conducted between 2002 and 2011 in 129 patients with biopsy-proven IMN in a single tertiary referral center in China. The primary outcomes were 20% and 50% decline in renal function and the progression to ESRD.

Results: All the 129 patients had nephrotic-range proteinuria (≥ 3.5 g/day) and declined renal function (chronic kidney disease (CKD) stages 2-4) at baseline. Of the 129 patients, 38 (30%) presented with proteinuria ≥ 8.0 g/day and 37 (29%) presented with CKD stages 3-4, 13 (10%) patients progressed to ESRD. Age at baseline (≥ 60 years) and the presence of FSGS and T1+T2 were independent risk factors of the progression to ESRD.

Conclusions: Age ≥ 60 years and CKD stages 3-4 at baseline and the presence of FSGS and T1+T2 were independent risk factors of the decline in renal function and the progression to ESRD in adult IMN patients with nephrotic-range proteinuria and declined renal function.

Funding: Government Support - Non-U.S.

FR-PO320
The Predictive Factors of Cisplatin-Induced Nephrotoxicity for Urothelial Cancer
Satoru Muto,1 Syuichiro Sugura,1 Yasuhiro Noma,1 Masahiro Inoue,1 Kousuke Kitamura,1 Shino Tokiwa,1 Keiseki Saito,1 Shuji Isotani,1 Raizo Yamaguchi,1 Hisamitsu Ide,1 Shigeo Horie,2 Urology, Teikyo Univ, Tokyo, Japan; 1Urology, Juntendo Univ, Tokyo, Japan.

Background: Though cisplatin (CDDP) shows excellent anticancer activity, its use has been restricted due to its damaging effect on the kidney. Our team designed a retrospective clinical study on renal damage in anticancer chemotherapy using CDDP.

Methods: This study included 63 patients with urothelial cancer who had received chemotherapy with CDDP from March 2000 to February 2012. Renal function were investigated at baseline, the first 10 days after CDDP administration, 3, 6, 12, 24 and 36 months later using the eGFR, MDRD formula, Cockcroft-Gault formula.

Results: Mean age was 65.5 ± 8.1 years and median follow-up period was 56 months (range; 3-146 months). In a short period of time after CDDP administration, the univariate analysis revealed the significant differences between the decreased renal function group and the unchanged or improved group in the renal function before CDDP administration, the volume of infusion on the day of CDDP administration, the volume of extracellular fluid administered on the day of CDDP administration and the urinary volume on the day of CDDP administration. In multivariate analysis, the renal function before CDDP administration and the urinary volume on the day of CDDP administration were significant predictive factor for the prognosis of renal function. Though GFR tended to worsen, significant change was not found. Examination of influential factors on significant reduction in GFR 36 months later revealed that in univariable analysis, the significant predictive factors were GFR during the first 10 days after CDDP administration.

Conclusions: Careful long-term follow-up is required after anti-cancer CDDP containing chemotherapy for urothelial cancer. Prevention of kidney function decline immediately after CDDP administration by ensuring sufficient volume of infusion and urine in concurrence with CDDP administration should be considered to prevent a decline in renal function over a prolonged period of time.

FR-PO321
Association of Systolic Blood Pressure with Cardiovascular Events in Patients with Advanced Kidney Disease
Shyamal K. Palit,1 Anna Jeanette Jovanovich,1 Alfred K. Cheung,2 James S. Kaufman,2 Gerard John Smith,3 Michel Chonchol,1 Jessica B. Kendrick,1 ‘Univ of Colorado Denver, Aurora, CO; 2VASLCHCS, Salt Lake City, UT; 3Univ of Utah, Salt Lake City, UT; 4VA New York Harbor Healthcare System, New York, NY.

Background: We performed an analysis on 1,099 patients with advanced kidney disease not yet on dialysis who participated in the Homocysteine in Kidney and End Stage Renal Disease study. Blood pressure was measured in a standardized fashion. SBP levels were examined in clinically defined cutoffs (<120, 120-139, 140-159 and ≥160 mmHg) and as a continuous variable. We used Cox proportional hazard models to examine the association between SBP levels and CVE defined as a composite of myocardial infarction, stroke and amputation.

Results: The mean eGFR was 18 ± 7 ml/min/1.73m². A total of 215 CVE occurred during a median follow-up of 2.9 years. After adjustment for age, gender and race there was an increased risk of CVE with a SBP ≥ 160 mmHg compared to a level <120 mmHg (HR 1.61, 95% CI 1.01-2.56). There was no increased risk of CVE with a SBP 140-159 or SBP 120-139 mmHg (HR 0.90, 95% CI 1.56-1.45 and HR 1.06, 95% CI 1.00-1.69, respectively). For every 1 mmHg increase in SBP, there was a 0.8% increased risk of CVE (HR 1.008, 95% CI 1.001-1.01). However, after further adjustment for hypertension, diabetes, history of cardiovascular disease, smoking, body mass index, eGFR and treatment arm, SBP ≥160 mmHg was no longer associated with an increased risk of CVE compared to a level <120 mmHg (HR 1.42, 95% CI 1.09-1.92). Similar results were obtained when SBP was modeled as a continuous variable (HR 1.005, 95% CI 1.00-1.01, per 1 mmHg increase in SBP).

Conclusions: After adjustment for known cardiac risk factors, SBP levels were not associated with CVE in patients with advanced kidney disease. Randomized trials are needed to determine the optimal SBP in patients with advanced kidney disease.

Funding: NIDDK Support

FR-PO322
Hypothyroidism and Impaired Kidney Function among National VA Chronic Kidney Disease Patients
Connie Rhee,1 Kamary Kalantar-Zadeh,1 Elani Streja,2 Jennie Z. Ma,2 Jun Ling Lu,3 Csaba P. Kovesdy.1,4 1Harold Simmons VA Health System, Orange, CA; 2Univ of Virginia, Charlottesville, VA; 3Univ of Tennessee Health Science Center, Memphis, TN; 4Memphis VA Medical Center, Memphis, TN.

Background: Hypothyroidism is a common condition in the general population with pervasive effects on virtually every organ system. Studies suggest non-diagnosis dependent chronic kidney disease (NDD-CKD) patients are disproportionately affected by hypothyroidism, but there is likely underrecognition of disease. We thus sought to examine the association between hypothyroidism and estimated glomerular filtration rate (eGFR) in the national VA NDD-CKD cohort.

Methods: We examined data from >400,000 adult patients with ≥1 thyrotopin (TSH) and ≥1 creatinine. The CKD-EPI formula was used to calculate eGFR. Using a random effects model that considered longitudinal TSH levels, we examined the association between TSH and eGFR in case-mix adjusted analyses. In analogous analyses, we examined the association between biochemical hypothyroidism (TSH<5mIU/L and eGFR).

Results: Among 468,739 patients with ≥1 TSH, 0.0% had biochemical hypothyroidism, 21.0% received levothyroxine (LT-4), and 23.3% had biochemical hypothyroidism and/or LT-4 use. Among 463,219 patients with 1,560,797 TSH measurements and complete covariate data, for every 10ml/min/1.73m² increase in eGFR, there was a 12% decrease in the odds of biochemical hypothyroidism (OR 0.88 [95% CI 0.87-0.90]). For every 10ml/min/1.73m² increase in eGFR, there was a 12% decrease in the odds of biochemical hypothyroidism from 0.88 to 0.90.

Conclusions: Among a nationally representative cohort of VA NDD-CKD patients, hypothyroidism is highly prevalent, and it is inversely associated with eGFR. Further studies are needed to determine the mechanistic link, directionality of association, and prognostic implications of hypothyroidism in CKD.

Funding: NIDDK Support, Veterans Affairs Support
FR-PO323
Short-Term Prognosis of Chronic Kidney Disease with Hyperuricemia Treated by Febuxostat: A Subanalysis from a Prospective Non-Controlling Safety/Tolerability Study Yugo Shibagaki,1 Iwao Ohno,2 Tatsuo Hosoya,2 Kenjiro Kimura,1 "Div of Nephrology and Hypertension, St. Marianna Univ Hospital, Kawasaki, Japan; 2Div of Nephrology and Hypertension, Jikei Univ School of Medicine, Tokyo, Japan.

Background: Hyperuricemia (HU) is a very common comorbid condition in patients with chronic kidney disease (CKD) and there is accumulating evidence that treatment of HU may reduce blood pressure (BP) level and progression of CKD.

Methods: We conducted a 24-week prospective, open-label, non-controlled study to investigate the safety, tolerability and efficacy of febuxostat in patients with HU and moderate to severe CKD (stage 3b to 5). 71 prevalent adult outpatients (55 males with average age 66.3 years) at two tertiary care hospitals who met the inclusion criteria (serum urate > 8 mg/dl, estimated GFR (eGFR) < 45 ml/min/1.73m², non-use of urate lowering drug in the previous month) were recruited from November 2011 to April 2012. All the participant received febuxostat. Starting dose of febuxostat was 10 mg qd, increased to 20 mg, 40mg qd in week 4, and week 8, respectively. We analyzed the data of this study to investigate change of BP, eGFR and proteinuria during treatment of HU with febuxostat.

Results: Serum urate level (mg/dl) at baseline/24 weeks were 9.9±5.5, 10.6±5.2, and 9.8±4.8, in stage 3b, 4, and 5, respectively. There was no significant change in BP between start and end of the study as a whole, although the diastolic BP was slightly but significantly lower at week 8 and 16. eGFR at 24 weeks were not significantly different from that at baseline in CKD stage 4 and 5. However, in CKD 3b, eGFR was significantly higher at 24 weeks compared with that at baseline. There were 13 patients who had data of proteinuria. There was no significant change in level of proteinuria although proteinuria tended to decrease in CKD stage 3b. Multivariate analysis revealed that greater reduction of serum urate predicted increase in eGFR (p=0.0055) and tended to predict reduction of proteinuria (p=0.063).

Conclusions: Greater reduction of serum urate level by febuxostat was associated with increase in eGFR, although it did not significantly change the level of BP and proteinuria.

FR-PO324
Elevated Level of C-Reactive Protein Identify African Americans with Metabolic Syndrome at High Risk of Developing Albuminuria Satyesh K. Sinha,1 Magda Shaheen,1 Deyu Pan,1 Susanne B. Nicholas,1,2 Charles R. Drew Univ of Medicine and Science, Los Angeles, CA; 3David Geffen School of Medicine at UCLA, Los Angeles, CA.

Background: African Americans (AA) have a higher prevalence of the metabolic syndrome (MetS) and chronic kidney disease (CKD) than whites. Inflammation and the MetS have been shown to be associated with renal impairment; however, it is unclear whether higher levels of serum inflammatory biomarkers may account for disparities in the development of albuminuria, as a marker for CKD in AA with MetS.

Methods: We analyzed data from the National Health and Nutrition Examination Surveys 1999-2008 of 7,369 adults aged ≥20 years with three or more components of the MetS according to the National Cholesterol Education Program’s Adult Treatment Panel III definition. Multivariate analyses were performed to test the relationship of race/ethnicity with urinary albumin excretion (UAEx) and serum C-reactive protein (CRP), adjusting for age, gender, smoking and components of the MetS.

Results: CRP and UAEx were significantly higher in AA (0.76±0.77mg/dl and 211.7±990.1μg/mI, respectively), compared to whites (0.54±1.05mg/dl and 48.5±344.0μg/mI, respectively), p<0.01. Adjusted logistic regression indicated that AA had higher odds for CRP≥3mg/dl (adjusted odds ratio [AOR]=1.4, 95% CI 1.15-1.76) and UAEx≥30mg/ dI (AOR=2.67, 95% CI 2.11-3.38), compared to whites, p<0.001. Also, adjusted linear regression showed a significant association between UAEx and CRP (Adjusted Coefficient; AC=0.15, 95% CI 0.07-0.23) and that the interaction term of CRP and race/ethnicity was statistically significant, p<0.001. The adjusted change in the UAEx for one unit change in CRP was higher among AA relative to whites (AC=0.63, 95% CI 0.39-0.87), suggesting a stronger relationship between CRP and UAEx in AA.

Conclusions: We conclude that elevated CRP may predict the higher risk of albuminuria in AA with the MetS compared to white.

Funding: Other NIH Support - NIH-NIMHD grant U54MD007598 (formerly U54RR026138), S21MD000103 and NIH/NCRR/NCATS CDU/UCLA CTSI Grant UL1TR000124

FR-PO325
Dialysis at Home—Could It Be a More Frequent Choice? Patrik Finne,1,2 Ilkka Helanterä,1 Virpi Rauta,1 Agneta V . Ekstrand,1 Eero Honkanen,1 Carola Gronhagen-Riska,1 "Dept of Nephrology, Helsinki Univ Central Hospital, Helsinki, Finland; 2Finnish Registry for Kidney Diseases, Helsinki, Finland.

Background: The proportion of dialysis patients on home dialysis (either peritoneal dialysis (PD) or home hemodialysis (HD)) varies greatly both between and within countries, which indicates that there is a potential for increasing its use in many places.

Methods: All patients who entered dialysis in Finland in 2000 to 2010 and were still on dialysis at day 91 from start (n=4984) were included. Patient data were retrieved from the Finnish Registry for Kidney Diseases. Data on contraindications for home dialysis was collected for a randomized sample of 200 patients on in-center HD in the healthcare district of Helsinki-Uusimaa (HUS), which has exceptionally high proportion of home dialysis (38%). A multinomial logistic regression equation with stepwise selection of explanatory variables was constructed based on the patients in HUS (n=1128) to estimate probability of home HD, PD and in-center HD. This model was applied to the patients in the rest of the country in order to estimate whether use of home dialysis could potentially be increased.

Results: Out of 30 evaluated variables, 11 were selected to the final model. The most important predictors of home dialysis were young age, high hemoglobin, high albumin and normal body-mass index (for PD). Polycystic kidney disease decreased probability of PD and increased that of home HD. The model identified in-center HD patients with large probabilities of either home HD or PD and indicated that use of home HD could potentially be increased from 0.2% to 8% and PD from 26 to 28%. Of the in-center HD patients in HUS, 93% had a reported contraindication of home dialysis in the hospital files. Notably, the model predicted in-center HD for half of patients who in fact had entered PD, which shows that indications for home dialysis vary between districts in Finland.

Conclusions: Our model identified a considerable proportion of in-center hemodialysis patients that could be suitable for either peritoneal dialysis or home hemodialysis. Conversely, the model predicted in-center HD for many patients who actually had entered PD, which shows that indications for home dialysis vary between districts in Finland.

Funding: Pharmaceutical Company Support - Bayer

FR-PO326
Time Course of Utilization of Alternative Dialysis Modalities Soorni Kuttikrishnan,1 Kamyar Kalantar-Zadeh,2 Jonathan Himmelfarb,1 Alfred K. Cheung,1 Onyebuchi A. Arah,1 Elani Streja,2 Vanessa A. Ravel,2 Allen R. Nissenson,2 Rajnish Mehrotra.1 1Univ of Washington; 2Univ of California, Irvine; 1Univ of California, Los Angeles; DaVita Healthcare Partners; 1Univ of Utah.

Background: The Institute of Medicine lists studying outcomes with different dialysis therapies among the top 100 priorities for comparative effectiveness research. Understanding the time course of accrual of patients to the various dialysis therapies is needed to adjust for bias inherent in such comparisons.

Methods: The time course of utilization of different dialysis therapies was analyzed in three-month increments from the date of first dialysis up to five years, among the 162,671 patients who started maintenance dialysis in 2007-11 in a large dialysis organization.

Results: Over 5 years, 23,837 (14.7%) patients were treated with alternative dialysis modalities: PD, 18,279 (11.2%), home hemodialysis (HD), 2653 (1.6%), frequent in-center HD, 1888 (1.2%), and nocturnal in-center HD, 1452 (0.9%). Only 54% of patients ever treated with PD, started treatment with this modality compared to 18%, 7%, and 24% for home HD, frequent HD, and nocturnal HD respectively. The median interval from the time of first dialysis to first ever treatment with home HD, frequent HD, and nocturnal HD was 9, 9 and 12 months respectively (Figure). The median time of treatment with PD, home HD, frequent HD, and nocturnal HD was only 18.3, 12.1, 5.6, and 9.7 months respectively.

Conclusions: The actual number of patients treated with alternative dialysis therapies is significantly larger than evident from point-prevalent counts. Most patients treated with alternative modalities do so only after at least some period of treatment with in-center HD and are treated for relatively short periods of time. These are important considerations when studying comparative effectiveness of dialysis therapies.

Funding: NIDDK Support

FR-PO327
Temporal Trends in Home Dialysis Training Eric D. Weinhandl,1 Robert N. Foley,2 Allan J. Collins.1 1USRDS Coordinating Center, MMRF, Minneapolis, MN; 2Univ of Minnesota, Minneapolis, MN.

Background: To compensate for the cost of home dialysis training, the Medicare End Stage Renal Disease (ESRD) Prospective Payment System (PPS) features a 51% increase in reimbursement for dialysis services during the first 120 days after dialysis initiation, as well as an add-on payment of $33.44 per training session after the first 120 days. Critics have argued that these mechanisms fail to properly compensate for the cost of home hemodialysis training. We used Medicare Quarterly Standard Analytical Files (QSAs) to assess temporal trends in peritoneal dialysis (PD) and home hemodialysis (IHHD) training between January 2003 and June 2012.

Methods: We searched outpatient facility claims between calendar years 2000 and 2012 for condition code 73 (self-care in training) in tandem with revenue center codes 0821 (HD), 0831 (PD), 0841 (continuous ambulatory PD), or 0851 (continuous cycling PD). For each patient with qualifying claims, we recorded the date and modality of the

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
First training session. For each month between January 2003 and June 2012, we tallied the number of patients who initiated either PD training or HHD training. To estimate trends, we fit fourth-degree polynomial functions to each time series of trainee counts.

**Results:** Counts of PD trainees reached their minimum in December 2006 (N = 427), and according to trend analysis, began increasing in July 2007, with sustained growth of 4 patients per month beginning in December 2008. In contrast, counts of HHD trainees tended to increase between April 2003 and April 2011, with a maximum in August 2010 (N = 177), but tended to decrease beginning in May 2011.

**Conclusions:** The introduction of the ESRD PPS coincided with sustained month-to-month increases in the number of patients in initial PD training, but was followed shortly thereafter by month-to-month decreases in the number of patients in initial HHD training.

**Funding:** NIDDK Support

---

**FR-PO328**

Suboptimal Initiation of Home Hemodialysis: Determinants and Clinical Outcomes

**Authors:** Annie-Claire Nadeau-Fredette, Karthik K. Tennankore, Joseph Kim, Christopher T. Chan. Div of Nephrology, Dept of Medicine, Univ of Toronto, Toronto, Canada.

**Background:** Suboptimal initiation of conventional hemodialysis (CHD) is associated with poor clinical outcomes. In this study, we aimed to ascertain the determinants and adverse events associated with suboptimal starts in home hemodialysis (HHD).

**Methods:** We conducted a retrospective cohort study including consecutive incident HHD patients from January 1996 to December 2011. All patients had HHD as their first renal replacement therapy or returned to HHD after kidney transplantation. A suboptimal start was defined by dialysis initiation either as an inpatient or with a central venous catheter. The primary outcome was time to first hospitalization, technique failure or death. Secondary outcomes included hospitalization rate, hospital days and determinants of suboptimal starts. Suboptimal starts were further categorized as unavoidable as adjudicated by two independent observers with pre-specified criteria.

**Results:** Among 95 incident HHD patients, 44 (46%) and 51 (54%) had optimal and suboptimal starts, respectively. A suboptimal start was associated with a shorter time to the primary outcome (log rank, P<0.001). In a multivariable Cox proportional hazards model, the hazard ratio for the composite outcome (comparing suboptimal to optimal starts) was 2.94 (95% CI: 1.49, 5.78; P=0.002). Suboptimal starts were further categorized as unavoidable as adjudicated by two independent observers with pre-specified criteria.

**Conclusions:** Suboptimal initiation of HHD is associated with adverse clinical events including early hospitalization. Given the high proportion of suboptimal starts in patients returning from transplantation, better incorporation of dialysis planning and renal replacement therapy education is warranted.

**Funding:** NIDDK Support

---

**FR-PO330**

The Magnitude of Phosphorus Mobilization during Dialysis in the Frequent Hemodialysis Network (FHN) Daily Trial Was Patient-Specific

**Authors:** John T. Daugirdas, Brett Larive, Thomas A. Deponent, Andreas Pietrzak, Tom Greene, Robert S. Lockridge, Juan Carlos Ayus, Michael V. Rocco, Glenn M. Chertow, J. Ken Leyboldt, Alp Akonur, Brent W. Miller, The FHN Trial Group.

**Background:** In the FHN Daily Trial we tracked 3 measures of phosphorus mobilization (M) to assess constancy of M status over time.

**Methods:** Monthly values of pre and postdialysis serum phosphorus (P) were used to compute the phosphorus reduction ratio (PRR), PRR/URR (U = urea) and Km, the intercompartment clearance of P from a theoretical very large remote compartment (Agar et al, CJASN 2011). Low PRR or PRR/URR and high Km correspond to high M status.

**Results:** Baseline PRR (%), PRR/URR (ratio), and logKm (ml/min) were 57.9 ± 9.8, 0.79 ± 0.13, and 4.56 ± 0.41. In baseline multivariate models, lower predialysis serum P (preP), male sex, younger age, and greater weight independently associated with higher M. Higher serum P associated with higher M (PPR/URR and Km) but here the effect size was small. In high or low M patient subgroups identified at baseline, preP-adjusted M indices were tracked over 12 months. Mean values (3x: n=120; 6x: n=125) are shown in the Table.

**Conclusions:** The original estimated treatment effects of frequent HD on mortality were attenuated by Bayesian analysis, illustrating that large estimates of treatment effects in trials with low power may overstate the true effects. Even so, in the Daily Trial posterior probabilities that HR < 0.8 are > 0.80, suggesting that daily dialysis is reasonably likely to substantially reduce mortality. As implemented by the FHN, frequent nocturnal dialysis is unlikely to substantially reduce, and might increase, mortality compared to conventional home dialysis.

**Funding:** NIDDK Support

---

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

Underline represents presenting author/disclosure.
FR-PO331

Short Delayed Hemodialysis Is Associated with Lower Serum Hepcidin Levels When Compared to Conventional Hemodialysis

Joshua Zaritsky, Anjay Rastogi, George E. Fischmann, Jieshi Yan, Barbara Gales, Tomas Ganz, Mark E. Westerman, Isidro B. Salusky.

Background: Hepcidin, a key regulator of iron homeostasis, may be the molecular link between inflammation and anemia in ESRD. Short delayed hemodialysis (DHD) patients (pts) typically require less recombinant erythropoietin (EPO) than conventional hemodialysis (CHD) pts. Therefore, we compared serum hepcidin levels between the two dialytic modalities.

Methods: We compared serum hepcidin levels, indicators of anemia, inflammation and iron status between 24 pts treated with DHD using the NxStage System One® and 54 CHD pts (Table). Serum hepcidin levels were measured by competitive ELISA.

Results: DHD pts were younger but there were no differences in the duration of ESRD. In DHD pts, hepcidin levels were lower than in CHD pts, which corresponded to less inflammation (as assessed by high sensitivity C-reactive protein (hs-CRP)). Hepcidin levels post-DHD were lower than pre-DHD (Figure). We previously reported hepcidin was independently predicted by ferritin and hs-CRP in CHD pts by both univariate and multivariate regression analyses (MVA). In DHD pts, hepcidin levels correlated with ferritin (r=0.7, p<0.001) and hs-CRP (r=0.4, p=0.05). MVA (R²=0.6) revealed that hepcidin was independently predicted by only ferritin (p=0.001). Additionally, MVA (R²=0.6) across both groups revealed that hepcidin remained predicted by ferritin (p=0.001) and hs-CRP.

Conclusions: We demonstrated that lower hepcidin values in DHD pts predominantly reflect a lower inflammatory state in this population. Since hepcidin appears to be cleared by DHD, future studies are needed to see if increased dialysis dosages could potentially lower serum hepcidin levels further and in turn decrease EPO requirements.

Funding: NIDDK Support, Private Foundation Support

FR-PO332

Evaluation of Change in Extracellular Fluid Status Using Calf Bioimpedance in Patients during One Year Frequent Hemodialysis


Background: Calf extracellular resistance (RE) reflects both plasma (RP) and interstitial (RInt) fluid. The aim of this study was to investigate whether: 1) calf normalized resistivity (CNR) satisfies the indications change in fluid status in frequent HD (FHD) patients, 2) the extent to which RE is affected by RP at different levels of fluid status.

Methods: Patients were switched from 3 to 6 times/week HD, RE and extracellular fluid (ECV) was measured at baseline (BL) and monthly over one year using the Hydrad 4200. Four electrodes and a blood pressure cuff were placed on the calf to separately measure RE and RInt at zero cuff pressure and at > systolic blood pressure (SBP) respectively. Change in calf resistance was related to reduction of local plasma volume (VP) (Fig. 1).

Results: In nine available patients’ body weight decreased significantly by the first month and then did not differ statistically in following months; SBP decreased continuously and CNR increased significantly from BL to the first month and remained approximately at the same level over one year (Fig 2). VP/ECV did not differ significantly between BL and at any month over the one year period (Table 1).

Conclusions: Significant improvement in extracellular volume fluid status in patients during one year of FHD was clearly indicated by CNR increase and SBP and ultrafiltration volume reduction. CNR was not affected by plasma volume changes at different levels of fluid load.

FR-PO333

Patient Survival, Treatment Survival and Hospitalization for Intensive Home Hemodialysis Patients Compared to Kidney Transplant Recipients

Karthik K. Tennankore, Joseph Kim, Christopher T. Chan.

Background: Patients receiving intensive home hemodialysis (IHHD, ≥16 hours/week) have comparable survival to US deceased donor kidney transplant recipients (KTRs). A comparison between Canadian IHHD patients and KTRs has not been conducted. We hypothesized that IHHD patients would have better outcomes compared to expanded criteria donor (ECD) and standard criteria donor (SCD) recipients.

Methods: We analyzed a cohort of IHHD patients and KTRs from 2000-2011. The primary outcomes were time to first hospitalization and time to treatment failure/death for IHHD patients compared to ECD, SCD and living donor (LD) KTRs. Treatment failure was defined as a permanent switch to an alternative form of dialysis for IHHD patients, and graft failure for KTRs.

Results: The cohort consisted of 173 IHHD patients, 204 ECD, 643 SCD and 679 LD KTRs. There were 1036 first hospitalizations and 286 treatment failures/deaths (Figure 1). After adjusting for comorbidity, age, gender, race, cause of end-stage renal disease and dialysis vintage, hospitalization risk favoured IHHD in the short term and transplantation in the long term. Time to treatment failure/death was shorter for IHHD patients. Table 1. Adjusted HRs for time to first hospitalization and time to treatment failure/death.

Conclusions: IHHD is associated with a lower risk of short-term hospitalization compared to transplantation. Outcome-risk in the long term favors transplantation.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>ECD (95% CI)</th>
<th>SCD (95% CI)</th>
<th>IHHD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to First Hospitalization</td>
<td>1.14 (0.86-1.50)</td>
<td>1.07 (0.86-1.50)</td>
<td>1.14 (0.86-1.50)</td>
</tr>
<tr>
<td>Time to Treatment Failure/Death</td>
<td>1.07 (0.75-1.50)</td>
<td>1.14 (0.86-1.50)</td>
<td>1.14 (0.86-1.50)</td>
</tr>
</tbody>
</table>

Key: IHHD = Intensive Home Hemodialysis; ECD = Expanded Criteria Donor; SCD = Standard Criteria Donor; KTR = Kidney Transplant Recipient.

Poster/Friday
FR-PO334

Staphylococcus aureus Bacteremia: Evaluation of Access Techniques in Home Haemodialysis
Renal Dept, Morriston Hospital, Swansea, Wales, United Kingdom.

Background: Vascular access-related Staphylococcus aureus bacteremia is a major cause of morbidity and mortality amongst haemodialysis patients. Recent studies have reported an increased risk of fatal infective metastatic complications with home haemodialysis patients using buttonhole cannulation.

Methods: Microbiologically reported cases of MRSA/ MSSA bacteremia were analysed in a retrospective cohort study at a renal tertiary referral centre over a 2-year period (January 2011 - December 2012).

Results: 26 episodes of MRSA/ MSSA bacteremia were identified from a population of 317 dialysis patients. Risk factors included vascular access type (VasCath vs. AVF), immunosuppression, diabetes and warfarin use. UK Renal Association Guidelines recommend that the annual Staphylococcus aureus bacteremia rate in the haemodialysis population should be less than 2.5 episodes per 100 HD patients and less than 1.0 for MRSA over 2 years. At our unit 0.55 episodes per 100 HD patients were identified for MSSA (3.19 including acute kidney injury) and 1.06 (2.66) for MRSA. This was in comparison to 12 episodes of MSSA in home HD patients and 8.11 in self-care. 61% of Staphylococcus aureus bacteremias were directly attributable to vascular access complications (infected AVF/ AVG, line sepsis, post- fistula formation). Clinical outcomes of blood culture positive Staphylococcus aureus bacteremia included death < 30 days, infective endocarditis and microbiologic recurrence.

Conclusions: This study highlights known concerns regarding increased infection rates in patients who self-cannulate using the buttonhole technique. As a result of this study, our centre has commenced the use of topical mupirocin in order to reduce the occurrence of MRSA/MSSA sepsis and therefore promote prolonged patency and AVF survival. The development of mupirocin resistance is being monitored. Further randomised controlled trials would assist in the evaluation of constant vs. different site cannulation in order to establish a superior technique and accurately inform the prevalent haemodialysis population.

FR-PO335

At-Home Short Daily Hemodialysis Attenuate Vascular Calcification
Hiromichi Suzuki, Hirokazu Okada, Tsutomu Inoue, Tsuneo Takanaka. Dept of Nephrology, Saitama Medical Univ, Iruma Gun, Saitama, Japan.

Background: Vascular calcification (VC) has a significant effect in cardiovascular disease on dialysis patients. However no pharmacological interventions have been demonstrated for prevention and/or attenuation of VC. Recent advances in frequent hemodialysis proves facilitation of hyperphosphatemia. It is proposed that there is a strong relation between VC and hyperphosphatemia. It is therefore likely that frequent hemodialysis reduced VC. Aim To examine whether at-home short dial dialysis hemodialysis reduces VC.

Methods: Using Volume Viewer software with a 16-detector CT scan, the total calcification volume of the aorta was calculated with a cut-off of 130 Hounsfield Unit. Abdominal CT scan was taken before and 2 years after the start of at-home short daily hemodialysis in 37 patients (average age 52 ± 7.0 years, male 33). The underlying kidney disease were chronic glomerulonephritis (33), diabetic nephropathy (2) and congenital kidney disease (2).

Results: The base line values of calcification scores of the abdominal aorta were 5.03 ± 5.85 (cm³) and at-home short daily hemodialysis reduced to 4.82 ± 4.72 at the end of the study. Besides, at-home short daily hemodialysis attenuated several factors contributing to vascular calcification including hyperphosphatemia.

Conclusions: This is the first demonstration that at-home short daily hemodialysis reduces calcification of the abdominal aorta through several factors including serum levels of phosphate.

Funding: Pharmaceutical Company Support - Baxter 2010 Renal Discovery Grant

FR-PO336

Removal Water from the Legs Does Not Explain Hypotension in Short Daily Hemodialysis
Alessandra Martins Bales, Luciana Loureiro Nardotto, Rafael Sanches Humel, Licia Costa Battaini, Bruno C. Silva, Rosa M.A. Moyzes, Manuel C. Castro, Rosilene M. Elias. HCFCMUSP.

Background: Previous studies on conventional hemodialysis (CHD) indicate that fluid loss during dialysis occurs from the legs. Whether the fluid loss from the legs is associated with hypotension symptoms in patients on short daily hemodialysis (SDH) is unknown.

Methods: Thirty-five conventional and fifteen short daily subjects on hemodialysis had segmental bioimpedance performed using the Inbody10 Analyzer, pre and post dialysis. Demographic and biochemical data was also obtained.

Results: Baseline characteristics were similar between CHD and SDH. For both groups, from pre to post dialysis, there was a reduction in the extracellular water (ICW) for each of the segments (leg, arm, and trunk), total body water (TBW), and ECW/TBW (p <0.05). The delta of legs ECW was higher on CHD than SDH [-5.4% (-7.3, -2.4) vs. -3.3% (-4.8, -0.7), p =0.009]. Hypotensive symptoms (Hypot+) were observed in 6 patients on SDH(37.5%) and 6 patients on CHD (17.1%). When comparing the subgroups of patients hypot+ and hypot-, the conventional group’s leg ECW/TBW was lower in hypot+ (p =0.003) as well as the hemoglobin (p =0.009). However, there was no difference between hypot+ and hypot- in these or any other parameters in SDH.

Conclusions: When comparing CHD and SDH, the removal of leg ECW was higher in CHD. Patients on CHD who had hypotension presented lower hemoglobin and lower ECW/TBW removal from the legs. This was not observed in SDH. Further studies are needed to better elucidate the hypotension pathogenesis on SDH, other than leg fluid removal.

FR-PO337

Health Related Quality of Life (HRQoL) in Community House Hemodialysis (CHHD) versus Home Hemodialysis (home HD)
Mark R. Marshall, 1 Sharen K. Supersad, 2 Renal Medicine, Counties Manukau DHB, Auckland, New Zealand; 2Renal Medicine, Northland DHB, Whangarei, New Zealand.

Background: CHHD is a novel way of increasing uptake of home HD for patients who have inadequate housing and/or other social circumstances. Community houses are staffed, and provided through a collaboration with a local patient support group. The houses provide pleasant and home-like settings. Patients share an HD machine with one other and organize their own rosters. Previously, we have shown comparable patient survival between CHHD vs. home HD (Marshall et al, AJKD. 2013;61:598-607). In this abstract, we explore whether HRQoL is also comparable.

Methods: All prevalent patients on CHHD or home HD in our service were invited to complete an anonymous KDQoL survey. This was done twice, firstly on 1/1/2007 and then on 1/1/2013. We compared HRQoL between CHHD vs. home HD patients, adjusting for mean vintage and age-and-albumin-adj usted Charlson comorbidity index (CCI, Bedhu et al, Am J Med 2008;106:609-13) as ecological variables.

Results: Results are presented as n, or means (SD). Data are pooled across era for analyses. The source population are those who received a survey, the study population those who returned it.

Funding: Government Support - Non-U.S.
FR-P0338
Procedure-Related Serious Adverse Events among Home Hemodialysis Patients—A Quality Assurance Perspective
Benc Wong, Deborah Lynn Zimmerman, Frances D. Reintjes, Mark J. Courtney, Scott Klarenbach, Graeme Dowling, Robert P. Pauly. Division of Nephrology and Transplant Immunology, University of Alberta, Edmonton, Canada. Division of Nephrology, University of Ottawa, Ottawa, Canada; Northern Alberta Renal Program, Alberta Health Services, Edmonton, Canada; Office of the Chief Medical Examiner, Edmonton, Canada.

Background: There has been reurgent interest in home hemodialysis (HD) in recent years, given the expected benefits and its excellent safety record. However, the potential for adverse events, including potentially catastrophic events, exists when patients are performing HD in their homes without supervision. There is a lack of literature on this important topic.

Methods: We present the experience of two adult home HD programs in Canada from 2001 to 2012, including a total of 190 patients and approximately 500 patient-years of treatments. We retrospectively reviewed all life-threatening adverse events occurring in our programs and examined our approach to patient training, re-training, and safety monitoring.

Results: We report 1 death and 6 potentially fatal adverse events yielding a crude rate of 0.060 events per 1,000 dialysis treatments. Six of 7 events involved significant blood loss (including 1 exsanguination); 5 of 7 events involved human error with lapses in protocol adherence; because such events are rare, evaluation of specific intervention strategies will require much longer follow-up.

Conclusions: Life-threatening adverse events in home HD are uncommon, but when they occur, should prompt review of home HD-related policies and procedures to make this therapy even safer.

FR-P0339
Cost Evaluation of In-Center Nocturnal Hemodialysis
Ben C. Wong, Robert P. Pauly, Mark J. Courtney, Scott Klarenbach. Division of Nephrology and Transplant Immunology, University of Alberta, Edmonton, Canada.

Background: There is interest in providing in-center nocturnal hemodialysis (ICNHD), typically conducted overnight (6-8 hours) thrice weekly. In addition to putative health benefits, this allows a dialysis unit to offer two additional shifts on alternate nights. We conducted a costing study to determine the incremental costs of ICNHD compared with in-center thrice-weekly conventional hemodialysis (CHD) from the health care perspective using data from our program that provides both ICNHD and CHD.

Methods: Using micro-costings methods, we identified health care resources that differ between INCHD and CHD, including staffing, dialysis materials, and utilities. The units of resource consumed for each strategy was determined, and the cost of each unit was determined from administrative data (CAN $ 2012) to determine incremental costs of ICNHD and CHD. Alternate scenarios examining nursing grade and ratio, full care (reference case being a 1:3 staff-to-patient ratio) vs. self-care (with attendant training costs), and differences in medication costs were examined.

Results: In the reference case, CHD was $54.89 less costly per dialysis treatment compared with ICNHD, with a difference of $856.82 per HD patient per year, with staffing costs accounting for >80% of the difference. Incremental annual costs for staffing, dialysis materials, and utilities were $7225.92, $1193.4, and $145.52, respectively. Fully independent ICNHD is approximately 50% more costly than HD, with an unplanned 1:20 HD nurse to patient ratio of 1.10; results in an incremental saving of $15,762.24 for ICNHD patients relative to CHD patients, including patient training costs of $7182 in the first year. If previously described reduction in medication use (erythropoiesis-stimulating agents, anti-hypertensives, phosphate binders) occurs, ICNHD is $5126.04 more costly than CHD.

Conclusions: Compared to CHD, provision of ICNHD is more expensive, largely driven by increased staffing costs. Alternate staffing models, including fully independent ICNHD, are more attractive. The incremental costs of ICNHD should be balanced with potential improvements in patient outcomes and employment, as well as capital costs associated with creating more CHD capacity if required.

FR-P0340
High Dose Home Hemodialysis and Conventional In-Center Hemodialysis: A Cost Utility Analysis
Frank Xiaojing Liu, Catrin Treharne, Bruce F. Culleton, Murat Arici, Lydia Lees, Baxter Healthcare Ltd., Compton, United Kingdom; Baxter Healthcare Corporation, Deerfield, IL; Abacus International, Oxfordshire, United Kingdom; Baxter Healthcare Ltd., Compton, United Kingdom.

Background: There has been resurgent interest in home hemodialysis (HD) in recent years, given the expected benefits and its excellent safety record. However, the potential for adverse events, including potentially catastrophic events, exists when patients are performing HD in their homes without supervision. There is a lack of literature on this important topic.

Methods: We present the experience of two adult home HD programs in Canada from 2001 to 2012, including a total of 190 patients and approximately 500 patient-years of treatments. We retrospectively reviewed all life-threatening adverse events occurring in our programs and examined our approach to patient training, re-training, and safety monitoring.

Results: We report 1 death and 6 potentially fatal adverse events yielding a crude rate of 0.060 events per 1,000 dialysis treatments. Six of 7 events involved significant blood loss (including 1 exsanguination); 5 of 7 events involved human error with lapses in protocol adherence; because such events are rare, evaluation of specific intervention strategies will require much longer follow-up.

Conclusions: Life-threatening adverse events in home HD are uncommon, but when they occur, should prompt review of home HD-related policies and procedures to make this therapy even safer.

FR-P0341
High Dose In-Center Haemodialysis and Conventional In-Center Haemodialysis: A Head-to-Head Cost-Effectiveness Analysis
Frank Xiaojing Liu, Catrin Treharne, Lydia Lees, Murat Arici, Bruce F. Culleton, Baxter Healthcare Corporation, Deerfield, IL; Abacus International, Oxfordshire, United Kingdom; Baxter Healthcare Ltd., Compton, United Kingdom.

Background: There has been resurgent interest in home hemodialysis (HD) in recent years, given the expected benefits and its excellent safety record. However, the potential for adverse events, including potentially catastrophic events, exists when patients are performing HD in their homes without supervision. There is a lack of literature on this important topic.

Methods: We present the experience of two adult home HD programs in Canada from 2001 to 2012, including a total of 190 patients and approximately 500 patient-years of treatments. We retrospectively reviewed all life-threatening adverse events occurring in our programs and examined our approach to patient training, re-training, and safety monitoring.

Results: We report 1 death and 6 potentially fatal adverse events yielding a crude rate of 0.060 events per 1,000 dialysis treatments. Six of 7 events involved significant blood loss (including 1 exsanguination); 5 of 7 events involved human error with lapses in protocol adherence; because such events are rare, evaluation of specific intervention strategies will require much longer follow-up.

Conclusions: Life-threatening adverse events in home HD are uncommon, but when they occur, should prompt review of home HD-related policies and procedures to make this therapy even safer.

FR-P0342
Effects of Randomization to Frequent In-Center Hemodialysis on Long-Term Mortality: Frequent Hemodialysis Daily Trial
Glenn M. Chertow, Nathan W. Levin, Gerald J. Beck, Paul W. Eagles, Tom Greene, Brett Larive, Marc V. Rocca, Alan S. Kliger, The FHN Trial Group, Stanford, Renal Research Institute, Cleveland Clinic; NIDDK, U Utah, Wake Forest, Yale.

Background: The FHN Daily randomized 245 subjects to “daily” (6 times per week) versus conventional (3 times per week) in-center hemodialysis (HD) for 1 year. Daily in-center HD resulted in favorable effects on the co-primary composite outcomes of death or change in left ventricular mass and death or change in self-reported physical health, and facilitated control of hypertension and hyperphosphatemia. We here describe effects on mortality over a mean follow-up of 3.7 years.

Methods: We obtained dates of deaths and transplants through July 2011 using linkage to the USRDS and queries to study centers. Long-term mortality was related to the initial randomized treatment assignment using Kaplan-Meier product limit estimates and Cox regression, without censoring transplants as the primary analysis.

Results: Most (90/100) surviving non-transplanted subjects randomized to daily HD reverted to 3 or 4 times per week HD within 2 months after the trial period. Numbers of deaths (all-cause, 3-year post-trial) among subjects randomized to the frequent and conventional groups, respectively, were 5 (0.041) and 10 (0.087) during the 1-year intervention period, 4 (0.034) and 6 (0.057) during the first year after the trial, and 12 (0.050) and 19 (0.089) subsequently. Overall, the relative hazard of mortality (daily versus conventional) was 0.54, 95% CI (0.32, 0.93), p=0.014; all censoring transplants the relative hazard was slightly attenuated: 0.60, 95% CI (0.34, 1.05), p=0.07.

Conclusions: The current results suggest that frequent in-center HD may reduce mortality long-term. Any benefits of frequent in-center HD must be balanced against potential risks including possible adverse effects on quality of life, increased burden and cost of therapy. These results should be interpreted cautiously, as most patients randomized to daily HD reverted to conventional HD after the 1-year intervention, and statistical power was limited by relatively few (56) deaths.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support.
The Impact of Home Haemodialysis on Facility-Based Growth and Total Program Costs in an Australian Dialysis Service

**Background:** In Australia, as elsewhere, the ever-rising dialysis population is placing increasing strain on an already stretched healthcare system. Yet, Australian home haemodialysis (HHD) has been shown to consume fewer resources, provide better patient outcomes and cost ~AUD $25,000/patient/year less than facility haemodialysis (FHD), which has been shown to consume fewer resources, provide better patient outcomes and cost ~AUD $25,000/patient/year less than facility haemodialysis (FHD). HHN patients are more likely to have attended a free healthcare system. In this study, the global program cost savings compared to the notional costs that would have accrued had all patients on HHN dialysis remained on FHD over the study period.

**Results:** Over the 12 years, the total HD population increased (69 to 138) but is predominantly accounted for by an increase in HHN (3 to 36). There was a relatively smaller proportional rise in HD (66 to 102). An increase in FHD was confined to the first 3 years (2000 to 2003) while the HHN program was being established. After 2003, FHD numbers have not altered significantly while HHN has continued to grow. Furthermore, the HHN program has saved AUD $6.33/mo patient compared to the global cost that would have accrued had all HHN patients been started on and stayed within the FHD program over the full 12 year period. The calculated savings is expressed as Agatston score and is measured at baseline and repeated after 1, 2 and 3 years of treatment. Apart from clinical characteristics and biochemistry, we will evaluate progression of albuminuria and serum creatinine.

**Conclusions:** Our HHN cohort now makes up 26.1% of our total HD population. Most HD program growth has been delivered by HHN since 2003. HHN has resulted in significantly lower healthcare costs while simultaneously maintaining a high quality of care.

**FR-PO343**

Is Progression of Arteriosclerosis in ESRD Patients Inhibited by Nocturnal Hemodialysis or Renal Transplantation? Baseline Results from the NOCTX Study

**Background:** Coronary artery calcification (CAC) is associated with cardiovascular mortality and mortality in patients with ESRD. Improvement of calcium-phosphate homeostasis and uremia by nocturnal HD or transplantation might favorably influence CAC compared to conventional HD and PD. The ultimate goal of this study is to assess whether nocturnal HD and transplantation are associated with less progression of CAC, compared with conventional HD and PD. Here we present our baseline data of CAC.

**Methods:** CAC score (CACS) will be measured with multislice CT of the heart in 4 different groups (4x40 pts): patients treated with conventional HD (3-4x/week, 3-4 hr), incident nocturnal HD (5-7x/week, 6-8 hr) and kidney transplantation after dialysis. CAC is expressed as Agatston score and is measured at baseline and repeated after 1, 2 and 3 years of treatment. Apart from clinical characteristics and biochemistry, we will evaluate inflammation markers and serum calcification inhibitors.

**Results:** So far, 93 patients underwent multi slice CT, mean age was 49.1±13.1 yr, 60.2% males. Mean duration of RRT (excluding periods with transplant) was 35.5±28.9 months. Two thirds of our patients had considerable coronary calcifications (31% CACS 0, 36% CACS 1-400, 32% CACS > 400). CACS was significantly higher in the Canadian as compared to the American Registry for Pregnancy in Dialysis Patients (ARDP). The primary outcome was the live birth rate.

**Conclusions:** We conclude pregnancy is safe and feasible in women with ESRD receiving intensive hemodialysis.

**FR-PO347**

Conversión a In-centre Nocturnal Hemodialysis Was Associated with Regression of Left Ventricular Mass

**Background:** There are limited prospective data on the cardiovascular effects of in-centre nocturnal hemodialysis (INHD), especially with the use of cardiac magnetic resonance (CMR), the current reference standard for evaluating cardiac effects of intensified dialysis schedules.

**Methods:** We conducted a prospective, 2-centre observational study of 67 prevalent patients randomized to NHD vs CHD. The predominant regimen actually used over 1 year. Despite the long duration of dialysis treatment there was no association between duration of dialysis and CACS. We confirm the relation of coronary calcification with age as mentioned in literature. The progression of calcification with the different treatment modalities will be followed up in the NOCTX study.

**Conclusions:** There is a significant coronary calcification in this Dutch cohort of patients treated with renal replacement therapy. Despite the long duration of dialysis treatment there was no association between duration of dialysis and CACS. We confirm the relation of coronary calcification with age as mentioned in literature. The progression of calcification with the different treatment modalities will be followed up in the NOCTX study.

**Funding:** Pharmaceutical Company Support - Novartis, Amgen, Baxter, Shire, Fresenius, Roche, Private Foundation Support

---

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

Underline represents presenting author/disclosure.
FR-PO348

Risk of Hospitalization with Home Daily Dialysis Using Slow Dialysate Flow Rates

Methods: We identified 2273 consecutive patients prescribed HD, (N=Stage SystemOne in US DaVita facilitates between Jan 2004 and Dec 2009. All patients received HD ≥5 days/week for ≥24 hours/day for at least 1 month. We matched 1942 of these HD patients by propensity scores to 5103 contemporaneous patients receiving home PD registered in the USRDS. Hospitalizations, deaths, transplants, and losses to follow-up for both groups were ascertained from the USRDS. Hospitalizations were categorized using the same definitions as in the USRDS 2012 data report. We used an Andersen-Gill model to compare hospitalization rates due to the composite of the pre-specified diagnostic categories of: cardiovascular, infectious, access-related, or bleeding.

Results: After matching, between-group standardized differences for all baseline characteristics were <10%. Mean age was 51 years, 32% were male, 73% were white, and 27% had diabetes. Arteriovenous fistulae were present in 64% of DHD patients. During 11,949 patient-years, 3952/7045 patients had 11,972 hospitalizations. The composite hospitalization rate was significantly lower for patients receiving DHD than those receiving PD (DHD: 0.69/patient-year; PD: 1.09/patient-year; HR 0.65 (95% CI 0.58-0.74); p < 0.001). The number of days spent in hospital per patient-year was 4.1 with HD and 7.5 with PD (p < 0.001). Overall, 61% of DHD vs. 37% of PD patients remained admission-free for the pre-specified diagnoses (p < 0.001). Analyses of secondary outcome yielded similar results.

Conclusions: Compared to PD, DHD was associated with fewer admissions and days spent in hospital. These results may have implications for those considering home-based renal replacement therapy options.

FR-PO349

Hemodynamic Profile of Patients with Left Ventricular Assist Device during Hemodialysis

Methods: Patients with HeartMate II LVAD received 182 intermittent HD treatments. The following parameters were retrospectively evaluated: vital signs, ultrafiltrate (UF) removal, HD duration, symptoms, adverse events and interventions during each HD session. Hemodynamically significant events were defined as systolic blood pressure (SBP, mmHg) < 80, lowest SBP > 80 with a drop > 20 mmHg from baseline, or inability to register a blood pressure using regular sphygmomanometer due to LVAD-induced reduction in pulse pressure.

Results: Of the 26 patients, HCO3 was 32 mmol/L in 24 patients, 34 and 36 mmol/L in two. A-B values were excluded. The primary outcomes were all-cause mortality and renal recovery 1 year after starting RRT. The de-identified database was analyzed using univariate and multivariate analyses. Only 4% were both alive and requiring RRT at 1 year. In multivariate analysis, older age, heart failure, lower preoperative creatinine, longer interval between cardiac surgery and RRT start, mechanical ventilation and intra-aortic balloon pump use were independently associated with increased 1-year mortality, whereas vasopressor and extracorporeal membrane oxygenation use were independently associated with renal non-recovery within 1 year.

Conclusions: Mortality is high for patients requiring RRT after cardiac surgery, but few survivors require long-term dialysis. An unexpected mortality risk factor was lower preoperative creatinine. This may reflect greater injury among patients with lower preoperative creatinines who require RRT.

FR-PO350

Abstract Withdrawn

FR-PO351

Outcomes and Prognostic Factors for Patients Requiring Dialysis after Cardiac Surgery

Background: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) may occur after cardiac surgery and is a risk factor for postoperative mortality. Long-term outcomes, particularly beyond hospital discharge, and their prognostic factors, have not been well studied.

Methods: This is a retrospective study of all adult patients requiring RRT for AKI within 30 days after cardiac surgery between Jan 2007 and Dec 2011. Patients receiving RRT preoperatively and patients receiving ventricular assist devices or cardiac transplants were excluded. The primary outcomes were all-cause mortality and renal recovery 1 year after starting RRT. We defined renal recovery as remaining alive and free of dialysis for 14 days. Outcomes were presented using Kaplan-Meier plots. Multivariate Cox proportional hazard analysis was used to assess factors associated with outcomes.

Results: 202 patients met the inclusion criteria. Of these, 39% recovered renal function within 1 year and 36% survived for 1 year after starting RRT.

FR-PO352

Acid-Base (A-B) Changes in Acute Kidney Injury (AKI) Patients with Hypercapnic Respiratory Failure Treated with 24-Hour (h) Sustained Low Efficiency Dialysis (SLED) with Regional Citrate Anticoagulation (RCA)

Background: Previous studies showed that hemodialysis induces transient Pco2 elevation in ESRD patients, returning to baseline post therapy. Metabolic acidosis and alkalosis have been reported with RCA. Studies of A-B changes in patients with respiratory and metabolic acidosis on mechanical ventilation and 24-h SLED-RCA are lacking.

Methods: We conducted a retrospective chart review of 268 AKI patients on CRT between Nov. 2009 and Oct. 2012. 32 had respiratory and metabolic acidosis. 26 had complete ABG data for over 72/h while on 24 h SLED-RCA with Qb 60ml/min, Qd 400 ml/min and Rxed 125X filter. Dialyse K was 4 mmol/L, Na was 140-142 mmol/L in all 26 patients, HCO3 was 32 mmol/L in 24 patients, 34 and 36 mmol/L in two. A-B parameters were collected at time(t)=0, 24, 48 and 72±6 h on SLED-RCA. Pairwise comparison between any two time points was performed using paired t test. P-value <0.05 was considered statistically significant.

Results: Mean age 49.8±17.13 years, 50% male, mean serum creatinine at t=0-h: 4.18±2.16 mg/dL. A-B parameters pre/post SLED-RCA are shown in table.

Conclusions: Fixed dialysate bicarbonate delivery with SLED-RCA reduced or did not worsen pCO2; meanwhile it efficiently corrected high anion gap metabolic acidosis while approximating a normal serum bicarbonate concentration.
FR-PO353
Factors Associated with Dose of Intermittent Hemodialysis in Acute Kidney Injury
Gunayumol Thammarong, Pongsathorn Gojaseni, Kolasorn Pakchotanon. Medicine, Phubolphol Adulyadej Hospital, Bangkok, Thailand.

Background: KDOQI guideline recommends delivering a Kt/V of 3.9 per week when using intermittent RRT in acute kidney injury. In Thailand, however, adequacy of hemodialysis in AKI patients is not routinely monitored. The aim of this study, therefore, was to assess the prescribed and delivered Kt/V and its associated factors in AKI patients undergoing intermittent hemodialysis.

Methods: A cross-sectional study was performed in Phubolphol Adulyadej hospital, directorate of medical services, Royal Thai Air Force during January 2012 to January 2013. Prescribed Kt/V was calculated from in vitro dialyzer clearance and actual body weight while delivered Kt/V was calculated using natural logarithm formula. Patient clinical data and dialysis prescription were analyzed to determine their association with dialysis adequacy.

Results: Fifty-two AKI patients, who collectively underwent 248 dialysis treatments, were studied prospectively. Mean (+ SD) age was 69.4 ± 16.9; 50% were male. At dialysis initiation, APACHE II score was 20.6 ± 6.2 and SOFA score 8.2 ± 3.6. Mean session length was 3.54 ± 0.81 h, and 78.9% used a femoral venous catheter. The results showed that the mean prescribed and delivered Kt/V were 1.28 ± 0.51 and 1.20 ± 0.58 respectively. Thirty-nine percent of the prescriptions were for a Kt/V less than 1.2 while 55.6% of treatments delivered a Kt/V less than 1.2. The independent determinants of adequate Kt/V (≥ 1.2) in a multiple logistic regression model were: blood flow rate ≥ 250 ml/min (odds ratio (OR) = 3.87, 95% confidence intervals (CI): 2.04-7.31), dialysis time ≥ 180 min (OR = 3.01, 95% CI: 1.03-8.81), female gender (OR = 2.80, 95% CI: 1.50-5.21), heparin used (OR = 2.45, 95% CI: 1.11-5.33) and actual body weight < 65 kg (OR = 2.38, 95% CI: 1.18-4.80).

Conclusions: More than half of patients with AKI are received an inadequate dose of dialysis. Barriers to adequate dose delivery were patient size, gender and inadequate dialysis prescription, i.e., blood flow rate, dialysis time and anticoagulant.

Funding: Government Support - Non-U.S.

FR-PO354
Inflammatory Cytokine Reductions with Sustained Low Efficiency Online Hemodiafiltration (Online SLED-f) Using High Cut-Off Dialyzer versus High-Flux Dialyzer in Sepsis-Related Acute Kidney Injury Patients
Khajohn Tiranathanagul, Jeeraluk Tunpornchai, Nattachai Srisawat, Wiwat Khajohn Tiranathanagul, Jeeraluk Tunpornchai, Nattachai Srisawat, Wiwat Chancharoenthana, Asada Leelavihanichkul, Kearsiad Pritapornsilp, Somchai Eiam-ong. Dept of Nephrology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn Univ, Thailand.

Background: Hypercytokinemia plays a central role in the pathogenesis and is related to the high mortality in sepsis-related acute kidney injury (S-AKI). The reductions of these cytokines have been reported to improve clinical outcomes. Sustained low efficiency online hemodiafiltration (online SLED-f) using high cut-off (HF) dialyzer could remove some inflammatory cytokines. Interestingly, the potential of enhancing cytokine removal by using newly designed high cut-off (HCO) dialyzer that could theoretically remove larger solutes has never been studied in SLED-f before.

Methods: This prospective randomized trial was conducted in 15 S-AKI patients to compare the efficacy of cytokine removal including IL-6, IL-8, IL-10, TNF-α, and VEGF by six-hour SLED-f between using HCO dialyzer (HCO-SLED-f>8) and HF dialyzer (HF-SLED-f≤7). The clinical parameters as well as the adverse effects including albumin loss were observed and compared.

Results: HCO-SLED-f provided significantly IL-8 and TNF-α reduction (p=0.012 for both) after treatment whereas HF-SLED-f could only demonstrate significantly TNF-α reduction (p=0.018). However, the degree of all cytokine reductions did not show significant difference between both treatment groups. There were significantly higher total albumin losses in effluent fluid in HCO-SLED-f group than HF-SLED-f group [4.72±(range 3.5-5.8) vs. 0.0(0.11) gram, p=0.010]. However, the percentage of plasma albumin reduction was not different between both groups (p=0.418). There were no significant differences in intra-dialytic blood pressure parameters during both puriﬁers.

Conclusions: In S-AKI, HCO-SLED-f could be safely applied and could reduce more types of cytokines when compared with traditional HF-SLED-f despite the degree of reduction did not signiﬁcantly diﬀerent. However, the higher degree of albumin loss should be considered when using HCO-SLED-f.

FR-PO355
Sustained Low Efficiency Dialysis (SLED) versus Continuous Renal Replacement Therapy (CRRT) for AKI in Critically Ill Patients
Abhijit Kitchlu, Karen E.A. Burns, John C. Friedman, David Klein, Robert M. Richardson, Neill Adhikari, Ron Wald. 1Div of Nephrology, U. of Toronto, Toronto, Canada.

Background: SLED, which reflects the use of conventional dialysis technology over an extended time, is increasingly used as a renal replacement modality in critically ill patients with AKI and hemodynamic instability. SLED may reduce the hemodynamic perturbations of HD, while obviating the resource demands of CRRT. Although SLED is being increasingly used in using non-cuffed ICU, few studies have evaluated its impact on clinical outcomes.

Methods: We conducted a cohort study comparing SLED (target 8 h/session, Qb 200 mL/min) to CRRT in four ICUs at an academic medical centre. The primary outcome was mortality 30 days after RRT initiation, adjusted for demographics, comorbidity, baseline kidney function, and Sequential Organ Failure Assessment (SOFA) score. Secondary outcomes were RRT dependence at 30 days and early clinical deterioration, defined as death or higher SOFA score at 48 h.

Results: We identified 158 patients who initiated treatment with CRRT and 74 with SLED. Mortality at 30 days was 54% and 61% among SLED- and CRRT-treated patients, respectively [adjusted odds ratio (OR) 1.07, 95% CI 0.56–2.03, as compared with CRRT]. RRT dependence at 30 days (adjusted OR 1.36, 95% CI 0.51–3.57) and early clinical deterioration (adjusted OR 0.73, 95% CI 0.40–1.34) were similar between groups.

Table 1: Baseline data

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRRT</th>
<th>SLED</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at RRT initiation (mean±SD)</td>
<td>62±17.2</td>
<td>62±17.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Pre-morbid creatinine (mean±SD)</td>
<td>130.6±91.7</td>
<td>135.3±83.8</td>
<td>0.57</td>
</tr>
<tr>
<td>Age at RRT initiation (median (IQR))</td>
<td>62</td>
<td>64</td>
<td>0.69</td>
</tr>
<tr>
<td>Pre-morbid creatinine (median (IQR))</td>
<td>130</td>
<td>130</td>
<td>0.94</td>
</tr>
<tr>
<td>Hemodiafiltration (yes/no)</td>
<td>76/4</td>
<td>47/27</td>
<td>0.001</td>
</tr>
<tr>
<td>Posterior colonic (yes/no)</td>
<td>28/40</td>
<td>16/38</td>
<td>0.62</td>
</tr>
<tr>
<td>Time mosaic on day of RRT initiation, min. (median (IQR))</td>
<td>24</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Time mosaic on day of RRT initiation, min. (median (IQR))</td>
<td>24</td>
<td>10</td>
<td>25</td>
</tr>
</tbody>
</table>

Conclusions: Notwithstanding the limitations of this small non-randomized study, our findings support similar clinical outcomes for patients treated with SLED vs CRRT. In hemodynamically unstable patients with AKI, trials to establish the non-inferiority of SLED are needed.

FR-PO356
Calcium Replacement Using Post Filter Replacement Fluid during Continuous Renal Replacement Therapy with Citrate Anticoagulation
Nithin Karakala, John M. Arthur, Ashita J. Tolwani. 1Medicine, Nephrology, Medical Univ of South Carolina, Charleston, SC; 2Medicine, Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Continuous Renal Replacement Therapy (CRRT) is the choice of dialysis modality in hemodynamically unstable patients with Acute Kidney Injury (AKI). Anticoagulation is required to prevent filter clotting and is done by using regional citrate anticoagulation or systemic heparin. The recent national calcium shortage has caused major problems in using citrate anticoagulation protocols.

Methods: This is a retrospective analysis of data from 4 patients. Gambio Prismaflex machines, with HF 1000 filter sets were used. Commercially available PrismaSof BGK 4:2.5 (potassium 4 meq/L and calcium 2.5 meq/L) was used as replacement fluid. Acid Citrate Dextrose A(ACDA)/was used as an anticoagulant. Calcium gluconate (6 grams in 250 ml of 0.9% normal saline) was used if the patients ionized calcium was less than 1 mmol/L.

Results: Patients were on CRRT for an average of 64.7 days, for a total of 24 days. During this period 4 filters clotted. The calculated Kaplan Meier Curve for time to filter clotting was 46 hours. The average delivered dose of dialysis was 39.66± 9.45 ml/kg/hr. The average systemic ionized calcium was 1.06±0.07 mmol/L. Calcium gluconate drip was needed in for a combined 13 days during this period with an average rate of 6.4±2.35 ml/hr.

Time to Filter clotting
Kaplan Meier Curve

Conclusions: Use of calcium containing post filter replacement fluid decreased the need for systemic calcium replacement during CRRT treatment. The above described protocol improved the filter patency and the delivered dose in patients who were not suitable for heparin anticoagulation and had filter clotting problem and maintained systemic calcium greater than 1 mmol/L.

FR-PO357
A Continuous Venous-Venous Hemofiltration Protocol with Anticoagulant Citrate Dextrose Formula A and a Calcium-Containing Replacement Fluid: An Easy Remedy for the National Calcium Shortage*

Background: Regional citrate anticoagulation (RCA) is used as an anticoagulant for continuous renal replacement therapy (CRRT). A systemic calcium (Ca++) infusion is required to replace the Ca++ lost in the effluent. The U.S. shortage of intravenous Ca++ has limited the use of RCA. We describe a continuous venovenous hemofiltration (CVVH)

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

445A
protocol with RCA using 2.2% anticoagulant citrate-dextrose A (ACD-A) and a commercially available dialysate containing Ca 2+ 3.0 meq/L, HCO 3- 35 meq/L and K+ 4 mmol/L (GFP-3019) as post-filter replacement fluid (RF), without need for Ca 2+ infusion.

Methods: We prospectively evaluated 5 patients on CRRT who had at least 3 episodes of clotting of the filter within 24 hours. Patients were switched to CVVH using ACD-A infused pre-blood pump with the Prismaflex device and titrated to achieve a post-filter ionized calcium (iCa 2+) level <0.5 mmol/L. The Ca 2+–containing dialysate was delivered as post-filter RS at rate 3.0 L/hr and titrated to maintain systemic ic a 2+ levels between 0.9–1.3 mmol/L.

Results: Mean age was 57±14 years and mean APACHE II score was 33±3.2. Study baseline mean serum chemistries were: Na+: 140±2.1 meq/L (range 136–145), K+: 4.2±0.4 meq/L, p: 7.2±0.07 (range 7.26–7.55), CO2: 47±9.8 (range 35–76), total Ca 2+: 8.08±1.09 mg/dL (range 6.6–10.8). Post-filter iCa 2+ ranged 0.27–0.63 mmol/L, and patient iCa 2+ ranged 0.81–1.24 mmol/L. Mean post-filter RS rate: 308±164 mL/min (range 3000–3600), mean ACD-A rate: 298±21 mL/hr (range 250–350). Mean blood flow rate: 200±17 mL/min (range 170–250), mean filtration fraction: 37±0.04% (range 28–48). Mean effluent flow rate: 38.6±6.7 mL/kg/hr (range 28.7–55.8). Median filter survival was 24.5 hrs (95% CI. 16.4–67.3).

Conclusions: CVVH using ACD-A and a Ca 2+–containing RF without a continuous Ca 2+ infusion was safely and effectively used. Due to the high HCO 3-, CO2, total Ca 2+, and Ca 2+–containing dialysate delivery, post-filter RS at rate 3.0 L/hr and titrated to maintain systemic Ca 2+ levels between 0.9–1.3 mmol/L was much improved.

FR-PO358

Relations of Volume Parameters in Continuous Renal Replacement Therapy

Harin Rhee,2 Ihm Soo Kwak,1 Eun Young Seong.1 Harin Rhee,1 Min Ji Shin,1 Byeong Yun Yang,1 Il Young Kim,2 Dong Won Lee,2 1Dept of Internal Medicine, Dept of Internal Medicine, Div of Nephrology, Medical School Hannover, Germany.

Background: In critically ill patients, acute kidney injury (AKI) is common and these patients often suffer from fluid overload. Once kidney failure occurs, renal replacement is initiated for volume overload, in this setting, successful volume management depends on an accurate assessment of fluid status. We investigated the relationship of volume parameters in AKI patients with continuous renal replacement therapy (CRRT).

Methods: Sixty AKI patients with CRRT ≥48 hours were enrolled. Volume status was determined by measuring central venous pressure (CVP), cardiac output ratio (C/O), and chest x-ray. We drew conclusions from these parameters and compared them with CRRT survival.

Results: Mean CVP, C/O and chest x-ray were 8.9±4.6 mmHg, 5.5±10.8, and 0.412±0.015. Mean IVCd and IVCci were 1.71±0.27 cm and 37.9±11.5%. Mean IVCci was significantly different between the two groups (treatment group 37.9±11.5 vs 25.2±18.1, p=0.036) was significantly different between the two groups. A significantly different in pre- and post-dialysis plasma AA levels was found.

Conclusions: This study is to evaluate the efficacy of rTM treatment to critically ill patients with septic shock requiring continuous renal replacement therapy (CRRT) and to compare with the control group. In critically ill patients with septic shock requiring CRRT, treatment with recombinant thrombomodulin may improve patients’ severity and coagulation disorders.

FR-PO360

Recombinant Human Soluble Thrombomodulin Administration Improves Septic Shock Requiring Continuous Renal Replacement Therapy: A Retrospective Cohort Study

Naoki Kurashima,1 Atsushi Ohkubo,1 Naofumi Yui,2 Tatemitsu Rai.2 1Dept of Clinical Engineering, Tokyo Medical and Dental Univ, Japan; 2Dept of Nephrology, Tokyo Medical and Dental Univ.

Background: Recombinant thrombomodulin (rTM) has emerged as a new treatment option for disseminated intravascular coagulation (DIC). In addition to its anticoagulant properties, rTM is considered to produce direct anti-inflammatory effect. The purpose of this study is to evaluate the efficacy of rTM treatment to critically ill patients with septic shock requiring continuous renal replacement therapy (CRRT).

Methods: A retrospective analysis of patients admitted to the intensive care unit of our hospital between June 2009 and April 2013 was performed. Patients diagnosed as septic shock requiring transitory CRRT were included. They were either treated with rTM (treatment group) or without rTM (control group) during CRRT. The primary outcome was decrease in DIC score on day 3 after initiation of CRRT. Secondary outcomes were changes in the severity of patients’ conditions on day 3 as assessed by Acute Physiologic and Chronic Health Evaluation II (APACHE II) score and the period of time required for withdrawal from CRRT. Data were expressed as group mean ± standard deviations. The Mann–Whitney test was used for comparison and a p value under 0.05 was considered statistically significant.

Results: Six and nine patients were assigned to the treatment and control groups, respectively. Baseline characteristics, including DIC and APACHE II score, showed no significant differences between the two groups. A significant decrease in the DIC score was seen in the treatment group compared with that in the control group (1.1±1.1 vs 1.4±2.1, respectively, p = 0.0184). Decrease in APACHE II score also showed significant improvement (treatment group 9.8±2.9 vs control group 4.0±5.8, p = 0.0339). The period until CRRT withdrawal was not significantly different between the two groups (treatment group 4.5±1.8 days vs control group 6.8±3.1 days, p = 0.1407).

Conclusions: In critically ill patients with septic shock requiring CRRT, treatment with recombinant thrombomodulin may improve patients’ severity and coagulation disorders.

Funding: Government Support - Non-U.S.
FR-PO361
Calcium and Phosphate Replacement during Continuous Renal Replacement Therapy with Regional Citrate Anticoagulation Predict Mortality in Critically Ill Patients

Wee Kim Fong,1 Markos George Kashioris,2 Venu Velagapudi,3 Abbasali Akhoundi,2 Kianoush Banaei-Kashani.1
1Anesthesiology, Mayo Clinic, Rochester, MN; 2Nephrology, Massachusetts General Hospital, Boston, MA; 3Critical Care, Massachusetts General Hospital, Boston, MA.

Background: During the recovery phase, the regenerating cells consume phosphorus for cell cycle and growth. Therefore increase phosphorus requirement during CRRT may be in proportion to critical illness recovery. On the other hand, increased calcium replacement requirement could indicate cell lysis. We hypothesized that the dosing of calcium and phosphate replacement during CRRT treatment, predicts hospital mortality.

Methods: We conducted a retrospective cohort study in eight intensive care units of a tertiary academic center in the United States. We collected demographic and laboratory data and constructed a database of critically ill patients who required CRRT with regional citrate anticoagulation, from December 2007 to January 2009. We performed logistic regression analysis to predict mortality, based on the amount of hourly calcium and phosphate replacement dose. We adjusted for severity of illness with the APACHE III score and comorbidities using the Charlson index score, independent of delivered dose of CRRT.

Results: We enrolled 595 patients into the study. The ICU and hospital mortality were 39.7% and 50.9%, respectively. The average APACHE III and Charlson score were 118 (95% CI 112.5 – 117) and 3.6 (95% CI 2.8 – 3.2), respectively. The median calcium and phosphorus replacement dose was 0.94 gr/h of CRRT (IQR 0.79 – 1.05) and 1.25 mmol/h of CRRT (IQR 1.08 – 1.8), respectively. In multivariate analysis, each additional incremental unit of the following was significantly associated with differential odds of death: APACHE III OR 1.014 (95% CI 1.007 – 1.02, p<0.01), calcium replacement dose OR 3.0 (95% CI 1.26 – 7.13, p<0.01) and phosphate replacement dose OR 0.67 (95% CI 0.52 – 0.86, p<0.01).

Conclusions: Increased calcium replacement and decreased phosphate replacement requirements during CRRT, were associated with increased mortality even after accounting for severity of illness and comorbid conditions.

Funding: Clinical Revenue Support

FR-PO362
Perspectives of Continuous Renal Replacement Therapy: A Paired Survey Study of Patients, Physicians, and Nurses

Andrew Allegretti,1 Gregory L. Hundemer,1 Katherine M. Cosgrove,1 Ednan Bajwa,3 Ishir Bhan.2
1Anesthesiology, Mayo Clinic, Rochester, MN; 2Pulmonary and Critical Care Div, Mayo Clinic, Rochester, MN; 3Critical Care, Massachusetts General Hospital, Boston, MA.

Background: Recent data in suggests considerable discrepancies between patients and providers with respect assessment of hemodialysis prognosis, but this data is lacking for patients undergoing continuous renal replacement therapy (CRRT). We sought compare the prognostic assessment of patients/health care proxies (HCPs) and their providers (physicians and nurses).

Methods: A multiple-choice questionnaire was given to a trial of participants around an index case of CRRT. Each trial included (1) a patient (or HCP) on CRRT, (2) his/her resident or attending ICU physician, and (3) his/her ICU nurse administering CRRT. Questionnaires were performed in medical and cardiac ICUs at a single tertiary care center. We assessed knowledge of the probability of patient survival to hospital discharge and the probability of requiring lifelong dialysis if discharged.

Results: Twenty two survey triads were completed. All patients/HCPs (n = 22/22) correctly identified the purpose of CRRT. Fifty five percent of patients/HCPs (n = 12/22) incorrectly thought CRRT improved the speed of renal recovery. Probability of survival to hospital discharge (accepted quartile: 25-49%) was correctly identified by 5/22% of patients/HCPs (n = 1/22), 50% of physicians (n = 11/22), and 45% of nurses (n = 10/22). Both physicians (p = 0.001) and ICU nurses (p = 0.002) were more likely than patients/HCPs to assess survival accurately. Probability of requiring lifelong dialysis if discharged (accepted quartile: 0-24%) was correctly identified by 35% of patients/HCPs (n = 6/17), 23% of physicians (n = 5/22), and 36% of nurses (n = 8/22). Seventy three percent of patients/HCPs (n = 16/22) felt that their doctors “completely” explained the purpose of CRRT.

Conclusions: Understanding of CRRT and knowledge of prognosis is poor among patients/HCPs and ICU providers. Patients may overestimate their level of understanding of CRRT. Further intervention is needed to improve this knowledge gap for patients/HCPs, physicians, and ICU nurses.

FR-PO363
Hemodialysis Initiation Associates with Highest Stress Risk in U.S. and European Populations

Albert J. Power,1 Len A. Usyvat,2 Daniele Marcelli,3 Neill D. Duncan,1 Charles D. Pusey,1 Peter Potanko,2 Bernard Canaud,3 Mondo Consortium.4 Imperial College London, London, United Kingdom; Renal Research Institute, New York, NY; Fresenius Medical Care (FMC), Germany; MONDO Research Consortium.

Background: Stroke is a major cause of death in the US with hemodialysis (HD) patients particularly at risk with rates >8x higher than the general population. Initiation of HD in the elderly appears to confer much greater stroke mortality. In the absence of published data we examined if this applied globally especially in younger patients.

Methods: The MONDO research initiative consists of HD databases from the US, Europe, Asia & Latin America [Usyvat, Blood Purif 2013]. All incident patients from US Renal Research Institute [RRI] clinics & Fresenius Medical Care [FMC] Europe clinics within 30d of their first ever dialysis [Jan 2010-May 2013] were studied with follow up for maximum of 2yrs with fatal & non-fatal hospitalized stroke defined by ICD-9 & 10 coding and excluding transient ischemic attack.

Results: We studied 1030 strokes in 37793 patients [FMC Europe n=32892; RRI n=4901]. Overall stroke incidence was 22.3 /1000 pt yrs [95%CI 21.0-23.8], higher in patients ≥65yrs old [13.5 vs 30.5 /1000 pt yrs, p<0.001] and similar between Europe & the US [22.1 vs 24.2 /1000 pt yrs, p=0.2].

Stroke incidence was highest within 6 months of HD initiation particularly driven by peak rates of non-fatal stroke [Fig 1]. Incidence of fatal stroke was consistently higher in Europe, greatest in the first 6 months of HD with rates 2-3x higher in patients ≥65yrs old.

Conclusions: The first 6 months of HD initiation are a time of maximal stroke risk in all patients, especially in older people, who experience greater stroke mortality. Urgent studies are required to reduce the disproportionately high incidence of stroke in HD populations with focus on modulating stroke risk by modifying the HD prescription.

FR-PO364
Identical Index Hospitalization and 30-Day Readmission Discharge Diagnosis Codes

Eduardo K. Lason, Weiling Wang, Franklin W. Maddux. Fresenius Medical Care, North America, Waltham, MA.

Background: Potentially preventable hospital readmissions are most likely those that have the same diagnosis between the index and 30-day readmission events. We preliminarily determined the most common diagnosis codes in hemodialysis (HD) patients.

Methods: All adult in-center HD patients, treated 3x/ week as of 1/1/11 in Fresenius Medical Care, North America facilities with at least one hospital discharge in 2011 were followed up to 12/31/11. Hospital readmissions within 30-days of discharge were recorded, along with the index primary discharge and readmission ICD-9 codes (also as classified into diagnosis categories). We sought to determine the most frequent pairs of similar hospital diagnoses.

Results: There were 164,258 hospital events in 64,128 patients in 2011. 50,380 (30.7%) 30-day readmissions occurred in 23,575 patients. There were 9,965 (17.8%) readmissions (852 valid ICD-9 codes) with the exact diagnosis as in the index admission. The 10 most common identical ICD-9 code pairs for index and readmission diagnoses are shown in the table. Fluid overload conditions that may present as shortness of breath and CHF rank #1, #2, and #7 on the list, totaling ~11.2% of readmissions. The mean time from discharge to readmission was 19.4 ± 8.3 days (IQR: 4.3–76.8, median: 5). The mean (weighted) rate of identical diagnoses was 22.7% for 30-day readmissions. 4,255 of 50,380 (8.4%) readmissions with identical diagnoses occurred within 7 days of discharge.

Conclusions: Among identically diagnosed readmissions, the most common potentially actionable condition is fluid related. The identical diagnosis rate of 8% of readmissions within 7 days of discharge indicate potential problems with transition to outpatient care and/or that some patients were discharged from the hospital prematurely. Further study is needed in these subgroups of patients to evaluate for actionable items to avoid readmissions.
FR-PO365
Shorter Hemodialysis Session Length Is Strongly Associated with Higher Rates of Mortality and Hospitalization

Steven M. Brunelli,1 Emmanuel A. Anum,1 Karthik Ramakrishnan,1 Donna E. Jensen,1 Nils-olov Stalhammar,2 Anum,1 Karthik Ramakrishnan,1 Donna E. Jensen,1 Gilbert Marlowe,1 Mahesh Ardelyx, Inc. This publication is supported by DaVita Healthcare Partners, Inc.

Background: Prescribing patterns of hemodialysis (HD) vary widely. Prior data demonstrate that shorter HD session length is associated with increased mortality. There is a paucity of data with respect to associations with cause-specific morbidity events. The objective of the current study was to determine the relationship between duration of HD and rates of cardiovascular (CV) mortality and events.

Methods: The records of in-center HD patients incident to dialysis (1-Jan-07 through 31-Dec-08), treated at DaVita within 30 days of first HD and having Medicare or Medicaid as a primary insurer were studied. Mean session length was calculated over days 91-180. Patients were at-risk for outcomes beginning on day 181 of HD and continuing until death, transfer of care, modality change, or end of study (31-Dec-09). Outcomes were identified through linkage to US Renal Data Systems claims data and included hospitalization for heart failure (HF)/fluid overload, myocardial infarction (MI), all-cause mortality, CV mortality, and a composite hospitalization for HF/fluid overload or CV mortality.

Results: Of ~150,000 DaVita patients, 39,497 patients qualified for study. All-cause mortality was greatest for patients receiving mean sessions <180 min (HR 1.57; CI95% 1.40-1.76) and lowest for those receiving mean sessions >240 min (HR 1, reference).

Conclusions: These data demonstrate a strong association between shorter dialysis session length and CV events causing hospitalization and death.

Funding: Pharmaceutical Company Support - Ardelyx Inc.

FR-PO366
Interdialytic Weight Gain and Cardiovascular Disease Outcomes

Steven M. Brunelli,1 Claudia S. Cabrera,2 David P. Rosenbaum,1 Emmanuel A. Anum,1 Karthik Ramakrishnan,1 Donna E. Jensen,3 Nils-olov Stalhammar,4 Bergur V. Stefansson,2 DaVita Clinical Research, Minneapolis, MN; 2DaVita Healthcare Partners, Denver, CO; 3AstraZeneca, Molndal, Sweden; 4Ardelyx, Inc., Fremont, CA.

Background: Patients with end-stage renal disease (ESRD) have a higher risk of cardiovascular (CV) disease-related morbidity and mortality than the general population. One putative risk factor for this is fluid accumulation between hemodialysis (HD) sessions; measured as interdialytic weight gain (IDWG). This analysis examined associative risks between IDWG and incident CV events and deaths.

Methods: Study patients were incident to HD (1Jan2007-31Dec2008) and were on in-center HD for at least 181 days. Exposures of interest were absolute and relative IDWG (IDWG as percentage of body weight), each considered as patients’ mean value over dialysis days 91-180. Outcomes are listed below and were obtained by linkage to USRDS claims data. Patients were considered at-risk from dialysis day 181 until death, care transfer, voluntary withdrawal, modality change, or study end (31Dec2009).

Results: Among the study population (N=39,497) mean age was 62 yrs; 55% male, 53% White, 56% had CVD and 3200 died in follow-up. Compared to β-blocker+RAS containing, or other RAS regimens were associated with lower all-cause mortality (HR [95% CI] 0.82 [0.69, 0.97] for RAS regimens, and 0.93 [0.84, 1.02] for β-blocker+RAS regimens), and discontinuing RAS regimens was associated with higher mortality (HR 1.22 [1.02, 1.46]). Similar results were seen when analyzing cardiovascular mortality.

Conclusions: RAS regimens are associated with lower risk of mortality for patients receiving hemodialysis, and may be preferred in this population. Further studies are warranted to identify additional effects of these agents.

Funding: Other U.S. Government Support

FR-PO367
Antihypertensive Medications and Mortality in Incident Hemodialysis Patients: A Marginal Structural Analysis of a National Cohort

Stephen M. Sozio,1,2 Tariq Shaikh,1,2 Wendy L. St. Peter,1,2 Karen J. Bandeen-Roche,1,2 Patti Ephraim,1,2 Jason Luly,1,2 L. Ebony Boulware,1,2 DeICD Network Patient Outcome Investigators; Johns Hopkins Univ; 1Chronic Disease Research Group.

Background: Despite the burden of hypertension in dialysis patients, the optimal blood pressure medication (BPM) regimen has not been determined.

Methods: We performed a retrospective cohort study of all adult patients initiating hemodialysis at Dialysis Clinic, Inc. facilities from 2003-2008 and prescribed a BPM at 6 months. We obtained clinical parameters, BPMs, and outcomes from linked dialysis electronic medical records, USRDS data, and the National Death Index. We classified BPM regimens into 4 mutually exclusive regimens: β-blocker, renin-angiotensin system agent (RAS), β-blocker+RAS containing, or other BPMs. We also allowed discontinuation of BPMs if they were no longer prescribed in follow-up. We quantified each regimen’s effect on all-cause and cardiovascular mortality using discrete time proportional hazards regression. Time-varying marginal structural models accounted for confounders and patient-level predictors of BPM prescriptions, including predialysis systolic BP and volume removal on dialysis.

Results: Among 11,291 hemodialysis patients, the mean age was 62 yrs, 55% male, 53% White, 56% had CVD and 3200 died in follow-up. Compared to β-blocker+RAS regimens, RAS regimens were associated with lower all-cause mortality (HR [95% CI] 0.82 [0.69, 0.97] for RAS regimens, and 0.93 [0.84, 1.02] for β-blocker+RAS regimens), and discontinuing RAS regimens was associated with higher mortality (HR 1.22 [1.02, 1.46]). Similar results were seen when analyzing cardiovascular mortality.

Conclusions: RAS regimens are associated with lower risk of mortality for patients receiving hemodialysis, and may be preferred in this population. Further studies are warranted to identify additional effects of these agents.

Funding: DoppiaPharmaceutical Company Support - Ardelyx Inc.
Results: Mean age was 55 yr. Participants with PBP 130-159 and ≥160 had lower odds of being in the lowest SPPB category compared to the 110-129 (reference) group (Table). Even when BP medication use was added to the model, each component of the SPPB showed the same pattern of association but results for balance were not statistically significant. Higher PBP is associated with lower odds of worst PF.

Conclusions: PF at traditionally targeted levels was associated with worse PF among patients on HD, independent of heart failure and BP medications. The risk-benefit tradeoff of aggressive BP control, particularly in low-functioning patients, should be reexamined.

Funding: NIDDK Support

FR-PO369
Characteristics and Outcomes of End-Stage Renal Disease Patients with Cardiac Rhythm Management Device Infections

Oluwaseun Opealaja, Ankit Sakhuja, Xiaofo Liu, Jesse D. Schold, Sankar D. Navaneethan. Cleveland Clinic, Cleveland, OH.

Background: Sudden cardiac death due to arrhythmias remains the leading cause of death in end-stage renal disease (ESRD). This has led to increased use of cardiac rhythm management devices (CRMD) in ESRD patients, contributing to the increased rates of CRMD infection-related hospitalizations. We studied the characteristics and outcomes of ESRD patients admitted with CRMD infections in a large national inpatient database.

Methods: We conducted a retrospective analysis of the Nationwide Inpatient Sample (NIS) discharge records (2005-2010). We identified patients with CRMD infections using the ICD-9 codes for device-related infections or other device procedure (change and/or removal) along with bacteremia, endocarditis or systemic infection. Logistic regression and linear regressions were performed to examine inpatient mortality, length of stay and cost in ESRD patients after adjusting for patient demographics, primary payer and hospital characteristics.

Results: Of the 88,008 admissions for CRMD infections, 6,751 of them (7.7 %) were ESRD patients. ESRD patients were younger and had higher proportion of African Americans and Hispanics. In the multivariable model, ESRD patients had higher odds (OR = 2.58, 95% CI: 2.2-3.1) of in-hospital mortality, compared to non-ESRD patients. Among survivors, the mean length of stay for ESRD patients was 18.1 days as compared to 11.9 days among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD patients (p<0.0001).

Conclusions: End stage renal disease patients admitted with cardiac rhythm management device-related infections have an increased risk of in-hospital mortality, length of stay and higher costs. Furthermore, ESRD patients most commonly require skilled nursing facilities following discharge, further increasing healthcare costs.

FR-PO370
Elevated Serum Total Cholesterol to High Density Lipoprotein (HDL) Ratio Is Paradoxically Associated with Improved Overall and Cardiovascular Mortality in Patient on Hemodialysis

Hamid Moradi,1 Elani Streja,2,3 Moti L. Kashyap,1 Nosratola D. Vaziri,1 Gregg C. Fonarow,3 Kamyar Kalantar-Zadeh.1,2
1Univ of California, Irvine; 2Harold Simmons Center, Orange, CA; 3Memphis Veterans Affairs Medical Center.

Background: In the general population, increasing serum total cholesterol to HDL ratios are associated with increased risk of cardiovascular (CV) mortality. This association of ESRD patients admitted with CRMD infections in a large national inpatient database.

Methods: We conducted a retrospective analysis of the Nationwide Inpatient Sample (NIS) discharge records (2005-2010). We identified patients with CRMD infections using the ICD-9 codes for device-related infections or other device procedure (change and/or removal) along with bacteremia, endocarditis or systemic infection. Logistic regression and linear regressions were performed to examine inpatient mortality, length of stay and cost in ESRD patients after adjusting for patient demographics, primary payer and hospital characteristics.

Results: Of the 88,008 admissions for CRMD infections, 6,751 of them (7.7 %) were ESRD patients. ESRD patients were younger and had higher proportion of African Americans and Hispanics. In the multivariable model, ESRD patients had higher odds (OR = 2.58, 95% CI: 2.2-3.1) of in-hospital mortality, compared to non-ESRD patients. Among survivors, the mean length of stay for ESRD patients was 18.1 days as compared to 11.9 days among non-ESRD patients (p<0.0001). The mean total charges during the hospitalization for the ESRD group was $158,640 as compared to $102,943 among non-ESRD group (p<0.0001). Among ESRD population, only 26.3% were discharged home (vs. 33.5% in non-ESRD group, p<0.001) and 51.1% were transferred to skilled nursing facilities following discharge, further increasing healthcare costs.

Conclusions: End stage renal disease patients admitted with cardiac rhythm management device-related infections have an increased risk of in-hospital mortality, length of stay and higher costs. Furthermore, ESRD patients most commonly require skilled nursing facilities following discharge, further increasing healthcare costs.

Funding: NIDDK Support

FR-PO371
Association of Lipid Profile with Mortality in Dialysis Patients of Hispanic Origin in the East versus West Coast

Hamid Moradi,1 Elani Streja,2,3 Nosratola D. Vaziri,1 Moti L. Kashyap,1 Csaba P. Kovesdy,1 Kamyar Kalantar-Zadeh.1,2
1Univ of California, Irvine; 2Harold Simmons Center, Orange, CA; 3Memphis Veterans Affairs Medical Center.

Background: We have previously shown that in Hispanic patients on maintenance hemodialysis (MHD) paradoxical associations exist between serum lipid levels and mortality. However, significant racial and ethnic differences exist in patients of “Hispanic” background. While the Hispanic population of the West Coast consists mainly of those from Mexico and Central America, on the East Coast there is a large Afro-Caribbean contingency. We hypothesized that major differences exist in association of dyslipidemia and survival in Hispanic MHD patients on the West versus East Coast.


Results: In this cohort there were 4,220 patients from the West and 965 from the East Coast. In the fully adjusted models, significant differences were noted in the association of lipid markers and mortality in Hispanic patients from the West when compared to the East Coast.

Funding: NIDDK Support

Poster/Friday

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

Underline represents presenting author/disclosure.
FR-PO372
Subgroup Analysis of Hemodialysis Patients with Elevated Serum High Density Lipoprotein (HDL) Cholesterol Levels Demonstrates Men and Those Younger Than 65 Years of Age Have the Greatest Risk of Overall and Cardiovascular Mortality
Hamid Moradi, Elani Streja, Moti L. Kashyap, Nosratola D. Vaziri, Gregg C. Fonarow, Kamyar Kalantar-Zadeh, Harold Simmons Center, Orange, CA; Univ of California, Irvine; Univ of California, Los Angeles.

Background: In the general population, increasing levels of HDL are associated with reduced cardiovascular (CV) mortality. We hypothesize that the association of serum HDL concentration and mortality in hemodialysis patients is different from the general population and that in subgroups of patients on dialysis, elevated serum HDL cholesterol level may be paradoxically associated with increased mortality.

Methods: We examined the survival impact of serum HDL level in a 3-year (6/2004-6/2007) control of 33,109 maintenance hemodialysis patients being treated in clinics of a large dialysis organization using Cox models adjusted for demographics and case-mix variables. Hazard ratio of overall and cardiovascular mortality for two selected dichotomized levels of serum HDL cholesterol concentrations (left: 30-<60 mg/dl; right: ≥60 mg/dl) were plotted in selected subgroups of the study population.

Results: In this cohort, the mean age (mean ± SD) was 60±15 years old and included 45% women and 61% diabetics. All-cause and CV mortality HR was 1.05 (1.00-1.10) and 3.7 (95%CI 1.3 to 4.9) respectively. The percent reductions of IL-8, IL-10, TNF-α, IL-12, and IL-10 during dialysis were not significant different between both groups.

Conclusions: Serum HDL cholesterol levels over 60 mg/dl are associated with increased all-cause and CV mortality in patients on hemodialysis and this risk is most pronounced in men and those younger than 65 years of age. Further studies are needed to determine the mechanisms responsible for these associations.

Funding: NIDDK Support

FR-PO373
Intradialytic Cardiac Function and Inflammatory Cytokine Changes during Acetate-Free Online Hemodiafiltration Compared with Standard Online Hemodiafiltration in End-Stage Renal Disease Patients
Kamowan Tangvoraphonkchai, Khajohn Tiranathanagul, Nattachai Srisawat, Paweena Susantithaphong, Kriang Tungsanga, Somchai Elam-ong, Kearskat Praditpornsilpa. Div of Nephrology, Dept of Medicine, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn Univ, Thailand.

Background: Acetate in standard dialysis fluid could suppress myocardial function and potentially induce cytokine production, resulting in intradialytic hypotension (IDH) in hemodialysis (HD) patients. Online hemodiafiltration (HDF) provides superior intradialytic hemodynamic stability over HD. The present study was aimed to investigate the potential additive hemodynamic benefits and cytokine changes of the novel acetate-free dialysis fluid in online HDF.

Methods: A randomized, double-blind, crossover clinical trial was conducted in 22 stable online HDF patients. The patients were randomly assigned to firstly receive either acetate-free or standard online HDF and then were switched to the other after one week. Clinical parameters, cardiac index (CI), cardiac output (CO), and peripheral vascular resistance (PVR) were hourly assessed as well as the cytokines (IL-2β, IL-6, IL-8, TNF-α, and TNF-α) were measured at pre- and post-dialysis in each study session.

Results: The baseline clinical and cardiac parameters were similar between acetate-free and standard online HDF groups. There were comparable changes of arterial pressure (p=0.86) and the incidences of composite IDH and other adverse events between both groups. The changes of CI, CO, and PVR during dialysis were comparable (p=0.53, 0.20, and 0.64 respectively). The percent reductions of NT-proBNP and troponin-T were not significantly different (p=0.99 and p=0.51). The changes of IL-2β, IL-8, IL-10, TNF-α, and IL-10 during dialysis were not significant different between both groups.

Conclusions: In stable online HDF patients, acetate in the standard dialysis fluid did not adversely affect cardiac and cardiac parameters. The hemodynamic stability provided by online HDF might protect the adverse effects of acetate. Therefore, utilization of the costly acetate-free dialysis fluid did not offer additional benefits for stable online HDF patients.

FR-PO374
Racial Differences in Intra-Dialytic Blood Pressure—Results from the HEMO Study
Finnian R. McCausland, Sushrut S. Waikar. Renal Div, Brigham and Women’s Hospital, Boston, MA.

Background: Racial differences in blood pressure control are evident in both the general and hemodialysis populations, with Blacks generally having higher blood pressure than non-blacks. We examined for differences in intra-dialytic blood pressure parameters according to race in a post-hoc analysis of hemodynamic data from the HEMO Study.

Methods: Data from 1825 participants were analyzed, using self-reported race (categorized as Black, Hispanic vs non-Hispanic white) as the exposure of interest. The association of race with nadir intra-dialytic systolic (SBP) and diastolic (DBP) blood pressure was analyzed with generalized linear regression models.

Results: The mean age was 57.8 years, 44.7% were diabetic. Blacks accounted for 62.3% and Hispanics for 5.9% of total participants. In unadjusted analyses, compared with non-Hispanic whites, Hispanic and Black participants had 2.9 (95%CI 0.3 to 6.1) and 3.2 (95%CI 1.3 to 5.9) mmHg higher (95%CI 1.8 to 6.4) DBP. Upon multivariable adjustment for potentially confounding covariates (including pre-dialysis BP), Blacks remained with significantly higher nadir SBP (3.2; 95%CI 1.8 to 4.6 mmHg) and DBP (2.0; 95%CI 1.2 to 2.8 mmHg). Similar patterns were found with post-dialysis systolic and diastolic pressures. There was no evidence for effect modification according to age in all models considered (p-interaction=0.2).

Conclusions: We found evidence for racial differences in intra-dialytic blood pressure control, with Blacks appearing to have less marked decline in SBP and DBP during dialysis compared with non-Hispanic whites. Further study is warranted to determine if intra-dialytic blood pressure stability is causally related to lower mortality in Black hemodialysis patients.

FR-PO375
A Predictive Score for Cardiovascular Mortality in Hemodialysis Patients: Retrospective Cohort Study
Stefan D. Anker, Iain A. Gillespie, Kai-Uwe Eckardt, Florian Kronenberger, Sharon Richards, Ronald L. Pisoni, Bruce M. Robinson, Daniele Marcelli, Marc Froissart, Jürgen Floege. 1Charité Campus Virchow-Klinikum, Greece; 2Amgen Ltd, United Kingdom; 3Univ of Erlangen-Nuremberg, Germany; 4Insbruck Medical Univ, Austria; 5Arbor Research Collaborative for Health, 6Fresenius Medical Care, Germany; 7Amgen Europe GmbH, Switzerland; 8RWTH Univ of Aachen, Germany.

Background: Simple clinical tools to assess HD patients’ cardiovascular disease (CVD) risk do not exist, hence clinicians often rely on the Framingham Heart Study score designed to assess ten-year CV risk in the general population. Accordingly, this study aimed to derive and validate a risk score for two-year CV morbidity and mortality (CVMM) in 2007-09 incident European adult HD patients recruited in the second Fresenius Medical Care-based ARO cohort (AROi) in Europe.

Methods: Using a modified Framingham approach, we derived and internally validated a two-year CVMM score in patients randomly assigned to either a development (N=4,831) or validation dataset (N=4,796). External validation was conducted in the DOPPS III cohort (N=10,615). Additional discrimination, compared to the Framingham score, was assessed.

Results: The two-year CVMM event rate was 22.6 per 100 person-years (95% Confidence Interval 21.9-23.4). Major risk markers included CVD history, increasing age, underlying diabetic nephropathy, high interdialytic weight change, high calcium and low hemoglobin levels. Traditional CV risk factors (gender, blood pressure, cholesterol) were absent. Our new risk score was predictive in AROii (c-index range 0.66-0.67) albeit less so in DOPPS (0.63). In contrast, the Framingham Score was not very predictive of CVMM in AROii (AUC 0.56). Additional discrimination analysis showed that 58% of patients’ outcomes were correctly reclassified using our risk model parameters.

Conclusions: Our risk score for CVMM in HD patients, which is easy to apply and interpret, represents a major improvement over the Framingham score, the use of which may cloud clinical judgment and should be discouraged in the HD population.

Funding: Pharmaceutical Company Support • Amgen (Europe) GmbH

FR-PO376
Associates of Cardiopulmonary Arrest during Hemodialysis
Huen-Chen Li, Shu-Fang Lin, Steven M. Brunelli, Jeffrey L. Hymes, Eduardo K. Lacson. 1Brigham & Womens Hospital, Boston, MA; 2Fresenius Medical Care, North America, Waltham, MA; 3DaVita Clinical Research, Minneapolis, MN.

Background: Cardiopulmonary arrest (CPA) during and immediately prior to or after hemodialysis (HD) treatment (i.e. peri-dialytic period) is a rare event (~7/100,000 treatments) that has a high case fatality rate. This study was designed to elucidate patient and procedural factors associated with peridialytic CPA in the largest cohort reported to-date.

Methods: Data from the period prevalent HD population of Fresenius Medical Care, North America over 2010 were analyzed. 924 in-center CPA events (cases) and 75,538 control, with Blacks appearing to have less marked decline in SBP and DBP during dialysis compared with non-Hispanic whites. Further study is warranted to determine if intra-dialytic blood pressure stability is causally related to lower mortality in Black hemodialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
sex, race, and diabetes status. A comprehensive multivariate logistic regression model screening for demographic, treatment, and laboratory factors was built to identify factors predictive of peridialytic CPA.

**Results:** All 924 cases were matched to 4614 controls: age (65.7 years), sex (50% male), race (60% white), and diabetes (72%). Missed HD sessions due to hospitalization (prior 30 days), coronary artery disease, heart failure, lower serum albumin and hemoglobin, lower dialysate potassium, higher serum calcium, higher erythropoiesis stimulating agent dose, and nPCR (j-shape) were associated with peridialytic CPA. The final model is shown in the table. Dialysate sodium, calcium, and buffer (bicarbonate + acetate) were not significant factors.

<table>
<thead>
<tr>
<th>Variables in the Final Model</th>
<th>OR (95% CI)</th>
<th>Variables Removed by the Stepwise Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMD 924 vs 2540 hours</td>
<td>1.14***</td>
<td>Fasting Serum Creatinine</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>1.27**</td>
<td>Fasting Plasma Glucose</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.27***</td>
<td>Serum Glucose - Albumin</td>
</tr>
<tr>
<td>Diabetes (p.val)</td>
<td>0.63***</td>
<td>% Intradialytic Weight Gain</td>
</tr>
<tr>
<td>Basophils (p/g/L)</td>
<td>0.62****</td>
<td>Treatment duration -10 minutes (95%CI)</td>
</tr>
<tr>
<td>Colcemid (mg/d)</td>
<td>1.15**</td>
<td>Mixed treatment without response (95%CI)</td>
</tr>
<tr>
<td>nPCR (j-shape)</td>
<td>0.81**</td>
<td>Baseline microalbumin - UG</td>
</tr>
<tr>
<td>ESA per treatment (per 1000h)</td>
<td>1.06*</td>
<td>Potassium (mg/L)</td>
</tr>
<tr>
<td>Dialysate Potassium (&lt;2K+ bath)</td>
<td>0.77*</td>
<td>Potassium (mg/L)</td>
</tr>
<tr>
<td>Dialysate pH (&lt;7.2)</td>
<td>2.60***</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** Markers of patient-related health status and modifiable procedural factors (dialysate potassium and ESA dose) are significant associates of peridialytic CPA. In addition to maximizing nutritional status, it may be prudent to limit exposure to low dialysate potassium (<2K+ bath) and to use the lowest effective ESA dose. However, further study of peridialytic CPA preventive strategies is needed.

**FR-PO377**

**Renin-Angiotensin System (RAS) Blocking Drugs Reduce the Risk of Death in U.S. Incident Hemodialysis (HD) Patients**

**Tariq Shaif,1 Wendy L. St. Peter,2 Stephen M. Sozio,1 Patti Ephraim,1 Karen J. Bandeen-roche,1 L. Ebony Boulware,1 John Hopkins Univ; 2Univ of Minnesota.**

**Background:** The optimum blood pressure medication (BPM) regimen for patients on HD remains unclear. We quantified the association of BPM regimens with mortality and CV death among HD patients. Our findings suggest that RAS agents may be preferred antihypertensive drugs for patients starting HD.

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

**FR-PO378**

**Association of Pre-Dialysis Blood Pressure with All-Cause Mortality and Stroke in Japanese Hemodialysis Patients: The Japan DOPPS**

**Masaaki Inaba,1 Angelo Karaboyas,2 Takashi Akiba,1 Tadao Akizawa,4 Akira Saito,5 Shunichi Fukuhara,6 Christian Combe,7 Bruce M. Robinson.2 1Osaka City Univ, Japan; 2Arbor Research, Ann Arbor; 3Tokyo Women’s Medical Univ, Japan; 4Showa Univ, Japan; 5Tokai Univ, Japan; 6Kyoto Univ, Japan; 7Univ Bordeaux Segalen, France.**

**Background:** The association of low blood pressure (BP) with high mortality is characteristic for hemodialysis (HD) patients. In Japan, HD mortality is lower but there is a burden of high BP. This analysis documents a positive and monotonic association of BP with mortality and stroke among Japanese HD patients, and examines the association separately for patients with and without antihypertensive medication (BP meds).

**Methods:** We analyzed 9,134 patients from Japan in phases 1-4 (1999-2011) of the Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective cohort study of in-center HD patients. The association of pre-dialysis systolic (SBP) and diastolic (DBP) BP with all-cause and stroke mortality was assessed using adjusted Cox regression.

**Results:** 34% had SBP ≥160 mm Hg. A U-shaped association between SBP and all-cause mortality was observed (Figure); no evidence of interaction (p=0.97) was found between SBP and use of BP meds. Both SBP and DBP were positively and monotonically associated with stroke mortality; hazard ratio (95% CI) was 1.24 (1.01-1.53) per 20 mmHg higher SBP and 1.23 (1.05-1.44) per 10 mmHg higher DBP. The association between SBP and stroke mortality was slightly stronger (p=0.09) among patients not on BP meds than on BP meds.

**Conclusions:** This analysis documents a positive and monotonic association of BP with stroke-related deaths in Japanese HD patients. High BP remains common, and while our analysis indicates that the prescription of BP meds to hypertensive patients might prevent against stroke-related death, additional study is warranted.
Results: During the follow-up period, 42 of the 128 patients died; 19 of those patients died of CVD. Skin autofluorescence did not have a significant effect on all-cause mortality. However, age, carotid artery intima-media thickness (IMT), serum albumin (adjusted HR 0.05; 95% CI 0.01-0.32), and hsCRP (adjusted HR 1.55; 95% CI 1.18-2.05) were independent predictors of cardiovascular mortality.

Conclusions: The present study suggests that skin autofluorescence is an independent predictor of cardiovascular mortality in non-Caucasian (Japanese) patients on chronic hemodialysis.

FR-P0380
Comparative Risk of Sudden Cardiac Death in Incident Hemodialysis (HD) and Peritoneal Dialysis (PD) Patients
Shuling Li,1 Charles A. Herzog,2,3 1NIDDK Support
Background: HD initiation is a vulnerable period with a markedly heightened risk of death. We previously reported that the hazard of sudden cardiac death (SCD) is markedly increased in incident HD pts in the first 90 days after dialysis initiation. Few published data exist regarding SCD rate in HD pts. The rate for HD pts decreased steadily with increasing time on dialysis, compared with a roughly stable rate for PD pts (See Table). Although risk of SCD associated with HD attenuated with increasing time on dialysis, it remained a significant 94% higher for HD pts vs PD pts even after 6 mos. of initiation.

Conclusions: The hazard of SCD is markedly higher for incident HD pts than PD pts, especially in the first 90 days after initiation. These findings highlight the importance of early prevention of SCD for HD pts at initiation.

Funding: NIDDK Support

References:
FR-PO382

Blood Pressure in Dialysis (BID) Study: A Pilot RCT Assessing Treatment to Two Different BP Targets  
Jose L. Vega,1 D. Miskulin,1 Jennifer J. Gassman,2 David W. Ploth,3 Manisha Jhamb,3 Christine Stidley,4 P. Zager,1 1Tufts Medical Center; 2Cleveland Clinic Foundation; 3Dialysis Clinic Inc.; 4Medical Univ of South Carolina; 5Univ of Pittsburgh; 6Univ of New Mexico.

Background: The optimal blood pressure (BP) goal for treatment of hypertensive hemodialysis patients is unknown. More aggressive BP lowering may reduce cardiovascular events, or it may not be tolerated due to intradialytic hypotension. Which BP measure (in-center, home or ambulatory BP readings) should guide management is also unknown. In the ongoing NIH-sponsored Blood Pressure in Dialysis (BID) Study, hypertensive HD patients are randomized to a pre-dialysis in-center BP of 110-140/90 mm Hg vs. 155-165/90 mm Hg.

Methods: We assess adherence with prescribed in-center standardized (SDUBPM), home (HBPM) and ambulatory (ABPM) monitoring. SDUBPM was taken each treatment day, after 5 minutes rest, 3 readings per sitting, per AHA guidelines. HBPM was to be done twice, 3 readings each sitting, on the day following the mid-week treatment. ABPM was done for 44 hours in one interdialytic period per quarter. We also compared the distribution of BPs across study arms over time.

Results: As of 05/01/13, blood pressure data were available for 51 randomized patients. Adherence with requirements for SDUBPM, HBPM and ABPM in the first 3 months (Q1) was 94, 54 and 16%, in Q2 was 84, 47, and 37%, and in Q3 was 79, 50, and 14% respectively. Boxplots of SDUBPM readings across treatment arms is shown in Figure 1. The mean (SD) separation between arms at the end of the 3rd, 6th, and 9th month was 12, 19, and 12 mm Hg, respectively.

Conclusions: Current data show adherence to staff-measured SDUBPM was substantially better than patient-measured HBPM or ABPM. Only 50% or fewer of patients perform HBPM or ABPM at a given timepoint. Separation in BP between treatment arms was achieved at month 3 and was maintained at month 9.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic Inc.

FR-PO383

Blood Pressure in Dialysis (BID) Study: Differences in Blood Pressure Measured inside versus outside the Dialysis Unit  
Jose L. Vega,1 D. Miskulin,2 David W. Ploth,2 Manisha Jhamb,3 Christine Stidley,4 P. Zager,1 1Tufts Medical Center; 2Cleveland Clinic Foundation; 3Dialysis Clinic Inc.; 4Medical Univ of South Carolina; 5Univ of Pittsburgh.

Background: Although ambulatory blood pressure monitoring (ABPM) is considered the ‘gold standard’ for assessing BP since multiple readings are obtained while patients are performing usual activities, they may be difficult to obtain. Pre-dialysis BPs taken in the dialysis unit are used to manage patients, though these may lead to over-treatment as patients are volume expanded. In the Blood Pressure in Dialysis (BID) study we obtain 44-h ABPM, intermittent Home BP and standardized pre-dialysis dialysis unit BP (SDUBPM). We compare differences across measures at baseline.

Methods: SDUBPM was measured each treatment day after 5 minutes rest prior to dialysis start. Home BPs were measured twice per day the day after the midweek treatment. ABPM was performed during a 44 h interdialytic period. We compared 44 h ABPM (day, night, full 44-hour) with the 2-week averaged SDUBPM (week before and during ABPM) and Home BP (average of week before and after ABPM).

Results: 51 patients had all 3 BP measurements within the allotted time frame. Comparisons of Systolic BP across measures are shown in the table.

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

Underline represents presenting/disclosure.

FR-PO384

Soluble Klotho Is Associated with Left Ventricular Function and Coronary Artery Stenosis in Dialysis Patients  
Maurits S. Buiten,1 Michaly K. De Bie,1 Bastiaan Van Van Dam,2 Annet Bouna-de Krager,1 J. wouter Jukema,1 Ton J. Rabelink,2 Joris I. Rotmans,3 Cardiology, LUMC, Leiden, Albinusdreef 2, Netherlands; 2Nephrology, LUMC, Leiden, Albinusdreef 2, Netherlands; 3Nephrology, MCA, Alkmaar, Netherlands; 4Nephrology, Spaarne Ziekenhuis, Hoofddorp, Netherlands.

Background: Dialysis patients suffer from a disproportionally high burden of cardiovascular disease which might be due to unique risk factors. Klotho, a protein linked to aging, has been suggested as such a factor. Recently an ELISA has become available to measure soluble Klotho (sKlotho). The purpose of the present study was to determine the relationship between sKlotho, coronary artery stenosis and left ventricular ejection fraction (LVEF) in dialysis patients.

Methods: Plasma levels of sKlotho were measured in dialysis patients. LVEF was measured using echocardiography. Coronary artery stenosis was determined by coronary CT scan. Coronary artery occlusion was defined as >50% luminal narrowing. Associations were analysed using linear regression.

Results: We included 129 patients (67±7 yrs old, 76% male, 65% HD as dialysis modality). Patients with a low sKlotho (<460pg/mL) had significantly more occluded coronary arteries compared to patients with a high sKlotho.

Conclusions: sKlotho was significantly associated with LVEF, however this association disappeared after adjustment for occluded coronary arteries. Furthermore, patients with high sKlotho used angiotensin receptor blockers (ARBs) and periportal dialysis more frequently and had significantly lower PTI.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic Inc.
Results: At baseline mean age was 64±14 years, and 445 (62%) of patients were male. The means (of pre- and post-dialysis measurements averaged) of SBP, DBP and PP were 159±27, 86±18 and 68±16 mmHg respectively. After a median follow-up of 2.9 years a total of 269 patients died. The means of both the pre- and the post-dialysis BP measurements was found to be more predictive for all-cause mortality, than the pre- or post-measurements alone. Patients in the highest tertile (>77mmHg) of DBP had an increased risk of mortality (hazard ratio (HR): 1.44, 95% CI: 1.03 - 2.02), versus patients in the lowest tertile (DBP<66mmHg): HR: 1.0; DBP 66 - 77mmHg: HR: 1.31, 95%CI: 0.93 - 1.74). A similar trend, albeit not significant was observed between mortality risk and SBP, and PP.

Conclusions: The mean of both the pre- and the post-dialysis BP measurements is a better predictor for mortality, than pre- or post-measurements alone. Baseline DBP is a better predictor of mortality risk than SBP and PP in ESRD patients.

FR-PO386
Blood Pressure Changes over Time in Patients with End Stage Renal Disease. Results from the CONVective TRAnsport Study (CONTRAST)
Irina Mostovaya,1 Michiel Bots,2 Muriel Grooteman,3 Marinus A. Van Den Dorpel,4 Pieter M. Ter Wee,5 Peter J. Blankensteijn.1 1Nephrology, Univ Medical Center Utrecht, Utrecht, Netherlands; 2 Julius Center for Health Sciences and Primary Care, Univ Medical Center Utrecht, Utrecht, Netherlands; 3Nephrology, VU Medical Center, Amsterdam, Netherlands; 4Internal Medicine, Maasstad Hospital, Rotterdam, Netherlands.

Background: Limited data is available on changes over time of blood pressure (BP) in dialysis patients. The aim of this study is to assess changes over time of BP in dialysis patients and evaluate the impact of age, gender, medical history and dialysis-treatment related characteristics on these changes.

Methods: Data from all 714 patients from the CONVective TRAnsport Study (CONTRAST), a randomized trial comparing online hemodiafiltration and low-flux hemodialysis, were used for this analysis. BP measurements [systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP) and pulse pressure (PP)] were performed at baseline and every 3 months up to 6 years, three times pre-, and three times post-dialysis. The changes in these and post-dialysis measurements were computed as the mean of all six BP measurements (7025 measurements per variable in total). The rate of change over time of these parameters was estimated using linear mixed effects models.

Results: At baseline mean age was 64±14 years, and 445 (62%) of patients were male. SBP, DBP, MAP and PP all declined over time. For every incremental 10 years of age at baseline, the yearly excess decline of SBP was 1.7mmHg (p=0.02), and the excess decline of PP was 1.9 mmHg (p=0.002). Patients with a dialysis vintage of >2 years experienced an excess decline in SBP of 2.0 mmHg (p=0.01) and an excess decline in DBP of 0.4mmHg (p=0.003), when compared to those with a vintage of <2 years. Males experienced an excess decline of SBP of 1.6mmHg (p=0.03) and an excess decline of PP of 1.2mmHg (p=0.02) when compared to females.

Conclusions: 1) In dialysis patients all parameters of BP (SBP, DBP, MAP, PP) decline over time. 2) Age, gender and dialysis vintage are important determinants of the rate of decline of BP in this patients group.

FR-PO387
Effect of Anticoagulation and/or Antiplatelet Drugs on Cerebrovascular Events in Hemodialysis Patients: Miyazaki Dialysis Cohort Study (MID Study)
Tatsunori Toida,1 Yuji Sato,1 Masao Kikuchi,1 Hiroyuki Komatsu,1 Shouichi Fujimoto.2 1Dept of 1st Internal Medicine, Faculty of Medicine, Univ of Miyazaki; 2Dept of Hemovascular Medicine and Artificial Organs, Faculty of Medicine, Univ of Miyazaki, Japan.

Background: The beneficial effect of antiplatelet (AP) and anticoagulant (AC) drugs on cerebrovascular (CV) events has been shown in the general population, but has not been clarified in hemodialysis (HD) patients. The aim of this study was to examine the association between the onset of CV events and these drugs in Japanese HD patients.

Methods: Patients with maintenance HD (n=1,551) were enrolled into the MID Study in December 2009 and were prospectively followed up for 3 years. CV events (cerebral infarction, cerebral hemorrhage, CH) were determined using head CT/ MRI in addition to typical neurological symptoms. Kaplan-Meier (KM) and Cox regression (CR) analyses were used to clarify the association between AP and/or AC drugs and CV events.

Results: A total of 51 and 74 patients developed CH and CI, respectively, with incidences of 13.1 and 19.2/1000 patient-year. KM analysis showed that CH events were significantly more common in patients with an anticoagulation therapy of AP and AC drugs than in other groups. CR analysis revealed that combination therapy (HR 5.06, 95% CI: 1.71-14.98) was factor contributing to CH, in addition to a past history of CH (HR 4.61, 95% CI: 2.03-10.48). The incidence of patients with a past history of CI was remarkably higher than those without this. CR analysis on the patients excluding those with a past history of CI revealed that the presence of atrial fibrillation (AF), diabetes mellitus and age were the predictive factors of CI, while AC and AP therapies were not significant factors. Antiplatelet alone (AP) or AC alone, no significant difference was observed in the frequency of CI events between warfarin users and non-users.

Conclusions: Combination therapy of AP and AC drugs is a risk factor for developing CH in patients with maintenance HD. HD patients with AF more frequently suffered CI than those without AF; however, preventive effects of AP/AC drugs against developing CI were not evident.
may affect the HF-mortality link in these patients (pts) has never been tested. The issue is important because SDB has been in part attributed to reversible pharyngeal edema secondary to volume expansion in HF pts and may therefore be a modifiable risk factor.

Methods: We investigated this problem in a cohort of 827 stage 5D-CKD pts. HF was assessed at baseline on the basis of clinical symptoms and radiological/echocardiographic examinations. At enrollment, participants provided self-reported information about snoring and were followed up for a median time of 28 months.

Results: 132 pts had HF at baseline. Overall, 194 pts were classified as heavy snorers, 308 as moderate snorers and 325 as non-snorers. During the follow-up, 233 pts died (CV causes: 54%). Both on univariate (P=0.001) and multiple (P<0.02) Cox analyses, HF significantly predicted the study outcomes whereas snoring did not (P=NS). However, snoring was a stronger modifier of the risk of HF for the study outcomes. In Cox models (including Framingham factors, anti-hypertensive treatment, CV comorbidities, diastolic blood pressure, CRP, P, Hb and albumin), the hazard ratios (HR) associated to HF were highest in heavy snorers (all-cause death:HR=2.9, P=0.001; CV death:HR=3.1,P=0.001), intermediate in moderate snorers (all-cause death:HR=1.5,P=0.01; CV death:HR=1.6,P=0.009) and not significant in non-snorers (all-cause death:HR=0.9; CV death:HR=0.8).

Conclusions: Snoring is an effect modifier of the HF-mortality link in stage 5D-CKD pts. Clinical trials are needed to verify whether intensified surveillance and treatment (UF intensification) of HF snorers on dialysis may translate into better clinical outcomes in these pts.

Funding: Government Support - Non-U.S.

FR-PO391
Early Cardiovascular Events in an Incident European Hemodialysis Cohort
Kai-Uwe Eckardt,1 Iain A. Gillespie,2 Stefan D. Anker,1 Sharon Richards,1 Daniele Marcelli,2 Marc Froissart,2 Jürgen Floege,3 Kai-Uwe Eckardt,1 Iain A. Gillespie,2 Stefan D. Anker,1 Sharon Richards,1 Daniele Marcelli,2 Marc Froissart,2 Jürgen Floege,3

Background: Hemodialysis (HD) initiation is associated with high all-cause and cardiovascular (CV) death rates. However, there is a paucity of data on the occurrence and potential causes of cardiovascular events (CVE) during this crucial period. No studies have examined risk by underlying CV cause.

Methods: This study aimed to decipher the early CVE risk in a European Fresenius Medical Care HD patient cohort (‘AROii’) with a dialysis vintage of <7 days (median 4d) and monthly rates of the composite fatal/nonfatal CVEs were calculated for the first 2 years on HD. High-risk periods were identified by comparing, with Rate Ratios (RRs), monthly first year rates with the second year rate. Constituent events were also examined.

Results: 2411 CVE were reported for 1454/6322 patients (23%). The first year rate (30.4/100 person-years (PY) [95% Confidence Interval (CI) 28.9-31.9]) greatly exceeded the second (19.4/100PY [CI 18.0-20.8]). Whilst incidence was generally highest in the first year, the high risk period extended to month 5 (28.7±2.2). Risk factors significantly predicted the study outcomes whereas snoring did not (P=NS). However, snoring was a stronger modifier of the risk of HF for the study outcomes. In Cox models (including Framingham factors, anti-hypertensive treatment, CV comorbidities, diastolic blood pressure, CRP, P, Hb and albumin), the hazard ratios (HR) associated to HF were highest in heavy snorers (all-cause death:HR=2.9, P=0.001; CV death:HR=3.1,P=0.001), intermediate in moderate snorers (all-cause death:HR=1.5,P=0.01; CV death:HR=1.6,P=0.009) and not significant in non-snorers (all-cause death:HR=0.9; CV death:HR=0.8).

Conclusions: Snoring is an effect modifier of the HF-mortality link in stage 5D-CKD pts. Clinical trials are needed to verify whether intensified surveillance and treatment (UF intensification) of HF snorers on dialysis may translate into better clinical outcomes in these pts.

Funding: Pharmaceutical Company Support - Amgen (Europe) GmbH

FR-PO392
Challenging Physical Activity in Dialysis Patients
Marine Paruze1, Ana Kollo-Labadees,2 Catherine Deforges-Lasseur,2 Marie Paule Guillodo,4 Martial Levannier,1 Daniel Teta,2 Denis Fouque,2 Nephrology, Hopital Edouard Herriot, Lyon, France; 1Dialysis, AURA Nord, Saint Ouen, France; 2AURAD Aquitaine, Gragnan, France; 3AUB Santé, Brest, France; 1Aren, Neufly/Seine, France; 2Nephrology, CHU, Lausanne, Switzerland; 3Nephrology, Centre Hospitalier Lyon Sud, Pierre Benite, France.

Background: Physical inactivity is a risk factor for mortality in dialysis patients and is still poorly documented during maintenance dialysis (MD). The Step by Step initiative aimed at evaluating the weekly physical activity on a large cohort of dialysis patients.

Methods: All French nephrologists were invited to participate in this national prospective multicenter observational study. 149 investigators included 1163 adult patients who were on MD since more than 3 months. Physical activity was assessed by the number of daily steps measured by a pedometer (model NO PE317C multifunction pedometer, USA) for 7 consecutive days.

Results: Median age was 63 yr (Q1 51-Q3 75), 66% were male. Most patients (95%) were on hemodialysis (median 3yr). 24% were diabetic, 69% had hypertension, and 22% had peripheral arterial disease. 63% were sedentary (>5000 steps/day) with a median of 3680 steps/day. Daily steps were lower on dialysis days (DD) (2912, 1439-3532) compared to non DD (4054, 2136-7108) (p<0.001). Physical activity decreased with age with 57% being sedentary between 50 and 65 yr and above up to 83% after 80 yr. Number of steps increased with dialysis vintage from 3620 steps in patients on dialysis for <5 yr (66% pts) to 4465 for dialysis time>10 yr (18% pts).

Conclusions: This survey, largest ever done, highlights the low level of physical activity in MD patients. Patients are mostly sedentary with a number of daily steps less than 5000. Activity is more reduced if they are older and on MD for a shorter time (suggesting that frail patients died earlier). These results confirm the need to enforce rehabilitation programs that promote intra and inter dialytic physical exercise.

Funding: Pharmaceutical Company Support - Amgen

FR-PO393
Advanced CKD Results in Reduced Cardiovascular Reserve with Loss of Adaptive Cardiac Alterations When Compared to Hypertension
Stephen M.S. Ting,1,2 Thomas Hamborg,2 Gordon McGregor,1 Kenneth Lim,4 Nicolas Aldridge,6 David Oxborough,2 Sudheer Koganti,1 Rosemary Bland,2 Robert Higgins,3 Prithwish Banerjee,5 Daniel Zehnder,2 1Univ Hospitals Coventry & Warwickshire NHS Trust; 2Warwick Medical School; 3Liverpool John Moores Univ, Unist, United Kingdom; 2Oregon Health & Science Univ.

Background: Oxygen consumption at peak exercise (VO2peak) is reduced in advanced CKD patients. To-date, no studies have examined whether the reduced functional measure of cardiovascular reserve in CKD is related to an impaired cardiovascular reserve. We also postulate that loss of adaptive cardiac alterations is a contributor to low VO2peak in CKD.

Methods: We assessed 136 kidney transplant-waitlisted patients in parallel with 80 healthy hypertensive subjects prospectively between 2010-2012. Cycle-ergometric exercise testing, TD-echocardiography, pulse wave velocity (PWV) were performed.

Results: VO2peak was lower in the CKD subjects compared with the hypertensives (19 vs 23 ml/min/kg; p<0.001). Independent predictors of VO2peak for CKD were PWV(coefficient, B=5.4), LV end-diastolic volume index(LVEDVI=0.1) & LV filling pressure(E/mean c'=0.1), in the hypertensives, these were LV mass index(B=0.4) & LVEDVI(B=0.4).

In demographic-adjusted multiple regression model, significant predictors in the CKD were E/mean c'=0.4(β=4.7) & albumin (β=0.43). In the hypertensives, it was LVEDVI(B=0.3).

Interestingly, higher LV mass index & LVEDVI were associated with greater VO2peak in the hypertensives than the CKD subjects.

FR-PO394
Exercise Anaerobic Threshold Predicts Survival Pre- and Post- Kidney Transplantation
Hasan Iqbal,1,2 Thomas Hamborg,2 Nicolas Aldridge,3 Nitya Krishnan,4 Prithwish Banerjee,5 Rosemary Bland,2 Robert Higgins,3,6 Daniel Zehnder,2 1Renal Medicine & Transplantation, Univ Hospitals Coventry & Warwickshire NHS Trust; 2Cardiology, Univ Hospitals Coventry & Warwickshire NHS Trust; 3Vascular Surgery, Univ Hospitals Coventry & Warwickshire NHS Trust; 1Metabolic & Vascular Health, Warwick Medical School, United Kingdom; 1Health Sciences Statistics & Epidemiology, Warwick Medical School, United Kingdom.

Background: Reduced anaerobic threshold (AT) carries a poor prognosis among patients with impaired cardiovascular reserve in advanced CKD. Our data is indicative of dysregulated LV function in CKD patients beyond predominantly ventricular wall changes that occur in otherwise healthy hypertensive patients.

Conclusions: This is the first study to suggest that impaired LV and arterial compliance are mechanistic factors resulting in reduced cardiovascular reserve in advanced CKD. Our data is indicative of dysregulated LV function in CKD patients beyond predominantly ventricular wall changes that occur in otherwise healthy hypertensive patients.

FR-PO394
Exercise Anaerobic Threshold Predicts Survival Pre- and Post- Kidney Transplantation
Hasan Iqbal,1,2 Thomas Hamborg,2 Nicolas Aldridge,3 Nitya Krishnan,4 Prithwish Banerjee,5 Rosemary Bland,2 Robert Higgins,3,6 Daniel Zehnder,2 1Renal Medicine & Transplantation, Univ Hospitals Coventry & Warwickshire NHS Trust; 2Cardiology, Univ Hospitals Coventry & Warwickshire NHS Trust; 3Vascular Surgery, Univ Hospitals Coventry & Warwickshire NHS Trust; 1Metabolic & Vascular Health, Warwick Medical School, United Kingdom; 1Health Sciences Statistics & Epidemiology, Warwick Medical School, United Kingdom.

Background: Reduced anaerobic threshold (AT) carries a poor prognosis among patients with impaired cardiovascular reserve in advanced CKD. Our data is indicative of dysregulated LV function in CKD patients beyond predominantly ventricular wall changes that occur in otherwise healthy hypertensive patients.

Conclusions: This is the first study to suggest that impaired LV and arterial compliance are mechanistic factors resulting in reduced cardiovascular reserve in advanced CKD. Our data is indicative of dysregulated LV function in CKD patients beyond predominantly ventricular wall changes that occur in otherwise healthy hypertensive patients.
Risk patients with reduced cardiovascular reserve had a better survival after receiving a functional cardiovascular reserve AT with overall survival in advanced CKD patients. High progressive (PG)(36 patients-48%) and non-progressive (NPG). score (CACS) was measured twice with one year interval. Patients were grouped to investigate the association of serum FGF-23 with progression of coronary artery calcification in hemodialysis patients. Increased Serum Levels of GDF-15 Are Associated with Cardiovascular Disease, Subclinical Atherosclerosis in Patients on Maintenance Hemodialysis (MHD) Takahiro Kuragano, Takeshi Nakanishi. Internal Medicine, Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Hyogo. Background: Disordered mineral metabolism is implicated in the pathogenesis of vascular calcification in hemodialysis (HD) patients. Fibroblast growth factor 23 (FGF-23) is the major regulator of phosphate metabolism. In this prospective study, we aimed to investigate the association of serum FGF-23 with progression of coronary artery calcification in HD patients. Methods: Seventy-four HD patients(36 male/38 female,mean age:52±14 years) were included. Serum FGF-23 levels were measured by ELISA. Coronary artery calcification score (CACS) was measured twice with one year interval. Patients were grouped as progressive (PG)(36 patients-48%) and non-progressive (NPG). Results: Age, serum phosphorus, baseline and first year CACS were found to be significantly higher in the PG compared to NPG group. Serum FGF-23 levels were significantly higher in PG (468±132 vs 190±272 pg/mL, p=0.04). Patients were divided into two groups according to baseline CACS (low group, CACS<30; high group, CACS>30). Serum FGF-23 levels were significantly correlated with the progression of CACS (ΔCACS) in the low baseline CACS group (r=0.510, p=0.006), but this association was not found in high baseline CACS group (r=0.11, p=0.44). In logistic regression analysis for predicting the PG patients; serum FGF-23, phosphorus levels and baseline CACS were retained as significant factors in the model. Conclusions: Serum FGF-23 was found to be related to progression of CACS independent of serum phosphorus levels. FGF-23 may play a major role in the progression of vascular calcification especially at the early stages of calcification process in HD patients. Funding: Government Support - Non-U.S. FR-PO396 Impacts of Dry Weight Determined by Calf Bioimpedance Ratio on Cardiot Stiffness and Left Ventricular Hypertrophy in Hemodialysis Patients Yi-Lun Zhou, Li-jie Ma, Fang Sun, Yang Shen, T.G. Cui. Dept of Nephrology, Chao-Yang Hospital, Capital Medical Univ, Bei-Jing, China. Background: Our previous study has shown that modification of bioimpedance technique by the measurement of bioimpedance ratio in the calf (Calf-BR = impedance at 200 KHz / impedance at 5 KHz) was a simple and practical method in assessing fluid status in hemodialysis patients. Under physiological conditions, the Calf-BR was positively related to the ratio of extracellular volume to total body water. However, the consequences of periodical dry weight (DW) adjustment under the guidance of Calf-BR every 3 month. In control group, the assessment of DW remained a clinical judgment. Carotid stiffness, left ventricular mass index(LVMi), and Calf-BR were measured at baseline and at the 12th month in both groups. Home blood pressure (BP) was monitored monthly. Dialysis-related adverse events were recorded. Results: No significant differences were observed in parameters between the two groups at baseline. Compared to control group, bioimpedance group had significantly lower values in terms of the annual averages of systolic home BP (147±1.5±3mmHg vs 152.6±16.9mmHg, p=0.019, carotid stiffness index β (10.7±3.3 vs 12.2±3.1, p=0.003), LVMi (155.2±15.64 g/m² vs 165.17±16.76 g/m², p=0.001), and the percentage of individuals with Calf-BR over target range (p=0.040) at month 12, with less annual averages of antihypertensive medications used and lower frequency of intradialytic hypotension, muscle cramp, and clotted angioaccess. Conclusions: Probing DW via periodical measurement of Calf-BR may have the potential to improve arterial stiffness and left ventricular hypertrophy. In addition, this intervention may also decrease incidence of intradialytic hypotension, muscle cramp, and arteriovenous fistula complications in hemodialysis patients. Funding: Government Support - Non-U.S. FR-PO397 The Progress in Malnutrition and Inflammatory Conditions Affect on Adverse Events and Mortality in the Patients on Maintenance Hemodialysis (MHD) Mukadder Bilgic,1 Nuket Bavbek.1 Dept of Internal Medicine and Nephrology, Turgut Ozal Univ, School of Medicine, Ankara, Turkey; 2Dept of Biochemistry, Turgut Ozal Univ, School of Medicine, Ankara, Turkey; 1Dept of Cardiology, Turgut Ozal Univ, School of Medicine, Ankara, Turkey. Background: Increased carotid intima media thickness(CIMT) was shown to be independent predictor of cardiovascular(CV) mortality in dialysis and general population. Growth differentiation factor 15(GDF-15), a member of the transforming growth factor superfamily, is produced by cardiomyocytes and atherosclerotic lesions under stress conditions such as inflammation. Increased GDF-GK820815 levels may be suggested as a powerful biomarker for cardiovascular diseases, atherosclerosis and mortality. We assessed associations between serum concentrations of GDF-15, mortality and CIMT in subclinical atherosclerosis in hemodialysis(HD) patients. Methods: Eighty-seven patients on maintenance hemodialysis and 45 sex and age-matched healthy controls were included in this prospective study. Serum GDF-15 levels were measured by ELISA. CIMT was assessed by Doppler ultrasonography. Association between serum GDF-15 level and mortality was assessed in Cox regression analysis with serum GDF-15 levels categorized into five groups according to median value(328.18 pg/mL). Patients were followed for 2 years and had cause-specific and all-cause mortality determined. Results: The mean serum GDF-15 levels were significantly higher in HD patients than controls (376.57±216.78 vs. 176.32±43.62 p=0.01, respectively). Serum GDF-15 levels were correlated to CIMT (r=0.607, P<0.01), CRP (r=0.250, P<0.01) and serum albumin (r=0.156, P=0.03). The multivariate analysis revealed that GDF-15 was found to be an independent variable of CIMT in HD patients. In the study, serum GDF-15 level was an independent marker of CV mortality when adjusted for age, CRP, history of diabetes mellitus. Conclusions: The relationship demonstrated between serum GDF-15, mortality, and carotid artery thickening suggests that GDF-15 may be a novel marker of atherosclerosis, inflammation and malnutrition in HD patients.
Cytokines
Effects of Acute Intradialytic Exercise on Blood Pressure and Circulating Cytokines

Maurice Dunng,
Nicollie C. Bishop,
Hamish M. Young,
James O. Burton,
Alice C. Smith.
School of Sport, Exercise and Health Sciences, Loughborough Univ, United Kingdom; Leicester Kidney Exercise Team, Univ Hospitals of Leicester, United Kingdom.

Background: Regular exercise can enhance the quality of life of haemodialysis (HD) patients. Intradialytic cycling (IDC) is increasingly offered on HD units but its potential restrictions on publications.

Methods: The MBD-5D is a multicenter, prospective observational study of hemodialysis patients with secondary hyperparathyroidism (SHPT) in Japan. Data from MBD-5D study were analyzed to assess the association between CTR and all-cause, CVD mortality and hospitalization across quartiles of CTR (Log rank test, P<0.0001, P<0.0001, and P<0.0001, respectively). In time dependent Cox regression analyses, all-cause death increased across quartiles of CTR in DM patients, but in non-DM patients CVD death was significantly higher in patients with the higher quartile of CTR compared to those with the lowest quartiles of CTR in non-DM and DM patients.

Higher CTR across quartiles was associated with greater risk of CVD hospitalization in non-DM patients, but not in DM patients.

Conclusions: CTR is associated with all-cause, CVD mortality and hospitalization in HD patients with SHPT.


FR-PO402
NT-proBNP is a More Significant Prognostic Biomarker for Mortality Than Troponin T in Incident Hemodialysis Patients

Ji Suk Han,
Hyung Jung Oh,
Hyang Mo Koo,
Chan Ho Kim,
Tae-Hyun Yoo,
Shin-wook Kang.
Dept of Internal Medicine, College of Medicine; Brain Korea 21, Yonsei Univ, Seoul; On behalf of the Clinical Research Center for ESRD Investigators, Korea.

Background: Numerous previous studies have demonstrated that cardiac and inflammatory biomarkers are significant predictors of cardiovascular (CV) and all-cause mortality in ESRD patients. However, these studies were limited by retrospective analyses, inclusion of small numbers of patients, mostly prevalent dialysis patients, and measurement of one or two biomarkers. In this study, we investigated the association between three biomarkers (NT-proBNP, cTnT, and hsCRP) and mortality in incident hemodialysis patients.

Methods: A prospective cohort of 864 incident hemodialysis patients from 36 centers of the CRC for ESRD in Korea was followed for up to 30 mo. CV and all-cause mortality were compared between ‘high’ and ‘low’ groups according to the median baseline values of biomarkers. Cox proportional hazard analysis was performed to determine the independent prognostic value of each biomarker for CV and all-cause mortality.

Results: CV survival rates were significantly lower in the ‘high’ NT-proBNP and cTnT groups compared to the corresponding ‘low’ groups. However, there was no significant difference in CV survival rates between the ‘high’ and ‘low’ hsCRP groups. All-cause mortality rates were significantly higher in all three ‘high’ groups. In multivariate Cox models, natural log value (Ln) of NT-proBNP and cTnT but not Ln hsCRP were found to be significant independent predictors of CV (Ln NT-proBNP, HR=2.228, P=0.002; and Ln cTnT, HR=1.274, P=0.015) and all-cause mortality (Ln NT-proBNP, HR=1.392, P=0.012; and Ln cTnT, HR=1.182, P=0.034). Moreover, among the three biomarkers, NT-proBNP had the highest positive predictive values for not only CV mortality (AUC=0.812, P<0.001) but also all-cause mortality (AUC=0.666, P=0.003).

Conclusions: Although high levels of NT-proBNP and cTnT, but not hsCRP, were independently associated with CV and all-cause mortality in incident hemodialysis patients, the prognostic value of NT-proBNP for mortality were higher than that of cTnT.

Funding: Government Support - Non-U.S.
FR-PO403
Real-Time Monitoring of Cardiovascular Status during Routine Hemodialysis
D. Miskulin,1 Klemens B. Meyer,1 John E. Moran,2 1Nephrology, Tufts Medical Center, Boston, MA; 2Intelemed, Inc, Pittsburgh, PA; 1Nephrology, Stanford Univ School of Medicine, Stanford, CA.

Background: Intracavitary hypotension (IDH) is common among patients on maintenance hemodialysis (HD) and may contribute to the high rate of cardiovascular (CV) events and mortality. Studies have shown IDH to be associated with impaired myocardial perfusion and stunning during HD.

Methods: 25 patients with a history of frequent hypotensive episodes during routine HD were monitored during 4 HD treatments using the CVInsight device (Intelemed, Inc), which captures and processes the signal from a standard pulse oximeter (Nonin Medical, Inc) to display the rates of change of pulse frequency and pulse amplitude. We assessed the device’s prediction of intradialytic events, but did not intervene on the basis of the CVInsight display. Events were defined as either active staff intervention because of perceived hemodynamic instability, such as reduction in ultrafiltration rate or administration of saline bolus, or a fall in systolic BP below 90 mm Hg.

Results: 22 patients (88%) experienced one or more events: 30 episodes of systolic BP < 90 mm Hg, 25 episodes of intervention for symptoms suggesting hypovolemia, including lightheadedness, cramping, and weakness. Events occurred a mean of 95 min. into treatment. A recognized event did not follow 22 false positive alerts; the device yielded 12 false negatives, failing to predict an event, for sensitivity 78.2 % and specificity 51.1 %. CVInsight device alerts occurred a mean of 53 min. into treatment, giving a mean lead time of 40 mins. to allow intervention to prevent CV events.

Conclusions: The CVInsight device provides non-invasive real-time monitoring of CV status during HD and predicts the majority of CV events with a lead time which would allow intervention to prevent such events.

Funding: Pharmaceutical Company Support - Intelemed, Inc

FR-PO404
Is There an Association between Copeptin and NT-proBNP in Hemodialysis Patients? Jae Won Yang, Jae Seok Kim, Seung-Ok Choi, Byoung Geun Han. Nephrology, Yonsei Univ Wonju College of Medicine, Wonju, Gangwon, Republic of Korea.

Background: Copeptin, precursor to vasopressin, is associated with body fluid volume and heart dysfunction. Therefore, this study was intended to investigate the level of copeptin and its relationship with fluid and heart dysfunction markers in patients with hemodialysis.

Methods: This study included forty-one patients with hemodialysis. At the time of their visit for hemodialysis treatment, laboratory data including NT-proBNP was collected and pre-dialysis volume status, laboratory data including NT-proBNP was collected and pre-dialysis volume status.

Results: The level of pre-dialysis copeptins was elevated in patients with LVDs vs. non-LVDs (22826.85±11739.56 pg/ml, P=0.000), pre-dialysis OH (1.75±1.03 vs. 3.15±1.90 liters, P=0.014). In addition, the ROC curve for discriminating LVDs from non-LVDs showed that the area under the curve (AUC) was 0.86 (95% confidence interval 0.77-0.94). When comparing the non-LVDs group with the patients without LVDs, patients with LVDs had higher levels of pre-dialysis copeptins than the patients without LVDs.

Conclusions: This study showed that hemocontrol system could be benefit from reducing IDH episodes, but there were no specific changes in other parameters. In addition, hemocontrol-high responsive patients had lower intradialytic BP and less amounts of ultrafiltration. The clinical consideration of these results will be needed in the future.

Funding: Government Support - Non-U.S.

FR-PO406
Frequent Nocturnal Hemodialysis Associates with Improvement of Prolonged QTc Intervals Benjamin Ka Thomson,1 Brad Urquhart,2 Shih-Han S. Huang,3 Christopher T. Chan,4 Robert M. Lindsay.5 1Western Univ; 2Western Univ; 3University of British Columbia.

Background: Sudden cardiac death remains the leading cause of death in hemodialysis (HD) patients. Prolongation of QTc intervals (as measured by the tangent method) increases sudden cardiac death risk in populations without kidney disease.

Methods: We performed a retrospective electrocardiograph (ECG) and chart review of HD patients. Our objectives were (1) to establish the effect of one of four different dialysis modalities on interdialytic QTc intervals, (2) to determine the effect of dialysis frequency and time on QTc interval and on the prevalence of borderline or prolonged QTc intervals, and (3) to determine if changes in QTc interval were simultaneous to changes in electrocardiographic left ventricular mass.

Results: Frequent nocturnal HD was associated with a decrease in QTc interval for all patients who initiated dialysis with prolonged QTc (468.2 ± 438.2 ms, P = 0.0134).

Funding: Government Support - Non-U.S.

FR-PO407
The Effects of Study Events and Treatment on Health-Related Quality of Life (HRQoL) in the EVOLVE Trial Andrew H. Briggs,1 2Patrick S. Parfery,3 Nasreen Khan,4 Spring Tseng,5 Bastian Dehmel,6 Glenn M. Chertow,6 Vasily Belozersky.7 1Univ of Glasgow, United Kingdom; 2Oxford Outcomes Inc; 3Memorial Univ; 4IMS Health; 5Amgen Inc; 6Stanford Univ School of Med.

Background: EVOLVE™ (Evaluation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) is a randomized, controlled trial evaluating the effects of cinacalcet in patients with secondary hyperparathyroidism (sHPT) on hemodialysis. The objective of this analysis was to assess the impact of study events and treatment on HRQoL.

Methods: HRQoL was assessed using EQ-5D and as a secondary endpoint, using the EQ-5D-5L, at baseline and at scheduled visits and after a study event. The pre-planned analysis assessed changes in EQ-5D from baseline to scheduled visits. We also conducted a regression analysis to assess change (first three months) and chronic (beyond three months) effects of major sHPT-related health events (see Table) on HRQoL and, including a randomized assignment (cinacalcet vs. placebo) to assess the residual effect of cinacalcet on HRQoL not mediated by events.

Results: Data on HRQoL were available for 3547 of 3883 subjects with a total of 1650 events in the placebo and 1502 in the cinacalcet arm. No difference in HRQoL was observed in the direct (naive) comparison of EQ-5D by treatment arm. The regression analysis (Table) showed significant effects of events. After accounting for events, there was a modest positive effect of cinacalcet on HRQoL.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-P0408
Coronary Intervention Reduces Mortality among Dialysis Patients with Acute Coronary Syndrome: Taiwan National Cohort Study
Chih-Chiang Chien.

Background: Patients on chronic dialysis have poor outcomes after acute coronary syndrome (ACS). Epidemiological data for Asian patients are scarce.

Methods: In the Taiwan National Health Insurance Research Database, we examined records of ESRD patients who initiated dialysis between 1999 and 2001. Patients were followed until death, end of dialysis, or December 31, 2008. Predictors of ACS and mortality were calculated using Cox models.

Results: A total 19974 incident dialysis patients were examined in this study. ACS was diagnosed in 1785 patients during follow-up (1.78/100 person-years): 832 (46.6%) had acute myocardial infarction (AMI), 615 (34.6%) had unstable angina, 152 (8.5%) had heart failure (HF), 129 (7.3%) had arrhythmia, 88 (4.7%) had peripheral vascular disease (PVD), and 29 (1.6%) had cerebrovascular disease. The hospitalization survival rate was 79.3%; the 1-year rate was 72.3%. Being elderly (HR 3.289, 95% CI: 1.23-1.49), male (HR 1.35, 95% CI: 1.23-1.49) and having baseline comorbidities (diabetes mellitus, hypertension, congestive heart failure, coronary artery disease, dysrhythmia, other cardiac and chronic obstructive lung diseases) had a higher incidence of ACS than did those without. Overall in-hospital mortality was 9.7%. The cumulative 6-month post-hospitalization survival rate was 79.3%; the 1-year rate was 72.3%. Being elderly (≥ 65 years old), and having DM or AMI were associated with an increased risk for mortality; PTCA was associated with a decreased risk (HR 0.77, 95% CI: 0.66-0.91).

Conclusions: ESRD dialysis patients had a high incidence of ACS and mortality. Being male, elderly and having baseline comorbidities were independent risk factors for ACS. Coronary intervention is possible benefits for dialysis patients.

FR-P0409

Background: Raised troponins in hemodialysis patients are prognostic indicators for cardiovascular (CV) risk and correlate with markers of uncontrolled SHPT. Though evidence suggests that control of the latter may reduce CV risk, however the effect of the calcimimetic agent, cinacalcet, remains uncertain.

Methods: This 2 year retrospective study compared trends in troponin and PTH along with CV morbidity and mortality among HD patients with severe SHPT receiving cinacalcet vs matched controls, not on this agent.

Results: PTH levels were lower at baseline in controls yet maintained, whereas troponin was similar and did not decrease over time. Conversely, both PTH and troponin levels decreased significantly from baseline in the cinacalcet group vs controls (table 1).

Conclusions: A comparison of HRQoL using the EQ-SD score at scheduled visits in EVOLVE showed no difference between randomized groups. A regression analysis showed large decrements in HRQoL after major hSHP-related health events and a modest improvement in HRQoL with cinacalcet.

Funding: Pharmaceutical Company Support - Amgen

FR-P0410
Serum Selenium Levels Correlate with Coronary Artery Flow Reserve in Hemodialysis Patients Elif Ari Bakir,1 Beyza Macunluoglu. 2 Nephrology, Kartal Research and Training Hospital, Istanbul, Turkey; 2Nephrology, Ukudar State Hospital, Istanbul, Turkey.

Background: The objective of this study was to assess the correlation between serum selenium levels and coronary artery flow reserve (CFR) as an indicator of endothelial dysfunction (ED) and accelerated atherosclerosis in hemodialysis (HD) patients.

Methods: Seventy chronic HD patients and 69 age and sex-matched healthy controls were included in the study. Plasma selenium levels were performed by high-performance liquid chromatography measurements. CFR was assessed by transluminal Doppler echocardiography.

Results: Serum levels of selenium (34.16[1m]:61.5 vs 52.4[1m]:5.51, p<0.001) and CFR values (1.73±0.11 vs 2.32±0.28, p=0.001) were lower in HD patients compared to controls. There was a significant positive correlation between CFR and serum levels of selenium (r = 0.676, p<0.001). A linear regression analysis showed that serum levels of selenium were independently and positively correlated with CFR (regression coefficient = 0.457, p<0.05).

Conclusions: This study was the first to show a positive and independent correlation between serum selenium levels and CFR as an indicator of ED and accelerated atherosclerosis in HD patients.

FR-P0411
Role of Monocyte Membrane Expression of Tumor Necrosis Factor Alpha (TNFα) Receptors in Altered Immune Response of Hemodialysis Patients Nathalie Neirynck, Griet Lrl Glorieux, Eva Schepers, Anemieke Dhoond, Raymond C. Vanholder. Nephrology Div, Ghent Univ Hospital, Belgium.

Background: TNFα is elevated in hemodialysis (HD) patients and very likely plays a role in a HD-related micro-inflammation. Signal transduction of TNFα depends on the membrane expression of TNFα-receptor 1 (TNFR1) and 2 (TNFR2). We hypothesized that changes in monocyte membrane expression of TNFR1 and TNFR2 could contribute to the altered monocyte function in HD patients. In this study, we compared the expression of membrane (m)TNFR1, mTNFR2 and mTNFα on monocytes in healthy controls and HD patients.

Methods: Whole blood samples from healthy controls (C) and predialysis samples of HD patients were labelled in vitro with fluorescent anti-mTNFR1, anti-mTNFR2 and anti-mTNFα at baseline and after stimulation with LPS (1 μg/ml, 30 min) (n = 8) and analyzed by flow cytometry. Monocytes were gated and the mean fluorescence (MFI) was measured.

Results: At baseline, there was no difference in monocyte mTNFR1, mTNFR2 or mTNFα expression between C and HD. After LPS stimulation, however, the expression of mTNFR1 and mTNFR2 was lower in HD compared to C, respectively 1265 vs 2266 (p < 0.05) and 840 vs 1324 (p < 0.05). A similar trend was observed for mTNFα (HD: 499 vs C: 782, p = 0.092). Comparing the expression after stimulation and baseline, a significant increase in mTNFα in C (2266 vs 753, p < 0.05) and decrease in mTNFR1 and mTNFR2 in HD (499 vs 681, p < 0.05) was observed. This lower expression of mTNFR1, 2 and mTNFα on monocytes in healthy controls and HD patients.

Conclusions: There was no difference in baseline expression of mTNFR1, mTNFR2 and mTNFα on monocytes in dialysis patients compared to healthy controls. However, after LPS stimulation, a lower receptor expression in dialysis patients was observed compared to controls. Our findings might play a role in the patho-physiology responsible for the depressed immune response in HD patients upon infection.

Funding: Government Support - Non-U.S.
FR-PO412
Relevance of Fibroblast Growth Factor and Vascular Endothelial Growth Factor in End Stage Renal Disease and Their Relevance to Cardiovascular Events
Vinoj K. Bansal, Kristiyanava Kaneva, Debra Hoppensteadt, Jawed Fareed. Pathology and Medicine, Loyola Univ Medical Center, Maywood, IL.

Background: Fibroblast Growth Factors (FGF) represent families of heparin binding growth factors and Vascular Endothelial Growth Factor (VEGF) also known as Vascular Permeability Factor are a potent mediator of angiogenesis and vasoclegenesis in various diseases. We hypothesized that both of these growth factors may be upregulated in End Stage Renal Disease (ESRD) and may contribute to the cardiovascular events.

Methods: This study included 119 ESRD patients undergoing maintenance hemodialysis after appropriate IRB approval and patient consent. Citrated blood samples were collected prior to and immediately after the dialysis session. The blood samples were centrifuged for 15 minutes at 3000 g at 4°C and platelet poor plasma (PPP) was extracted. Citrated plasma was frozen at -70°C. Samples collected from ESRD patients were analyzed for the circulating levels of FGF-23 by using a sandwich ELISA kit (Millipore, St. Charles, Missouri). The VEGF expression was carried out using Quantikine sandwich ELISA method (R&D Systems, Minneapolis, Minnesota). Plasma samples collected from normal male and female (n = 80) comprised the normal group.

Results: The FGF-23 levels ranged from 0 to 3934 pg/ml (Mean = 1861 pg/ml with S.E.M = 151) in contrast to the normal levels of 18.4 ± 6.1 pg/ml. Of the 119 patients, 67 (56.3%) had greater than 1000 pg/ml FGF-23 levels. The VEGF levels ranged broadly from 8.2 to 3673 pg/ml (Mean = 141 pg/ml with S.E.M = 50.1) in contrast to the normal levels of 8.7 ± 4.2 pg/ml. Of the 119 patients, 16 (13.4%) had VEGF levels greater than 100 pg/ml of which 4 (3.36%) had levels greater than 1000 pg/ml. No correlation was observed between the VEGF and FGF23 levels.

Conclusions: End Stage Renal Disease represents a complex polypathologic disorder where growth factors such as VEGF and FGF-23 play an important role.Both of these growth factors are upregulated in ESRD and may contribute to the cardiovascular and cerebrovascular events. Newer targets to modulate these growth factors may be useful in the therapeutic management of these patients.

FR-PO413
Posterior Reversible Encephalopathy Syndrome in End Stage Kidney Disease: Not Strictly Posterior or Reversible
Mark N. Canney, Dearbhla Kelly, Michael Clarkson. Dept of Renal Medicine, Cork Univ Hospital, Ireland.

Background: Posterior Reversible Encephalopathy Syndrome (PRES) is an uncommon clinicoradiological condition that can result in severe brain injury. Little is known about PRES in kidney disease despite the presence of recognised risk factors including hypertension and immunosuppression. This study aimed to define the incidence of PRES in an End Stage Kidney Disease (ESKD) population and identify potential aetiological factors.

Methods: This was a retrospective observational study. The database of adult incident ESKD patients in South West Ireland was interrogated over the period 2002 to 2012 and cross referenced with the patient database of the Department of Radiology to identify cases of PRES. Those cases were further assessed by a detailed review of their hospital record. The patients who accept the enrollment to the study will be randomly divided into the next two groups; the Group A, treated by EVAL membrane; the Group B, treated by several high flux membrane such as PS. The entry criteria of the patients are the age more than 70 years old, the dialysis vintage less than 180 days. The target number of the entry is 800 in each Group. The 5 year-survival, changes in the nutritional status, occurrence of complications and others are the end points.By June 5th 2013, 601 patients have recruited to the study.

Conclusions: Based on this interim analysis there are no clinically noteworthy differences between EVAL and PS for elderly dialysis patients.

Funding: Pharmaceutical Company Support - AASHIKASEI MEDICAL CO., LTD.

FR-PO416
Serum Levels of Free Retained Organic Solutes and Outcomes in Hemodialysis Patients
Tariq Shafi,1 Timothy W. Meyer,2 Thomas H. Hostetter,3 Michal L. Melamed,4 Yang Liu,1 Tanushree Banerjee,5 Neil R. Powe.5

Background: Uremic toxins are heterogeneous group of substances. Hemodiafiltration with on-line endogenous reinfusion (HFR) dialytic method needs an optimal combination of the membrane permeability and cartridge resin bed. In this study, SELDI-ToF and ESI-QTOF Mass Spectrometry for separation of three different membranes and identification of pre cartridge ultrafiltrate (UF) obtained from dialysed patients using three different membranes.

Methods: 25 dialysed patients were treated with three membranes: polyphenylene High Flux (pHF), polyphenylene Super High-Flux (pSHF) and Synclear 0.2 (Sync 0.2). UF samples were collected at 30, 60, 90, and 120 min during the dialysis, were loaded on ProteinChip and analysed by SELDI-ToF. Differences in protein profiles, in terms of molecular weight and peaks intensities, were detected by statistical analysis. UF samples from Sync 02 treatment were analyzed by ESI-QTOF.

Results: Proteinic profiles at 30 min of dialysis, showed higher cluster peaks intensities for the pHF with respect to the pSHF and Sync 0.2 membranes. On the contrary, at 60 and 240 min, the cluster peaks intensities decreased for pHF and increased for pSHF and Sync 0.2. Cluster peaks in the range of 30-60 kD and 60-100 kDa, had the lower number of detected peaks and intensities, for the pHF, while the Sync 0.2 showed the higher permeability, especially for the species >60 kDa, during all treatment. Several inflammatory proteins were identified by ESI-QToF.

Conclusions: The results of this study demonstrate that, compared to pHF and pSHF, the Synclear 0.2 membrane offers the higher permeability and efficiency, showing its potential use for the clearance of high molecular toxins.

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

460A
FR-PO417

Pegloticase, a Recombinant Uricase for the Treatment of Advanced Gout, Maintains Therapeutic Concentrations during Dialysis

Anthony J. Bleyer,1 David E. Wright,2 Alan Gliecklich,1 1Wake Forest Univ Sch Med, Winston-Salem, NC; 2Savient Pharmaceuticals, Inc.

Background: Patients (pts) commonly proceed to dialysis with advanced tophaceous gout and information on the use of urate-lowering medications in the dialysis population is scant. Pegloticase is reserved for pts with chronic gout who are refractory to current oral treatments and does not require dose adjustment based on renal function. Here we present results from a pharmacokinetics/pharmacodynamics study of pegloticase in hemodialysis (HD) pts.

Methods: A single intravenous dose of pegloticase (8mg) was administered to pts (age 18-75 years; N=12) without gout. The pegloticase infusion was completed over a 2-hour period at 3 hours prior to the Day 1 HD. A second HD was monitored on Day 4. Pts received prophylactic antihistamine and corticosteroid prior to the pegloticase infusion. Blood samples were drawn pre-HD and hourly over 4 hours post-HD during the Day 1 and Day 4 HD sessions.

Results: Mean age of this cohort was 44 years, 58% were male, 25% were white, 67% were black, and mean BMI was 28.6 kg/m². HD vintage was 6.4 years and 2 pts had a prior kidney transplant. Mean arterial and venous pegloticase concentrations across sampling times during the Day 1 and Day 4 HD sessions are shown in the figure.

Baseline mean serum uric acid was 5.98 mg/dL; by 3 hours post-infusion serum uric acid was undetectable and remained so through the final serum sampling at 72 hours. One AE of headache was possibly related to study drug.

Conclusions: In this Phase 1 study, pegloticase concentration was not affected by a single HD session and remained stable following a second HD session 3 days later. Serum uric acid levels in this cohort fell to non-detectable levels by 3 hours post-infusion. While additional research is needed, these data support the use of pegloticase in patients with chronic tophaceous gout in HD.

Funding: Pharmaceutical Company Support - Savient Pharmaceuticals

FR-PO415

Increasing Fracture Rates in Elderly Dialysis Patients in the United States

Anna Mathew,1 John D. Wagner,2 Lisa M. Rosen,2 Kenar D. Jhaveri,1 Steven Fishbane.1 1Div of Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY; 2Dept of Biostatistics, Feinstein Institute for Medical Research, Great Neck, NY.

Background: Fractures cause excess morbidity in dialysis patients. New approaches for bone mineral disorders in end stage renal disease have recently evolved. This study aims to determine if rates of fractures in dialysis patients have declined.

Methods: Using an overdispersed Poisson regression model, we modeled fracture counts from 935,221 dialysis patients in the United States Renal Data System (USRDS) from 1992 to 2009 for the primary outcome of central fractures (hip and vertebral) requiring hospitalization. The first 90 days of dialysis were excluded. The study population was stratified by the demographic characteristics of age, race and gender.

Results: From 1992 to 2004, central fracture rates increased from 12.5 to 25.3 per 1,000 person-years. After 2004 fracture rates stabilized but did not decline. The overall p-value<0.0001 indicated a significant increase in central fracture rates from 1992 to 2009. With stratification by age and race, the sharp rise in central fracture rates was explained almost entirely by patients 65 year or older in age, and occurred primarily in white patients. Taken together, the striking rise in bone fractures occurred almost exclusively in elderly, white patients with 22.7 fractures per 1,000 person-years in 1992 to 48.4 fractures per 1,000 person-years in 2004.

Conclusions: Central fracture rates have increased from 1992 to 2004, mostly in white, elderly dialysis patients and despite availability of new treatments. Untreated loss of bone volume and density in ESRD may contribute to these findings, and a “one size fits all” treatment paradigm for bone disease may be harmful to some dialysis patients. Further studies on diagnosis and management of bone disease in elderly dialysis patients are warranted.

Funding: NIDDK Support

FR-PO418

Low Hip Bone Mineral Density Predicts Mortality in Maintenance Hemodialysis Patients: A Five-Year Follow-Up Study

Siinee Dithabanchong,1,2 1Div of Nephrology, Saint Louis Univ, Saint Louis, MO; 2Div of Nephrology, Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Phayathai, Bangkok, Thailand.

Background: Bone loss is common among hemodialysis patients and may contribute to increased mortality. The degree of bone loss is related to the severity of vascular calcification which may explain the increased mortality risk. Studies that investigated the relationship between bone loss and mortality in maintenance hemodialysis patients are limited.

Methods: Eighty-three maintenance hemodialysis patients underwent the measurements for bone mineral density (BMD) of the hip and lumbar spine by DEXA scan and coronary artery calcification (CAC) by multi-slice CT. The relationship between BMD and mortality were analyzed after adjustments for relevant cardiovascular and CKD risk factors after 5 years of follow-up.

Results: The average follow-up duration was 48±15 months. Mortality occurred in 26 patients (31.3%): twelve (46%) were from cardiovascular causes. Eighty percent of the patients had reduced total hip BMD (t-score<-2) at baseline. Total hip BMD showed negative relationship with CAC scores. In univariate Cox regression analyses, age, cardiovascular disease (CVD), dyslipidemia, increased c-reactive protein, increased CAC scores and decreased hip BMD (HR=0.007, 95%CI=0.01,0.136, P<0.001) were associated with mortality. There was no relationship between lumbar BMD and outcome. Low hip BMD remained independently associated with mortality after adjustments for age, gender, DM, CVD, dyslipidemia, serum albumin, c-reactive protein, CAC score, dialysis vintage, serum phosphate and alkaline phosphatase levels (HR=0.001, 95%CI=0.005, P<0.005). In Kaplan-Meier survival curve, patients with total hip BMD in the lowest tertile displayed the worst survival (P<0.045).

Conclusions: Low hip BMD is common among maintenance hemodialysis patients and has the ability to predict mortality independent of cardiovascular and CKD risk factors.

Funding: Private Foundation Support

FR-PO420

Mineral and Bone Disorder Medication Use Patterns in U.S. Dialysis Patients

Akeem Yusuf,1,2 Wendy L. St. Peter.1,2 1USRDS Coordinating Center, MMRF; 2Univ of Minnesota.

Background: Chronic kidney disease mineral and bone disorder (CKD-MBD) management involves use of multiple therapeutic agents. We describe CKD-MBD medication use trends in US Medicare Part D enrolled dialysis patients.

Methods: We created annual cohorts of adult dialysis patients (2007-2010) using Centers for Medicare and Medicaid Services End-Stage Renal Disease database linked with Medicare Part D data. We included patients ≥18 years, alive on December 31 of the previous year, with Medicare Parts A, B and D coverage from January 1 to earliest of death or December 31 of the present year. Medication use was defined as ≥1 claim for an oral medication (or administration record for intravenous (IV) Vitamin D) during follow up, with stratification by low-income subsidy (LIS) status and dialysis organization. Medication groups included prescription phosphate binders, oral and IV vitamin D analogues and calcimimetics. We calculated odds of medication use for LIS vs. non-LIS patients and for patients from various dialysis organizations using logistic regression, adjusted for age, sex, race, vintage and dialysis organization, where appropriate.

Results: Phosphate binders (~85% of patients) and IV vitamin D (77.5%-79.3%) were most common CKD-MBD medications used from 2007-2010 followed by calcimimetics (31.0%-33.3%), and oral vitamin D analogues (8.5%-9.9%). Sevelamer was the main phosphate binder used (~53%); with decreasing use of calcium acetate and lanthanum over study period. Paricalcitol and calcitriol constituted majority of IV and oral vitamin D use, respectively. The odds of using trade name phosphate binders, IV vitamin D and cinacalcet were significantly higher for LIS vs. non-LIS patients and DaVita patients were more likely to use lanthanum, sevelamer and cinacalcet and less likely to use calcium acetate, while Fresenius patients had highest use of IV Vitamin D.

Conclusions: LIS vs. non-LIS and DaVita vs. other provider patients were more likely to be prescribed expensive trade name oral CKD-MBD medications, after adjustment for some factors that affect prescribing. Further research is needed to see if higher use of trade name CKD-MBD agents is associated with better clinical outcomes.

Funding: NIDDK Support

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

461A
Costs Associated with Mineral and Bone Disorder Medications in Dialysis Patients

Akeem Yusuf,1,2 Wendy L. St. Peter,1,2 USRDs Coordinating Center, MMRF,1 Univ of Minnesota.

Background: Dialysis-related chronic kidney disease mineral and bone disorder (CKD-MBD) medications (meds) represent a large portion of Medicare Part D costs in these patients (pts). This has implications for pts, providers and Medicare when these meds are included in the dialysis bundle in 2016. We describe costs associated with these meds in US Medicare Part D-insured dialysis pts.

Methods: Using Medicare standard analytic files linked with Medicare Part D data, we created annual cohorts of dialysis pts (2007 through 2010). We included pts ≥18 years, alive on Dec 31 of each year, with Medicare Parts A, B and D coverage from Jan to Dec. Per member per month (PMPM) net Part D payment and per user per month (PUPM) out-of-pocket (OOP) meds costs for each Part D-covered CKD-MBD med and med class were computed, with stratification by low-income subsidy (LIS) status and dialysis organization.

Results: In 2010, PMPM net Part D costs were $555.22 and $278.65 for all Part D meds and CKD-MBD meds respectively. There was a 22% vs. 36% increase in total Part D vs. CKD-MBD Part D med costs from 2007 to 2010. CKD-MBD meds represented about 50% of overall net Part D costs in 2010 (Phosphate binders/(PB) 30%, cinacalcet 19%, oral vit D 2%). Between 2007 and 2010, PMPM Part D costs were highest among DaVita pts for cinacalcet, sevelamer carbonate and lanthanum as compared to other dialysis providers. PUPM OOP costs for PB decreased from 2008 to 2009 while OOP costs for sevelamer carbonate had a sustained year-to-year increase. PUPM OOP costs for all CKD-MBD meds were much higher for pts without LIS vs. with LIS.

Conclusions: PMPM net costs increased faster for CKD-MBD meds compared to all Part D meds in dialysis pts, despite relatively stable use within medic classes from 2007-2010. This was mainly due to increases in net Part D PMPM spending for sevelamer and cinacalcet. OOP costs for PB were reduced in 2009, due to availability of generic calcium acetate. However, pts without LIS, on average, had high PUPM OOP costs for brand name CKD-MBD meds. In a bundled environment, there will be incentives to shift to generic PB and reduce use of cinacalcet, particularly with no MBD performance measures in place.

FR-PO424

Effect of Frequent Nocturnal Hemodialysis (NH) or Renal Transplantation (RT) on Cognition

Bradley S. Dixon,1 John M. Vanburen,2 Jacob J. Oleson,1 Robert S. Lockridge,2 James R. Rodrigue,1 Jane S. Paulsen,1 John B. Stokes,1 Univ of Iowa; 1Univ of Virginia; 2Harvard Med School.

Background: It is unknown whether frequent hemodialysis or renal transplantation will reverse the cognitive impairments seen in patients with end stage kidney disease on conventional hemodialysis.

Methods: We performed a prospective cohort trial analyzing the effect of switching from conventional hemodialysis 3 days per week (HD) to either nocturnal hemodialysis (NH) 6 days per week or renal transplantation (RT) on tests of memory and learning (Rey Auditory-Verbal Learning Test, AVLT and Brief Visuospatial Memory Test, BVTM), executive function (Trails B test) and psychomotor processing speed (Buttons and Digit-Symbol tests). Participants were measured at baseline, 4 and 12 months and tested for significant change at follow-up using a linear mixed model.

Results: A total of 77 patients switched to nocturnal hemodialysis (n=18), received a renal transplant (n=28) or remained on conventional hemodialysis (n=31). Baseline characteristics were not significantly different between the groups. 48 patients (62%) returned for their 12-month study visit (67% NH, 46% RT and 74% HD) at a mean ± SD follow-up of 14.0 ± 2.2 months. Patients who received a renal transplantation showed improvement in AVLT (p<0.01) and Digit-Symbol test (p<0.01) but not BVTM, Trails B or Buttons. Treatment with nocturnal hemodialysis did not improve any of the cognitive tests and BVTM declined (p=0.02). Surprisingly, patients remaining on conventional hemodialysis showed improvement in the Digit-Symbol test (p<0.01) and Buttons test (p=0.05) and a decline in verbal fluency (p<0.001) but no change in AVLT, BVTM or Trails B.

Conclusions: After 13 months, renal transplantation improved auditory/verbal memory and processing speed but not executive function. In this small study, no improvement in cognitive testing was seen with initiating nocturnal hemodialysis.

FR-PO425

Cognitive Function and All-Cause Mortality in Hemodialysis Patients

Mark J. Sarnak,1 Hocine Tighiouart,2 David A. Drew, Kristina Lou, Saeed Kamran Shaffi, Tammy Scott, Li Fan, Daniel E. Weiner. Tufts Medical Center, Boston, MA.

Background: Cognitive impairment is highly prevalent in dialysis patients. Although advanced dementia is associated with mortality, it remains unknown whether milder degrees of cognitive impairment, and which components of this impairment, are associated with mortality.

Methods: 292 patients enrolled in the Dialysis and Cognition Study underwent a detailed battery of previously validated cognitive tests. Principal factor analysis was used to derive two summary factors representing memory and executive function. Mortiﬁvable Cox proportional hazards models were used to evaluate the association of the individual tests, as well as the memory or executive memory component with all-cause mortality.

Results: Mean (SD) age was 63 (16) years, 53% were women and 23% African American. 146 patients died during a median follow up of 27.4 months. Higher executive function scores were associated with lower risk of mortality. In contrast, memory was not associated with mortality.

Conclusions: These data suggest that patients starting dialysis patients have greater risks of the commonest types of cancer.

Funding: NIDDK Support

FR-PO422

End-Stage Renal Disease Due to Multiple Myeloma in the United States, 2000-2010

Scott Reule,1,2 Donal J. Sexton,1,2 Craig Solid,1 Shu-cheng Chen,1 Allan J. Collins,1 Robert N. Foley,1 USRDs Coordinating Center, MMRF, Minneapolis, MN; Medicine, Univ of MN, Minneapolis, MN.

Background: As management has advanced rapidly, we combined US census data with data from the USRDs patients to determine whether incidence rates and survival of ESRD from myeloma and light chain deposition disease (MM) have improved correspondingly.

Methods: A total of 13,832 of 1,140,882 (1.2%) patients initiated dialysis due to MM between 2000 and 2010. Using incidence rates for 2000 to calculate expected incidence rates for subsequent years (based on age, sex and race/ethnicity), standardized incidence ratios peaked in 2001 at 1.19, declining subsequently to 0.86 in 2010.

Results: Characteristics of MM patients included older age (≥65, 63.7% vs. 43.7%), white race (76.3% vs. 65.1%), catheter for hemodialysis (94.9% vs. 82.4%), and <1 year of prior hematology/oncology care (49% vs. 76.3%). When adjustment was made for demographics, MM was associated with a greater likelihood of death (adjusted hazards ratio [AHR] 2.32) and a lower likelihood of living for (AHR 0.018) and receipt of (AHR 0.2) of a renal transplant. Among patients with myeloma, likelihood of death remained unchanged, transplant rates increasing in 2008-2010 (AHR 4.21 for 2008-2010 vs. 2000-2004) and then decreasing in AHR 0.80. Regional variation in outcomes was apparent, as patients in the South were more likely to die (AHR 1.04 Vs. the Northeast), and less likely to be listed (AHR 0.49) or receive a transplant (AHR 0.41).

Conclusions: While ESRD due to MM has declined in the United States, outcomes on dialysis remain poor and exhibit substantial geographic variation.

Funding: NIDDK Support

FR-PO423

Cancer Risk in Incident Dialysis Patients in the United States, 2005-2009

Robert N. Foley,1,2 Craig Solid,1 Shu-cheng Chen,1 Allan J. Collins,1 USRDs Coordinating Center, MMRF, Minneapolis, MN; Medicine, Univ of MN, Minneapolis, MN.

Background: Few recent large-scale epidemiological studies are available to determine whether patients starting dialysis therapy are at greater risk of cancer than the general population.

Methods: Hence, we set out to address this information gap among 112,699 patients aged 65 or more with Medicare insurance and no prior history of malignancy that started maintenance dialysis in the United States between 2005 and 2009 and were followed for 1.7 years. We used age, sex and race-specific incidence rates from the US general population (Statistics Epidemiology and End Results (SEER) database, (United States) National Cancer Institute) to calculate expected rates for cancer of any cause, and for the 10 most common types, based on the demographic profile of the dialysis population. Actual cancer rates were calculated from Medicare hospital admissions claims.

Results: All cancers studied occurred more frequently than expected (P < 0.05) in dialysis patients. For any cancer, actual and expected incidence rates were 14,747 and 682 per 100,000 per year, respectively, an actual-to-expected incidence ratio of 21.6. Incidence ratios for individual cancers were as follows: prostate 5.3, breast 5.1, lung and bronchus 3.0, colon and rectum 3.9, melanoma 2.8, urinary bladder 8.4, non-Hodgkin lymphoma 5.5, kidney 17.3, uterus 3.8, and leukemia 8.2.

Conclusions: These data suggest that patients starting dialysis patients have greater risks of the commonest types of cancer.

Funding: NIDDK Support

FR-PO421

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

Underline represents presenting author/disclosure.
FR-PO426

End-of-Life Inpatient Cost Trajectories for Patients with Chronic Kidney Disease Compared with Those with Other Chronic Conditions

Kenn B. Daratha,1 Ann M. O’Hare.2 1Beth Israel Deaconess Medical Center, Boston, MA; 2Brigham and Women’s Hospital, Boston, MA; 3DaVita Clinical Research.

Background: The cost of caring for patients receiving chronic dialysis is extremely high, due mostly to high rates of inpatient utilization. To date, little is known about cost trajectories toward the end of life in patients with kidney disease in relation to those with other chronic conditions.

Methods: We conducted a longitudinal study among 7,065 adults who were hospitalized at the time of death in the State of Washington in 2011 (WA-CHARS). We estimated inpatient costs during the last year of life for members of this cohort with the following chronic conditions: heart failure (HF-39% of all terminal cases with select chronic conditions), chronic obstructive pulmonary disorders (COPD-35%), metastatic cancer (METs-21%), kidney failure without renal replacement therapy (CKD-21%) and kidney failure with renal replacement therapy (ESRD-8%).

Results: Patients with ESRD were more likely than those with other chronic conditions to have at least one inpatient hospitalization (84%) in the year preceding the terminal hospitalization, as compared with 73% for patients with HF, 71% for CKD, 67% for COPD and 67% for METs. Total costs in the last year of life were also highest for patients with ESRD (Figure 1).

Conclusions: Among non-insulin dependent diabetics on HD, TZD use versus SU use was associated with 43% lower all-cause mortality. There was no difference in mortality seen for insulin users.

Funding: NIDDK Support, Private Foundation Support

FR-PO427

Thiazolidinedione Use Is Associated with Improved All-Cause Mortality Compared with Sulfonylureas among Non-Insulin Dependent Diabetic Hemodialysis Patients

Katherine E. Lynch,1,2 Connie Rhee,2 Steven M. Benavoli,1,3 Beth Israel Deaconess Medical Center, Boston, MA; 2Brigham and Women’s Hospital, Boston, MA; 3DaVita Clinical Research.

Background: Among diabetics on hemodialysis (HD), there are conflicting data as to whether thiazolidinediones (TZD) use improves or worsens survival. Previous studies have compared TZD users to non-users. However, non-user control groups are known to have at least one inpatient hospitalization (84%) in the year preceding the terminal hospitalization, as compared with 73% for patients with HF, 71% for CKD, 67% for COPD and 67% for METs. Total costs in the last year of life were also highest for patients with ESRD (Figure 1).

For patients with COPD and METS no relationship was found between costs in the last quarter of life and terminal hospitalization costs. A positive relationship was observed between costs in the last quarter of life and the cost of terminal hospitalization for patients with HF (=0.12, p=0.001), CKD (=0.15, p<0.001) and ESRD (=0.17, p=0.002).

Conclusions: Among chronically ill patients who died in the hospital, the cost of the terminal hospitalization and overall inpatient costs during the final year of life were markedly higher than for other chronic conditions.

Funding: Private Foundation Support

FR-PO428

High Prevalence of Elevated Non-A1c Glycemic Indices in Chronic Dialysis Patients without Documented Diabetes

Neal Mittman.1 Lin Ma,2 Mark E. Williams,3 Julia I. Brennan,3 Chimu M. Jani,3 Curtis D. Johnson,4 Franklin W. Maddux,2 Eduardo K. Lascin.2 1Long Island College Hospital, Brooklyn, NY; 2Fresenius Medical Care, North America, Waltham, MA; 3Joslin Diabetes Center, Boston, MA; 4Spectra Laboratories, Rockleigh, NJ.

Background: Quarterly glycosylated hemoglobin (A1c) has been the standard of care for assessing glycemic control in the general population and in dialysis patients. However, serum fructosamine (SF) and glycated albumin (GA) have both been proposed as alternative markers in dialysis. Based on our previous work (Desiraju et al, 2005), we hypothesized that non-diabetic (NDM) ESRD pts (normal A1c, <5.6%) may exhibit undetected hyperglycemia when assessed by alternative glycemic indices.

Methods: We explored simultaneous measurement of SF and GA in NDM pts by A1c criteria in a national sample of 1192 NDM pt from 26 FMCNA facilities. Residual blood from routine monthly specimens was used for analysis. We report on mean values in these pts for the period January-March 2013.

Results: The cohort’s mean age was 56 years, 45% female, 43% white, 55% black, and 21% on PD. Fewer than 60% of these non-diabetics had all three glycemic markers within the normal non-diabetic range. More than 50% had elevated SF, 16% had elevated GA, and 15% had increased levels of both. More than 90% of pts with elevated GA had concurrently elevated SF. However, more than 70% of pts with elevated SF had normal GA.

Conclusions: To our knowledge, there are no published data assessing alternative glycemic markers in non-diabetic dialysis pts and the potential impact on morbidity of elevated values. We and others have reported that elevated levels of SF and/or GA are predictive of morbidity and mortality in diabetic dialysis pts. Therefore, further analyses of these NDM patient subgroups is needed to determine the significance of these elevated glycemic indices.

Funding: NIDDK Support, Private Foundation Support

FR-PO429

Biochemical Variables and Survival of Patients with Type 1 Diabetes on Renal Replacement Therapy

Jasko Helve,1 Mikko Haapio,1 Per-Henrik Groop,2 Carola Gronhagen-Riska,3 Patrik Finne.4 1Dept of Nephrology, Helsinki Univer Central Hospital, Helsinki, Finland; 2Finnish Registry for Kidney Diseases, Helsinki, Finland.

Background: End-stage renal disease is one of the most serious complications of type 1 diabetes. Yet, data are limited regarding factors that predict survival of patients with this complication. Our aim was to estimate the effect of biochemical variables on survival of type 1 diabetes patients on renal replacement therapy (RRT).

Methods: An incident cohort of all patients with type 1 diabetes entering chronic RRT (n=834) in Finland 2000-2011 was followed up until death or end of follow-up on 31 December 2011. All data came from the Finnish Registry for Kidney Diseases. Creatinine, albumin, urea, ionized calcium, phosphorus, hemoglobin, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and HbA1c were measured from blood or plasma before the initiation of RRT. Main outcome measure was adjusted relative risk of death according to biochemical variables. Cox proportional hazards models were used for these analyses.

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

Underline represents presenting author/disclosure.

463A
Results: When measured before RRT and adjusted for age and sex, low serum creatinine, albumin and hemoglobin, and high C-reactive protein concentration predicted increased mortality. Further adjustment for comorbidities, and initial treatment modality of RRT showed that the most important predictors of death are low creatinine and albumin and high C-reactive protein.

Conclusions: Among type 1 diabetes patients entering chronic RRT, biochemical variables independently associated with survival are creatinine, albumin and C-reactive protein. They reflect nutritional status, proteinuria, liver function, and ongoing inflammatory process. Anemia also associates with worse survival. Treatment of these might improve survival.

Funding: Private Foundation Support

FR-PO430

Propensity-Matched Comparison of New Onset Diabetes Mellitus between Incident Peritoneal Dialysis and Hemodialysis Patients "Chin-Ching Huang, 1,2 Che-yi Chou, 1,2 "Divs of Nephrology, China Medical Univ Hospital, Taichung, Taiwan; 1Graduate School, China Medical Univ, Taichung, Taiwan."

Background: New-onset diabetes mellitus (NODM) is associated with poor outcome in patients treated with hemodialysis (HD) or peritoneal dialysis (PD). PD pts were exposed to extra glucose load from daily dianeal dwelling,we ask the question “Are PD pts more prone to develop NODM after dialysis?”. We used a propensity score (PS) matching approach to study this subject. We aim to compare the incidence and outcome of NODM by intention-to-treat analysis in a propensity-score matched HD and PD cohorts.

Methods: All HD and PD pts in Taiwan Renal Registry Database (include all pts who survived ≥ 1M after dialysis) were analyzed from 1995 to 2005. Pts were followed until death, renal transplantation or up to December 31, 2008. We attempted to correct for differences between patient characteristics using a PS-matching method. We matched each PD pt with 4 HD pts with a similar PS. PS accounted for factors recorded in the database, including age, sex, body weight, primary renal disease and co-morbidity. We compared the incidence and survival outcomes of NODM in PD and PS-matched HD pts. Predictors of NODM and mortality were studied using Cox models.

Results: We analyzed 2548 non-DM incident PD pts and 10192 PS-matched HD pts with 5.9±3 years follow-up. Mean age of PD pts were 50.2±14.7y vs. 50.2±14.4y of matched HD pts.During follow up , 13% of PD patients and 22% of PS-matched HD pts developed NODM. The crude incidence of NODM was 2.2%y for PD pts, lower than 3.7%y for HD pts (p<0.001). The risk of NODM after starting dialysis is approximately 50% lower (HR 0.48) for PD pts compared to HD. Male gender, a lower serum albumin and lower hematocrit were independently linked to increased NODM risks. After adjusting for covariates, regardless of dialysis modality, patients who developed NODM had increased overall mortality (HR 3.628, p<0.001) than those did not.

Conclusions: In a PS-matched Chinese cohort, incident pts receiving HD carry a higher risk of developing NODM than those receiving PD. The pts with NODM are associated with a higher SMR compared to PD pts. Male gender, a lower serum albumin and lower hematocrit were independently linked to increased NODM risks. After adjusting for covariates, regardless of dialysis modality, patients who developed NODM had increased overall mortality (HR 3.628, p<0.001) than those did not.

Funding: Government Support - Non-U.S.
FR-PO434
Oxidant Stress, Quality of Life and Physical Function in Chronic Kidney Disease Patients Are Improved by Intradialytic Aerobic Cycling Program Myriam Rouchon Insard,1 Céline Coutard,2 Céline Forte,3 Cuinccin Christine,3 Nathalie Boissuex,1 \textsuperscript{1} AURA Arvegnie, Chamalières; \textsuperscript{2} UFR STAPS, Univ BP Aubière; \textsuperscript{3} Cardiologie, Clinique, Durtol; \textsuperscript{4} Biologie, Gen Bio, Clermont-Ferrand.

Background: In Chronic Kidney Disease (CKD), oxidant stress plays a central role in the development of cardiovascular diseases. This study aimed to determine if an intradialytic aerobic cycling training protocol, by improving aerobic fitness, could reduce oxidant stress and other related CKD disorders as lipid profile and quality of life (QOL) of these patients.

Methods: Eighteen haemodialysis patients randomly were assigned to either intradialytic exercise training (cycling) group (EX; n = 8) or a control group (CON; n = 10) for 3 months. Aerobic fitness (6 min walk test), pro/antioxidant status (in plasma: 15F2-isoprostanes [F₂-isoP], oxidized LDL [ox-LDL], in erythrocytes: SOD, GPX, GSH/GSSG), lipid profile (total cholesterol, HDL, LDL, TG), and QOL (SF36QD) were measured at baseline and 3 months later.

Results: Intradialytic training protocol had beneficial effects on pro/antioxidant status, aerobic fitness, lipid profile and QOL. Indeed, at 3 months: i) IsoP concentrations were significantly lower in EX compared to CON (-35.7 %) ii) performance on the 6 min walk test significantly increased by 23.4% in EX, but did not change in CON and iii) plasma TG were significantly reduced in EX (-23%) without modification in CON iv) QOL was clinically improved and significantly for the Mental Component Summary (+2.2% in EX vs -2% in CON).

Conclusions: These results show that intradialytic aerobic cycling training protocol exerts beneficial effects in CKD patients by reducing the most sensitive and reliable marker of OS (IsoP) and by improving their lipid profile, physical function, and QOL.

FR-PO435
Association of Daily Physical Activity with Bone Mass in Hemodialysis Patients Kei Yoneki,1 Atsuhiko Matsunaga,1 Jun Kitagawa,1 Ryota Matsuzawa,1,2 Akira Ishii,1 Yoshifumi Abe,1 Manae Harada,1 Yasuo Takeuchi,1 Atsushi Yoshida,1 Kouju Kamata.1 Kitasato Univ, Sagamihara, Japan; 2Sagami Junkanki Clinic, Sagamihara, Japan.

Background: Low bone mass is a leading cause of fracture. Although daily physical activity is recommended as a preventative measure against bone loss in healthy adults, the effects of physical activity on bone mass in hemodialysis (HD) patients are unclear. This study aimed to determine whether daily physical activity is associated with bone mass in HD patients.

Methods: This observational, prospective study consisted of two parts: cross-sectional Study 1 and longitudinal Study 2. At the beginning of Study 1, 165 HD outpatients (87 men and 78 postmenopausal women; mean age, 68.88 years) who visited our HD center 3 times a week were recruited. Clinical characteristics including age, sex, body mass index, HD duration, and medications (active vitamin D) were recorded from clinical records in both parts of the study. Biochemical parameters including serum phosphorus, corrected calcium, and intact parathyroid hormone levels were also measured. With respect to bone mass, the stiffness index was assessed by quantitative ultrasound of the calcaneus. With respect to physical activity, the number of steps walked per day was measured using an accelerometer. In Study 1, the association between physical activity and bone mass was assessed by multiple regression analysis for each sex. In Study 2, participants were divided into two subgroups according to physical activity based on results from Study 1 (≥5,000 steps per day or not), and two-way analysis of variance (ANOVA) was used to identify the effect of physical activity on bone mass for each sex after a 2-year follow-up.

Results: Multiple regression analysis adjusted for clinical characteristics and biochemical parameters in Study 1 indicated that physical activity was significantly associated with bone mass in HD patients of each sex (P<0.05, respectively). ANOVA showed that changes in bone mass were significantly different between the two HD patient subgroups for each sex (P<0.05, respectively) in Study 2.

Conclusions: Decreased daily physical activity is strongly associated with bone loss in HD patients.

FR-PO436
Functional Impairment and Survival of Dialysis Patients Wil P.D. Lemahieu,1 Maarten Naessens,2 Johan M.J. De Meester,3 Nephrology, Imelda Hospitals, Bonheiden, Belgium; 2Nephrology, Univ Hospitals Gasthuisberg, Leuven, Belgium; 3Nephrology, St. Nicolas Hospitals, Sint Niklaas, Belgium; 4Nephrology, Jessa Hospitals, Hassel, Belgium.

Background: This study aimed to explore functional status of dialysis patients, its possible overlap with classical medical parameters and impact on survival.

Methods: 3753 prevalent (95% coverage) Flemish dialysis patients completed a survey on 3 fields: medical (disease, wound care, amputations, hospitalization), ambulatory autonomy (ability to walk, recent falls, type of balance, means of transportation to/from dialysis facility) and care dependency (need for assistance with meals, drug management, incontinence and nursing home residency). Patients ≥75 years vs those younger were compared by Student’s T test. Clustering of individual survey items was assessed by principal components analysis. This was complemented by follow-up on 15 months’ mortality and Cox proportional hazards analysis including all survey items, gender and age.

Results: Only 15% of all patients was completely impairment-free versus 28% suffering from at least one impairment in each field. For those ≥75 years this was respectively 6% and 38% versus 25% and 19% for the younger cohort. Two distinct clusters of patients could be identified: 32% had impairments in all but one (‘recent falls’) items of ambulatory autonomy and care dependency, and in 11% all except ‘hospitalizations’ medical field items clustered. Overall 15 months’ mortality was 16%. The number of impaired items (‘no’ or 0-1 vs ‘mild’ or 2-4 vs ‘severe’ or > 4) composing the major patient cluster had the strongest effect on mortality.

Conclusions: Diminished ambulatory autonomy and increased care dependency cluster in an important fraction of Flemish dialysis patients. This clustering does not correlate with classical medical factors but is none the less associated with increased mortality.

FR-PO437
Race and Frailty Differences in a Prevalent Hemodialysis Cohort Nancy G. Kintner,1 Rebecca H. Zhang,1 William M. McClellan,1 Quinilyn A. Soltow,1 Janice P. Lea.2 1Biosciences & Bioinformatics, Emory Univ, Atlanta, GA; 2Medicine, Nephrology Div, Emory Univ, Atlanta, GA; 3Medicine, Pulmonology Div, Emory Univ, Atlanta, GA.

Background: Among non-dialysis dependent persons with chronic kidney disease (CKD), blacks are more likely than whites to be identified as frail. No prior research has investigated race and frailty patterns among prevalent end-stage renal disease (ESRD) patients undergoing dialysis, a population in which blacks appear to have better survival and quality of life.

Methods: Setting & Participants: 745 prevalent ESRD patients undergoing hemodialysis 2009-2011 in 7 Atlanta dialysis clinics and 7 San Francisco Bay Area dialysis clinics for whom frailty indicators were assessed. Measurements: Study coordinators interviewed participants; measured grip strength, walk speed and body composition; and reviewed charts for clinical and laboratory parameters. Vintage, primary ESRD diagnosis, and receipt of pre-dialysis nephrology care were identified in United States Renal Data System files. Using the Fried frailty index (recent unintentional weight loss, reported exhaustion, low grip strength, walk speed, low physical activity), frailty was defined as the presence of 3 or more criteria and pre-frail by the presence of 1 or 2 criteria.

Results: In this prevalent hemodialysis cohort (median vintage = 3 years) with mean age = 57, almost 75% were classified as pre-frail or frail. However, the adjusted analysis showed that the risk for being classified as frail was 40% lower among blacks compared with whites (p < .05). Peripheral vascular disease and low serum albumin were additional significant predictors of frailty.

Conclusions: We observed a lower risk for frail status among black compared with white hemodialysis patients, in contrast with higher frailty risk reported for black compared with white non-dialysis CKD patients. Examination of frailty patterns among black and white CKD patients in the transition to ESRD may offer increased understanding of apparent paradoxes in survival and well-being associated with race among patients with kidney disease.

Funding: NIDDK Support, Other NIH Support - PHS Grant UL1 RR025098 from the Clinical and Translational Science Award program, NIH, NCRR

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
FR-PO438

Frailty: The Strongest Predictor of Quality of Life in Dialysis Patients
Jun Chul Kim,1 Ki-soo Park.2 1Div of Nephrology, CHA Gumi Medical Center, CHA Univ, Gumi-si, Gyeongsangbuk-do, Korea; 2Dept of Preventive Medicine, Gyeongsang National Univ, Jinju, Gyeongsangnam-do, Korea.

Background: Frailty is a growing concern in maintenance dialysis (MD) patients, which is significantly related to the higher incidence of disability, hospitalization and mortality. However, there is no report evaluating the relation of frailty with quality of life (QOL) in this population.

Methods: We only included ambulatory MD patients aged ≥20y on hemodialysis (HD) or peritoneal dialysis (PD) ≥3mo, without hospitalization for the last 3mo. Study participants completed the Korean version of Kidney Disease Quality of Life Short Form 36 (K-DQOL SF-36) and other data were obtained by medical record and at 12mo. Frailty phenotype composed of the following components; 1) unintentional weight loss ≥4.5 Kg or 5% of the previous body weight for the last 1y; 2) p2 physical inactivity, 3) p2p physiological function (PF) score <75 and vitality score <55 as surrogates for weakness/slowness and exhaustion, respectively. Low PF score was scaled as 2 points and other components as 1 point for each. Those with ≥3 points were considered as ‘frail’.

Results: 1,658 (1,255 HD, 403 PD) patients evaluated aged 55.9±12.9y (mean/SD) on MD for 5.2±4.5y; 55.7% were male. Compared to the non-frail, frail patients (34.9%) showed significantly (all P-values <0.001) lower scores in Physical Component Score (PCS) (43.7±18.7 vs. 70.4±14.7), Mental Component Score (MCS) (45.9±20.0 vs. 65.8±17.1) and kidney disease (KD) related health concerns such as burden of KD (26.5±24.3 vs. 39.9±26.3), symptom/problems (72.4±16.6 vs. 84.4±12.0) and effect of KD on daily life (63.9±20.6 vs. 77.8±16.5). In multiple regression analysis, frailty was found to be the strongest predictor (all P-values <0.001) for worse conditions of PCS (B=-25.1), MCS (B=-20.1), burden of KD (B=-14.1), symptom/problems (B=-12.7) and effect of KD on daily life (B=-15.3) after adjustment for age, gender, vintage, dialysis modality, co-morbidity, blood hemoglobin, serum albumin and creatinine.

Conclusions: Frailty is significantly related to poor outcomes in KD and related health concerns and can be very useful predictor for QOL even in a relatively healthy MD patients.

FR-PO439

Predictors of Physical Performance in Patients on Maintenance Haemodialysis: A 12 Month Follow-Up Study
Ying Wang,1 Cathie Sherrington,1 Martin P. Gallagher,1 Alan Cass,2 Paul Snelling,1 Meg J. Jardine.3 1The George Institute for Global Health, NSW, Australia; 2Centre for Health Research.

Background: Poorer physical quality of life is associated with worse outcomes among people with end stage kidney disease (ESKD). While muscle metabolism is known to be impaired, the associations of strength and performance in ESKD remain poorly understood.

Methods: We recruited 51 maintenance haemodialysis (HD) patients and 10 healthy volunteers to a longitudinal study. Physical performance (Short Battery Performance Test-SBPT) and strength (ankle dorsiflexion strength-AS) were assessed at baseline and 12 month follow-up. A subgroup of 28 dialysis participants underwent neuropathy assessment (Total Neuropathy Score-TNS). Linear regression was used for normally distributed variables and correlation for skewed variables.

Results: Fifty HD patients and 9 controls completed the study. At baseline, HD participants had poorer physical performance than controls (respectively median SBPT scores 10 and 12, p=0.002) but similar strength (respectively mean AS 13.9 and 14.2, p=0.6). Neuropathy was inversely correlated with physical performance (r=-0.46, p=0.011) but not strength (r=0.2). At 12 months, strength and physical performance were significantly reduced in the HD group, compared with baseline (mean AS 11.0 versus 13.9, p=0.001; SBPT 9 versus 10, p=0.001, respectively). Neuropathy had deteriorated over 12 months (mean TNS score 7.48 at 12 months versus 6.48 at baseline). Among HD participants, poorer physical performance at baseline was predicted by age (p=0.001), diabetes (p=0.007), strength (p=0.001) and neuropathy (p=0.011) while deterioration over 12 months was predicted by age (p=0.001), diabetes (p=0.008), and strength (p=0.001). Poor strength at baseline was predicted by age (p=0.001) and diabetes (p=0.041) with no strong predictors of deterioration (age, p=0.096; diabetes, p=0.57).

Conclusions: Haemodialysis patients have poor physical performance that is not explained by muscle strength alone. Physical performance and strength deteriorated over 12 months in a stable haemodialysis cohort. Better understandings of the underlying mechanisms of the poor physical health in ESKD are needed.

Funding: Government Support - Non-U.S.

FR-PO440

Physical Activity Energy Expenditure and Quality of Life in Maintenance Hemodialysis Patients with and without Major Comorbidities
Marina Albuquerque Dantas, Jean M. Monteiro, Claroscio Plácido Santos, Gildele Barreto Lopes, Antonio Alberto Lopes. Federal Univ of Bahia, Salvador, Brazil.

Background: Maintenance hemodialysis (MHD) patients with comorbidities have, in general, lower physical activity (PA) levels and poorer health-related quality of life (HRQOL). We investigated associations between physical activity energy expenditure (PAEE) and HRQOL in patients with > 3 mo. on MHD, separately by groups with and without major comorbidities.

Methods: Cross-sectional analysis of data of 660 MHD patients in the Prospective Study of the Prognosis of Chronic Hemodialysis Patients (PROHEMO) developed in 4 clinics in Brazil. The International Physical Activity Questionnaire was used for PA. The following comorbidities were considered in the analysis: diabetes, heart failure, coronary disease, cerebral vascular disease, peripheral vascular disease, pulmonary diseases and cancer; 217 patients were diagnosed and 423 were not diagnosed with any of these comorbidities. Metabolic equivalent of task (MET) was used for determining PAEE and categorized by the median (≤498 and >498 kcal/week). SF-36 was used for scores of 8 primary HRQOL scales and the physical (PCS) and mental component summaries.

Results: Among patients without comorbidities, HRQOL scores were higher in those with PAEE=498 kcal-week for all scales, with difference in score (DS) > 4 points for PCS (DS=-4.7), vitality (DS=-6.8), role emotional (DS=-9.6), pain (DS=-7.8), role physical (DS=-14.9), and physical functioning (DS=-13.6). Associations of higher PAEE with better HRQOL were not markedly changed after linear-regression adjustments for age, sex, education, economic class, marital status, and living with family. In patients with comorbidities, the associations followed the same directions and were not substantially different from those without comorbidities (interaction coefficient PAEE*comorbidity=0.2).

Conclusions: The results based on PAEE provide further support for potential beneficial effects of physical activity on the health of MHD patients, both for those with and without major comorbidities, but it is not possible to establish causal links or the direction of the association due to the cross-sectional design of the study.

FR-PO441

Differences in Health Status and Healthcare Delivery between Men and Women Starting Dialysis Therapy in the United States: 1995-2010
Ahad Abdalla,1 Alish Hannigan,2 Liam F. Casserly,1,2 Austin G. Stack.1,2 1Medicine and Nephrology, Univ Hospital Limerick, Limerick, Ireland; 2Graduate Entry Medical School, Univ of Limerick, Limerick, Ireland.

Background: Differences in survival between men and women may be related to their health status at the start of dialysis and differences in care delivery prior to dialysis initiation. The aim of this study was to compare health care status and healthcare delivery among men and women in the national US Renal Data System Registry.

Methods: We compared baseline health indicators in 1, 220, 000 incident US patients (662, 985 men and 557,015 women) who commenced dialysis from 1995-2010. Comparisons were made across 10 comorbid conditions, and 6 measures of pre-dialysis care delivery (anaemia, nutrition, pre-dialysis care, timing of dialysis initiation, dialysis modality). The timing of dialysis initiation was assessed using the CKD-EPI equation. Multivariable logistic regression was used to compare gender differences for each outcome with the generation of adjusted odds ratios (OR). SAS v9.3 was used for all statistical analysis. Ethical approval was received from the University Hospital Ethics Committee.

Results: The likelihood of having a major medical disease was significantly lower for women than men for most conditions listed with the exception of diabetes, heart failure and stroke. However, women were significantly more likely than men to have a low body mass index, hypeobulinemia at dialysis initiation and were more likely to have dialysis initiated late. These differences persisted when consideration was taken into account for case mix.

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

Dialysis: Epidemiology, Outcomes, and Clinical Trials: Non-Cardiovascular - I

FR-PO442
Fibroblast Growth Factor 23 and the Risk of Infectious Hospitalizations
and Deaths in Hemodialysis Patients: Results from the HEMO Study
Kristen L. Jablonski,1 Jessica B. Kendrick,1 Alfred K. Cheung,2,3 Tom Greene,3
Michel Chonchol.1 1Univ of Colorado Denver, Aurora, CO; 2VASLCHCS, Salt
Lake City, UT; 3Univ of Utah, Salt Lake City, UT.
Background: Fibroblast growth factor 23 (FGF23) acts as a phosphaturic factor.
Recently, FGF23 has been suggested to be a regulator of innate immunity, as it has the
potential to inhibit the enzyme 25-hydroxyvitamin D-1-hydroxylase in monocytic cells,
with concomitant effects on intracrine responses to 1,25-dihydroxyvitamin D.
Methods: The HEMO Study was a randomized multicenter study evaluating the effects
of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Serum intact
FGF23 levels were measured in stored serum samples obtained at baseline and annually in
1,340 HEMO participants. Quartiles of FGF23 concentrations were chosen as the primary
predictor variable, with the lowest quartile serving as the reference category. Time-dependent
Cox proportional-hazards models were used to examine the association between FGF23
levels with a composite of hospitalizations and death attributed to an infectious cause.
Results: Participants had a mean age of 57±14 years, 55% were females and 46%
were white. During a median follow-up of 3.0 years, 499 (37%) participants had an event
attributed to an infectious cause. Median (IQR) serum FGF23 levels was 3118 [726,
12928] pg/mL. Overall, median levels of FGF23 rose during follow-up (p=0.01). After
adjustment for potential confounders available in the database, including inflammatory
markers and usage of calcitriol, higher serum FGF23 levels were directly associated with
higher risks of the infectious composite. Compared to the first (lowest) quartile, the HR
(95% CI) for infections were as follows: second quartile, 0.95 (0.72-1.25); third quartile,
1.41 (1.06-1.89) and fourth quartile, 1.58 (1.14-2.21). Similar results were obtained when
FGF-23 was examined as a continuous variable (HR; 1.10, 95% CI 1.02-1.13 per doubling
of FGF23; p=0.01).
Conclusions: In the HEMO study, higher serum FGF23 levels were independently
associated with infectious hospitalizations and death in time-dependent Cox regression
models.
Funding: NIDDK Support

FR-PO443
Associations of Serum 25-Hydroxyvitamin D and 1,25-Dihydroxyviatmin D
Levels with Infectious Hospitalization and Infectious Death in the HEMO
Study Anna Jeanette Jovanovich,1 Jessica B. Kendrick,1 Alfred K. Cheung,2,3
Tom Greene,3 Michel Chonchol.1 1Div of Renal Diseases and Hypertension,
Univ of Colorado Denver, Aurora, CO; 2VA Salt Lake City Healthcare System,
Salt Lake City, UT; 3Univ of Utah, Salt Lake City, UT.
Background: Determine whether serum vitamin D levels are related to infectious
hospitalization and death in subjects requiring hemodialysis.
Methods: The HEMO Study was a randomized multicenter study evaluating the effects
of high-dose vs. standard-dose and high-flux vs. low-flux hemodialysis. 25-hydroxyvitamin
D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)2D) levels were measured in stored
serum samples obtained at baseline and annually in 1,340 subjects. Serum 25(OH)D and
1,25(OH)2D level quartiles were chosen as the primary predictor variable, the lowest
quartile served as the reference category. Time-dependent Cox proportional-hazards models
were used to examine the association of vitamin D levels with infectious hospitalization
and infectious death.
Results: Mean age was 57±14 years, 55% were female, and 46% were white. During
a median follow-up of 3.0 years, 499 (37%) subjects were hospitalized for or died of
an infectious cause. Median [IQR] serum 25(OH)D and 1,25(OH)2D levels were 19.1
[14.2, 26.6] ng/mL and 6.3 [2.9,14.5] pg/mL, respectively. After adjustment for potential
confounders available in the HEMO cohort including inflammatory markers and use of
calcitriol, the highest quartile of 25(OH)D was associated with a reduced risk of infectious
hospitalization and death (HR 0.72, 95% CI 0.53-0.97; p=0.03) compared to the lowest
quartile. When 25(OH)D was evaluated as a continuous variable, higher levels of 25(OH)
D were associated with a reduced risk of infectious death and hospitalization (HR 0.84,
95% CI 0.72-0.98 per doubling of 25(OH)D; p=0.02). There was no association between
1,25(OH)2D levels with infectious events (HR; 1.02, 95% CI 0.0.95-1.08 per doubling of
1,25(OH)2D; p=0.64).
Conclusions: Low serum 25(OH)D level, but not 1,25(OH)2D level, is independently
associated with infectious hospitalization and infectious death in subjects requiring
hemodialysis.
Funding: NIDDK Support

FR-PO444
Infectious Hospital Admissions among Prevalent Hemodialysis and
Peritoneal Dialysis Patients from 1993 to 2011 Tricia L. Roberts,1 Robert
N. Foley,1,2 David T. Gilbertson,1 Craig Solid,1 Allan J. Collins.1,2 1USRDS
Coordinating Center, MMRF, Minneapolis, MN; 2Medicine, Univ of Minnesota,
Minneapolis, MN.
Background: In the past two decades, infectious hospital admission rates have
increased among hemodialysis (HD) patients, while admissions for peritoneal dialysis (PD)
peritonitis have fallen close to those for HD vascular access infection. However, infectious

Poster/Friday

admissions traditionally have been defined by principal ICD-9-CM diagnosis codes which
could be susceptible to shifts in billing practices. Rates using both principal and secondary
diagnosis codes have not yet been assessed.
Methods: We included U.S. Medicare period prevalent HD (N=305,901 in 2011) and
PD (N=23,558 in 2011) patients from 1993 to 2011. Admission rates were computed for allcause infection, bacteremia/sepsis, PD peritonitis, and HD vascular access (VA) infection.
Two methods defined infectious admissions from inpatient claims using principal diagnosis
codes only, method 1 (M1), and principal and secondary diagnosis codes, method 2 (M2).
Rates were adjusted for age, gender, race, and primary ESRD diagnosis using model-based
adjustment and a Poisson model.
Results: For all-cause infection, admission rates were 1.5 to 2.0 times higher with
M2 than M1 (in 2011 among HD and PD, respectively, 462 and 551 admissions per 100
patient months with M1; 903 and 935 with M2). All-cause infectious admission rates
among PD patients were generally stable across years and higher than HD; however, by
2011, admissions with infection (M2) increased among HD patients to levels similar to
PD. Rates were 2 to 4 times higher for M2 than M1 for bacteremia/sepsis (in 2011, 123
and 82 with M1; 282 and 201 with M2) and for PD peritonitis (81 with M1; 354 with M2).
With M2, PD peritonitis admissions were 2 to 4 times higher than HD VA infection (88
with M1; 118 with M2).
Conclusions: Rates for admissions with infection were strikingly high compared to
those for the purpose of infection. Results suggest that attention is needed to address lack
of improvement in the last two decades in all-cause infectious admissions among dialysis
patients using both methods and high admissions with peritonitis among PD patients.
Funding: NIDDK Support

FR-PO445
Spinal Epidural Abscess in Hemodialysis Patients Jennifer Marie White,1
Chan Jin,1 Rhonda E. Colombo,1 Stephanie L. Baer,1,2 Usman Afzal,1 Kristina
W. Kintziger,1 Mufaddal F. Kheda,1 Lu Y. Huber,1 Puja Chebrolu,1 N. Stanley
Nahman.1,2 1Georgia Regents Univ, Augusta, GA; 2Augusta VAMC, Augusta, GA.
Background: Spinal epidural abscess (SEA) may be a serious infectious comorbidity
in hemodialysis (HD) patients. SEA may be the result of bacteremia (BAC), but other
factors are possible. We have previously shown that BAC occurs in over 20% of incident
HD patients, suggesting a significant risk for this condition (Chebrolu, IDSA, 2012). To
more fully address the role of BAC and other co-morbidities associated with SEA, we
queried the United States Renal Data System (USRDS).
Methods: All incident HD cases from the USRDS for calendar years 2005-2008 were
queried for a diagnosis of SEA, BAC and several potential clinical covariates using ICD-9
diagnosis codes submitted for Medicare billing. Descriptive statistics and log-binomial
regression analysis were performed.
Results: For the 4-year period of study, 355,084 patients were available for analysis.
The median age was 65 years. SEA was identified in 660 (0.19%) patients. Vascular access
type at the initiation of HD included AVF in 47,732 (13.4%), AVG in 14,179 (4.0%) and
vascular catheter in 293,173 (82.6%) patients. Of the demographic variables, black race
[relative risk (RR) 1.218, 95% confidence interval (CI) 1.025- 1.447] and female sex [RR
1.179, 95% CI 1.009-1.379] carried significant risks for SEA. Infectious comorbidities,
including diagnosis of BAC [RR 7.757, 95% CI 6.432-9.355], MRSA infection [RR 2.684,
95% CI 2.192-3.286] and hepatitis C [RR 1.660, 95% CI 1.223-2.253] were associated
with the highest risk. Of the non-infectious factors, diabetes mellitus [RR 1.515, 95% CI
1.278-1.797] and vascular catheters [RR 1.347, 95%&#8232;CI 1.008-1.800] carried an
increased risk of SEA.
Conclusions: SEA is an uncommon but serious complication of HD. The risk of SEA
is highest in patients with infectious co-morbidities, especially BAC, but diabetes and the
presence of a vascular catheter are also significant risk factors.

FR-PO446
Nontuberculous Mycobacterial Infections and End Stage Renal Disease in
the Outpatient Setting Rhonda E. Colombo,1 Puja Chebrolu,1 Mufaddal F.
Kheda,1 N. Stanley Nahman,1,2 Kristina W. Kintziger.1 1Georgia Regents Univ,
Augusta, GA; 2Charlie Norwood VA Medical Center, Augusta, GA.
Background: Nontuberculous mycobacteria (NTM) have been implicated as an
uncommon cause of peritonitis complicating peritoneal dialysis (PD) and in periodic reports
of infection in hemodialysis (HD) patients. We previously characterized NTM infections
among hospitalized ESRD patients on HD (Colombo, JIM, 61(2), 2013). However, NTM
may have an indolent presentation and be diagnosed in the outpatient setting. We thus
conducted a retrospective analysis of the USRDS to describe NTM diagnoses during
outpatient visits among the incident ESRD population.
Methods: All patients newly diagnosed with ESRD between 2005-2007 were queried
for a diagnosis of NTM infection and potential clinical covariates using ICD-9 diagnosis
codes. Medicare Part B claims were the source of outpatient data. Classification of NTM
disease was via querying separate codes for pulmonary (PULM), disseminated (DISS),
cutaneous (CUT), and “other” (OTH) NTM. Univariable and bivariable descriptive analysis
was conducted on all variables of interest.
Results: During the three year period, 345 individuals had an outpatient visit with
an associated NTM diagnosis. Of these, 241 (69.9%) had not been identified in previous
hospitalization data. Demographics included: 55.9% male, 59.4% white, and 57.7%  70
years. HD was the initial treatment modality for 90.7% of individuals. There were 110
(31.9%) PULM, 11 (3.2%) CUT, 61 (17.7%) DISS, and 163 (47.3%) OTH cases. Underlying
pulmonary disease was significantly more common in patients with PULM NTM (p =
0.02), particularly bronchiectasis (p < 0.0001). HIV, documented in 19.4% of cases, was

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
467A


associated with DISS disease (40.98%, p<0.001). Significant differences (p<0.05) were also seen with age distribution; DISS was more common in patients under age 50. Nearly half (49.6%) of all patients resided in the Southern US at time of diagnosis.

**Conclusions:** Although rare, NTM may infact outpatient ESRD patients. Type and presentation of NTM infection in ESRD varies depending on underlying comorbidities. NTM is most likely to be diagnosed in a cohort of chronic HD patients.

**Method:**

**Results:** Out of 24 HD patients (age 60±13.7 years, 58% male, 46% diabetic, 42% Black), 15 were randomized to receive low-salt intervention. At baseline ThQ and Na-Cal ratio were not correlated (r=0.2; P=0.4). Analysis employing a LMM in a subgroup of 8 patients who completed the study indicated that the intervention resulted in reduced thirst as quantified by the ThQ (P<0.001). In the same subgroup non-significant decreases of Na-Cal ratio, ThQ and IDWG were observed between baseline and the average of the last three months.

**Conclusions:** The interim analysis of our RCT of salt intervention demonstrates that changes in dietary salt intake associates to reduce thirst.

**FR-PO448**

**Alignment of Dialysate (DNa) and Serum Sodium (SNa) in Chronic Hemodialysis (HD) Patients:**

**Methods:** At 4 participating HD clinics, pts with SNa<54 (137 mEq/L) received HD with DNa aligned to the average of the last 4 SNa measurements. “Aligned” were matched to “unaligned” pts (from 44 not participating clinics) based on SNa, SBP, and saline administration. Hospitalization (Hosp) rates per pt year (pt-yr) were compared using linear mixed-effects models.

**Results:** Aligned (n=84) and unaligned (n=84) pts were similar at baseline (68±13 yrs, 50% male, 3.7±3.7 yrs vintage, 62% diabetics and 28% pts with catheters; P>0.05). Treatment effects were significant for pre-HD wt and interH wt gain (IDWG). Although not reaching statistical significance, trends in all parameters suggest alignment to be favorable change in all-cause hosp rates from 2.6 to 1.9/pt-yr and 2.4 to 1.6/pt-yr were observed for aligned and unaligned pts, respectively (p=0.4). Changes in fluid-related hosp rates from 0.3 to 0.3/pt-yr and 0.4 to 0.1/pt-yr were observed for aligned and unaligned pts, respectively (p=0.7).

**Conclusions:** Although our findings suggest that hypochloremia is a risk factor for mortality in HD patients, further studies are needed to confirm findings and to determine if Cl level is a direct mediator of increased mortality, or a proxy of an alternative mortality predictor in this population.

**FR-PO449**

**Hypochloremia as a Novel Risk Factor of All-Cause Mortality in Hemodialysis Patients:**

**Methods:** Using DaVita clinical data, we identified 104,675 maintenance HD patients who underwent treatment from 2001-2007. Associations between time-averaged Cl level and all-cause mortality were estimated in the overall cohort and within subgroups of race/ ethnicity using Cox regression.

**Results:** Patients were on average 61.1±15 years old and included 45% women and 59% diabetics. In the overall cohort, there was an inverse association between Cl levels and all-cause mortality in unadjusted, case-mix, and case-mix and malnutrition-inflammation complex syndrome adjusted analyses (reference Cl 99–<101mEq/L). In subgroup analyses of race/ethnicity adjusted for case-mix and malnutrition-inflammation complex syndrome covariates, a similar pattern of association was observed among non-Hispanic Caucasians, African-Americans, and Hispanic patients. Among Asians, lower Cl levels were associated with increased mortality, whereas higher Cl levels were not associated with greater risk.

**Conclusions:** Our findings suggest that hypochloremia is a risk factor for mortality in HD patients, future studies are needed to confirm findings and to determine if Cl level is a direct mediator of increased mortality, or a proxy of an alternative mortality predictor in this population.

**FR-PO450**

**Recovery of Renal Function in Patients Treated for End-Stage Renal Disease:**

**Methods:** During the study period, 1,841,248 patients were started on dialysis for ESRD. 55,533 (3.6%) of them recovered renal function. From 1996 to 2010, there was a four-fold increase in the number of patients who achieved recovery of renal function (1152 to 5907) and a 2.5 fold increase in the proportion who recovered (2.1% to 5.2%). Recovery of renal function was almost twice as likely in White compared to Black patients (4.4% vs 2.3%, p<0.0001). A greater proportion of hemodialysis patients achieved recovery compared to peritoneal dialysis patients (2.2% vs 0.6%, p<0.0001). 97% of patients who recovered renal function did so by 6 months. Recovery was more likely to occur in patients with baseline GFR ≥ 15 ml/min/1.73m² (6%) and in patients with acute tubular necrosis (28.5%). By 3.5 years after recovery, 50% of patients with recovered renal function had either died or returned to ESRD therapy.
Conclusions: We conclude that the rate of renal recovery has increased over time. Trends in early starts, an increase in AKI patients entering the ESRD program and less stringent acceptance criteria for dialysis therapy may contribute to the observed increasing recovery rates. Genetic studies may be warranted to explain the dramatic differences in rates of recovery between White patients and minority groups.

Funding: NIDDK Support

FR-PO451
Loss of Residual Renal Function in the First Year on Hemodialysis
Stephan Thijssen, Zachary Z. Brener, Len A. Usvyat, Peter Kotanko. Renal Research Institute, New York, NY; Beth Israel Medical Center, New York, NY; Fresenius Medical Care, Waltham, MA.

Background: Residual renal function (RRF) is important for several crucial aspects in kidney disease patients and is a powerful predictor of survival. RRF is generally believed to decline relatively quickly after initiation of hemodialysis (HD). We studied the time course of residual renal urea clearance (Kru) as a surrogate of RRF in the first year on HD.

Methods: Data for the first year on HD were extracted for incident patients who started HD between 12/2000 and 09/2009. Missing Kru values were imputed using the "next observation carried backward" method. We analyzed the subset of patients who had a Kru >0 ml/min in the first month on HD and who survived at least 18 months. The time course of Kru over the first 12 months on HD was fit using a 4th order polynomial function. The first derivative of this function was used to assess the instantaneous rate of change in Kru.

Results: The analysis cohort comprised 1,654 patients (age 60.4±14.5 years, 61% male, 56% diabetic, 57.3% white, 36.6% black). Average Kru in the first month was 3.3 ml/min (95% CI: 3.06-3.49). The figure shows the time course of Kru over the first 12 months on HD (top panel) and the instantaneous rate of decline in Kru (bottom panel). Kru declined at a rate of about 0.36 ml/min/month. This rate of loss progressively decelerated and reached a stable rate of decrease of around 0.05 ml/min/month from month 9 onwards.

Conclusions: In this U.S. cohort of incident HD patients from Renal Research Institute clinics, Kru declined slower than we had expected. Comparisons with other North American clinics, Kru declined slower than we had expected. Comparisons with other North American.

FR-PO452
Angiotensin II Receptor Blockade Does Not Reduce Renal Function Decline in Hemodialysis Patients: A Randomized Controlled Trial
Krista D. Kjaergaard, Christian D. Peters, Bente Jespersen, Kathrine S. Laurlsen, Jens K. Madsen, Marija K. Novosel, Birgitte Pedersen, I.N. Tietze, Bo M. Bibby, Charlotte Strandhave, J. Dam Jensen. Dept of Renal Medicine, Aarhus Univ Hospital, Denmark; Dept of Nephrology, Aalborg Univ Hospital, Denmark; Dept of Internal Medicine, Region Hospital Viborg, Denmark; Dept of Internal Medicine, Fredericia Hospital, Denmark; Dept of Public Health Institute of Biostatistics, Aarhus Univ, Denmark.

Background: Glomerular filtration rate (GFR) declines during chronic dialysis treatment. In peritoneal dialysis, ramipril as well as valsartan reduces GFR decline. Observational studies suggest that similar treatment may preserve renal function in hemodialysis (HD).

Methods: A multicenter randomized placebo-controlled double-blinded trial initiated by the investigators with one year follow-up. Primary outcome was the rate of GFR decline. Methods: Inclusion criteria were urine output >300 mL/24h, HD vintage <1 year, and cardiac ejection fraction >30%. Patients were randomized to the ARB irbesartan (300 mg daily), or placebo. Target systolic blood pressure (BP) was 140 mmHg. GFR was estimated as the mean of creatinine and urea renal clearance and measured at baseline, 1 week and 3, 6, 9, 12 months.

Results: Of the 82 patients randomized (placebo n=41/irbesartan n=41), 56 completed one year of treatment. Patients were similar at baseline: males 26/30, (mean±SD) age 62.1±14.6/61±16 years, HD vintage 168±95/171±93 days, HD time 10±2/11±3 hours/week, urine volume 1.31±0.71/1.45±0.79 L/24h, GFR 4.8±2.3/5.7±3.3 mL/min/1.73m². The target BP level was reached in both groups and adverse event rates were comparable. GFR declined by 1.6(0.2;0.9) (mean,95%CI) in the placebo group and 1.71(0.2;3.3) mL/min/1.73m²/year in the irbesartan group, p=0.29. Urine volume decreased with 431(179;684) in the placebo group and 129(46;144) mL/24h/year in the irbesartan group, p=0.26. In each group, four patients progressed to anuria.

Conclusions: In HD patients, the decline in GFR and urine volume over one year was not affected by irbesartan treatment. We found no evidence against that irbesartan could be safely used in HD patients.

Patients with end-stage kidney disease experience high rates of morbidity and mortality, reporting profoundly impaired quality of life. Greater knowledge of how patients experience different facets of long-term dialysis could inform the design of targeted and effective interventions.

**Methods:** This is a multinational cross-sectional survey using the 23-item CHOICE questionnaire in 2145 long-term outpatient haemodialysis patients in Europe and South America. Patients' ratings of satisfaction with overall care and specific aspects of dialysis care were evaluated.

**Results:** 2145 (78.1%) haemodialysis patients completed the survey. Fewer than half (46.5% [95% confidence interval (CI), 44.5 to 48.6%]) rated their dialysis care as excellent overall. Within countries, global perceptions of care were uninfluenced by most patient characteristics except age and depressive symptoms; older patients were less critical of their care (adjusted odds ratio for excellent rating (AOR) 1.44 [CI 1.03-2.04] for patients 70 years or older compared to those 18-49 years) and those with depressive symptoms were less satisfied (AOR for excellent rating 0.56 [CI 0.44 to 0.71] for patients with a higher depression score).

**Conclusions:** Patients treated with in-centre haemodialysis are least satisfied with the amount and reliability of information they receive during their care, particularly from nephrologists. Meeting patients' expectations of information, prognostic, the likelihood of kidney transplantation and patients' options when choosing dialysis treatment may improve patients' satisfaction with dialysis care.

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

---

**GFR for Dialysis Initiation and Patient Survival: A Physician-Based Analysis**

**Comparison of Survival by Dialysis Modality: Korean Nation-Wide Prospective Cohort**

**Conclusion:** The impact of dialysis modality on survival has still some controversies. Given possible differences in patients' characteristics, cause and rate of death among different countries, the issue needs to be further evaluated in various cohorts. Methods: We compared all-cause mortality between haemodialysis (HD) and peritoneal dialysis (PD) using unmatched (n=1,060) and propensity score (PS) matched (n=556) cohorts. Data came from a Korean nation-wide prospective cohort for end-stage renal disease, in which patients starting dialysis therapy from September 1, 2008 to June 30, 2011 were enrolled.

**Results:** Patients (HD vs PD: 69.4% vs 30.6%) were followed up for 16.3±7.9 months. PD patients were significantly younger and had lower body mass index, lower proportion of diabetes, and larger urinary volume compared to HD patients. Infection was the most common cause of death (31.9% in overall, 29.2% in HD, 41.7% in PD). Multivariate Cox regression with unmatched cohort showed PD tended to be associated with 37% lower risk of death compared with HD [hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.36-1.08]. In PS-matched cohort, cumulative survival probabilities from day 90 for PD and HD were 96.9% vs 94.1% at 12 months (p=0.14) and 94.3% vs 87.6% at 24 months (p<0.05). PD revealed 51% lower risk of death compared with HD (HR 0.49, 95% CI 0.25-0.97).

**Conclusion:** PD therapy shows superior survival to HD in the early period of dialysis even after adjusting differences in patients' characteristics between two modalities.

**Funding:** NIDDK Support

---

**Lower Serum Sodium Level Predicts Higher Risk of Infection-Related Hospitalization and Death in Maintenance Hemodialysis Patients**

**Background:** Hyponatremia is associated with increased mortality in patients with chronic kidney disease, but the specific factors contributing to mortality are unknown. This study investigated the association of serum sodium level (sNa) with risk of infectious disease in hemodialysis (HD) patients.

**Methods:** This observational cohort study included 332 patients who underwent maintenance HD in our dialysis unit in May 2009. The mean of 3 monthly measurements of glucose-corrected sNa before each dialysis session in May, June, and July 2009 was applied as baseline sNa. The primary endpoint was the first infection-related hospitalization (IRH), and secondary endpoints were infection-related death (IRD) and death of any cause.

**Results:** 915 physicians and 2241 patients were included, with median follow-up time 33.7 months; early and late groups included 1111 and 1130 patients, respectively, defined based on their physicians. The two patient groups had very similar characteristics. Both unadjusted mortality rates (15.6 per 100 patient-years, early group, vs. 16.1, late group) and the adjusted hazard ratio for death (0.98, early vs. late, P=0.72) showed group similarity. For patients who developed ESRD, mean eGFRs were 13.3 and 11.8 mL/min/1.73 m² for early and late groups, respectively.

**Conclusion:** Patient survival appears to be independent of physician behavior regarding GFR levels for dialysis initiation.
Data were analyzed using Cox hazards modeling, adjusted for baseline demographics and characteristics, or laboratory data. Patients were followed up from May 1, 2009 until transfusion of first HD, or until January 31, 2013.

Results: Mean sNa was 138.9 mEq/L (tertile 1: 138.0-139.9 mEq/L, n=104; tertile 2: 138.0-140.0, n=116; tertile 3: >140.0 mEq/L, n=112). During a median follow-up of 45.0 months, 57 patients experienced IRH (6.4±1.0% patients-year overall; 89.7/1,000 in tertile 1; 57/1,000 in tertile 2; 28/1,001 in tertile 3), 68 patients died, and 15 of the 68 deaths (22%) were IRDs. Higher sNa was associated with lower risk of IRH (unadjusted hazard ratio (HR) per 1 mEq/L: 0.86; 95% confidence interval (CI), 0.79-0.94; p=0.0005, and adjusted HR, 0.90; 95%CI, 0.81-0.99; p=0.036). Higher sNa was associated with lower risk of all-cause mortality (unadjusted HR, 0.80; 95%CI, 0.69-0.93; p=0.003, and adjusted HR, 0.76; 95%CI, 0.61-0.96; p=0.019), but was not associated with all-cause mortality (unadjusted HR, 0.87; 95%CI, 0.81-0.95; p=0.001, and adjusted HR, 0.92; 95%CI, 0.84-1.02; p=0.115).

Conclusions: Lower sNa was a predictor of higher risk for infection-related hospitalization and death in maintenance HD patients.

FR-PO458
Hypoalbuminemia, Renal Transplantation, and Survival in Prevalent Hemodialysis Patients
James R. Smith, Colin C. Geddes, Neal Padmanabhan, Div of Nephrology & Hypertension, Beth Israel Medical Center, New York, United Kingdom.

Background: Hypoalbuminemia is strongly associated with increased mortality among hemodialysis (HD) patients, and guidelines suggest that renal transplantation is contraindicated in those with a predicted survival less than 5 years. The aim of this study was to assess the influence of hypoalbuminemia on mortality and subsequent transplantation in a prevalent HD cohort.

Methods: All prevalent patients attending 6 HD units receiving HD for >90 days on 04/06/2007 were included. Laboratory data averaged over 3 months was extracted from a prospectively maintained electronic patient record, as were demographics, hospital admissions, and transplant wait-list status. A Cox regression model was used to analyze the impact of serum albumin (sAlb) as well as phosphate and calcium on 5-year survival. Data were analyzed using Cox hazards modeling, adjusted for baseline demographics, age, sex, number of years on HD, vintage, and weight. Pre-HD serum phosphate and calcium were not associated with survival. 117 patients were transplant wait-listed at census date; 51 had a sAlb ≥3.7g/dL, with 93.6% alive at 5 years. Of the 52 prevalent patients, 5-year survival was 63.3% when mean sAlb was >3.7g/dL, falling to 38.8% if 3.3-3.69g/dL, and 16.5% if <3.3g/dL. This remained significant when corrected for age, sex, wait-list status, diabetes, HD access, alfacalcidol use, HD vintage, and serum weight. Pre-HD serum phosphate and calcium were not associated with survival. 117 patients were transplant wait-listed at census date; 51 had a sAlb ≥3.7g/dL, with a 5-year survival of 70.6% compared with 86.4% for those with a sAlb ≥3.7g/dL. However sAlb was not predictive in multivariate analysis. 31 (60.8%) of those wait-listed with a sAlb ≥3.7g/dL were transplanted, with 93.3% alive at 5 years; while 47 patients (71.2%) wait-listed with a sAlb <3.7g/dL were transplanted, with 93.6% alive at 5 years. Of the 8 patients wait-listed with a sAlb <3g/dL, 4 received a transplant, all surviving to 5 years, while only 1 of the 4 not transplanted survived.

Conclusions: In this large, well-defined HD cohort, mild hypoalbuminemia averaged over 3 months predicted reduced survival independent of other factors known to influence survival. However hypoalbuminemia alone may be less important in those deemed otherwise suitable for renal transplant wait-listing.

FR-PO459
Education Predicts Non-Compliance with Maintenance Hemodialysis
KanaNoshiro, Kobena A. Dadzie, Nijal R. Sheth, Nikolas B. Harbord, James F. Winchester. Div of Nephrology & Hypertension, Beth Israel Medical Center, New York.

Background: During a recent disaster in New York, Hurricane Sandy, stranded patients had incomplete knowledge of their hemodialysis(HD) parameters and required triage. We therefore sought to understand the depth of factual knowledge about the patient’s individual dialysis prescription. It is known that missed/shortened HD times are associated with increase in hospitalization and mortality. We aimed to identify baseline characteristics which may be predictive of non-compliance with HD therapy.

Methods: We conducted a cross sectional study of 100 randomly selected HD patients at a HD center in Manhattan. Patients participated in a 1:1 interview about their socioeconomic status, educational background, and knowledge on hemodialysis and kidney disease. Relevant information from their medical records were retrieved. IRB approval was obtained.

Results: Level of education (=high school diploma) appeared to correlate with missed treatments. 27 patients were classified as “skippers” (absent for >3% of scheduled HD); and was associated with less education, less knowledge of potassium rich foods, higher, kidney transplant, more frequent shortening and delay of HD, and more prescribed times on each HD. There were no significant differences in age, sex, number of years on HD, satisfaction, and knowledge of phosphorus rich foods, vascular access, or cause of renal failure. Though not statistically significant, there was a trend towards patients who work being less likely to skip HD.

FR-PO460
Prevalence of Protective Immunoglobulin G Antibody in Maintenance Hemodialysis Patients in Korea
Jong-woo Yoon, Myung Jin Choi, Youngki Lee, Jwa-kyung Kim, Ja-Ryong Koo, Jung-woo Noh. Internal Medicine, Hallym Kidney Research Institute, Chuncheon, Gangwon, Korea.

Background: Hepatitis A is one of the most common acute infectious diseases and usually does not cause chronic disease process. But around 1% of it progress to life-threatening fulminent hepatitis. In the past, seroprevalence of anti-HAV was higher, but recently it has been decreasing in Korea. The incidence of acute hepatitis A in 2010 is 10-fold higher than 20 years before. It shows more severe clinical course and composes more than 80% of inpatient hepatitis care. ESRD is associated with increased propensity to infection, more severe clinical outcomes. DOQI guidelines suggest active immunization and having protective antibody for hepatitis A if seronegative is found. But the prevalence of protective immunoglobulin G antibody in maintenance hemodialysis patients is not known.

Methods: 171 ESRD maintained more than 3 months dialysis duration were evaluated for seroprevalence of protective immunoglobulin G antibody and its antibody titer for hepatitis A. Individuals with evidence of acute and chronic infection were excluded.

Conclusions: In this large, well-defined HD cohort, mild hypoalbuminemia averaged over 3 months predicted reduced survival independent of other factors known to influence survival. However hypoalbuminemia alone may be less important in those deemed otherwise suitable for renal transplant wait-listing.

FR-PO461
N-DEPTH–Nephrology DVT and Pulmonary Embolism Prophylaxis Study in Hospitalized Patients
Jule Pinter, Azim S. Gangji, Catherine M. Clase, Christine M. Ribic. Medicine, Div of Nephrology, McMaster Univ, Hamilton, Canada.

Background: The prevalence and mortality rate of venous thromboembolism (VTE) among patients on dialysis has been reported to be higher than previously thought. However, the prophylaxis prescription practice, VTE and bleeding risks in hospitalized patients with endstage renal disease (ESRD) have not been studied adequately.

Methods: This single centre, retrospective chart review examined the rate of VTE prophylaxis in adult patients treated with chronic dialysis (>3 months) on index admission during Sept 2008 to March 2010. Patients admitted for ≤ 48 hours, suspected VTE, bleed or renal transplant were excluded. VTE prophylaxis was defined as administration of prophylactic doses of heparin within 24 hours of admission. We assessed 27 VTE risk factors per patient based on the 8th edition of ACCP guidelines; VTE events objectively confirmed by imaging and major bleeds were adjudicated.

Conclusions: A total of 2183 admissions of which 238 patients formed the study cohort. 45 (18.9%) patients were ineligible for prophylaxis due to therapeutic anticoagulation (AC), prophylactic anticoagulation, heparin allergy or severe thrombocytopenia on admission. Of the 193 eligible patients, 71(36.8%) received VTE prophylaxis. The number of baseline VTE risk factors (range 1 to 7; p=0.59), anticoagulant or antiplatelet use and typical VTE risk factors such as Immobility (22.3%), recent surgery (13.5%), a history of malignancy (16.1%) or of VTE (4.7%) did not predict the prescription of VTE prophylaxis.

VTE events (1 pulmonary embolism, 1 deep vein thrombosis) occurred in 2 (1.6%) eligible patients not receiving prophylaxis, no events occurred in those receiving prophylaxis (p=0.53). There was no difference in minor or major bleeds among those that did (n=5) and did not receive prophylaxis (n=12; p=0.31).

Conclusions: Compliance assessment should include educational level, and efforts should be made to improve understanding and motivation for HD treatment to achieve adequate adherence. It may be necessary to direct specialized educational resources to these patients.
Background: Detection and treatment of Latent Tuberculosis Infection (LTBI) is a concern in patients with kidney failure (KF) wait-listed for a kidney transplant, since post-transplant reactivation of LTBI is associated with catastrophic outcomes. There are several diagnostic tests available to determine the presence of LTBI: the Tuberculin Skin Test (TST), Quantiferon-TB Gold (QFT-G), and ELISPOT (T-SPOT.TB). Our objective was to compare the diagnostic performance of these tests for LTBI in the KF population.

Methods: We conducted a systematic review of studies from PubMed, Scopus, EMBASE, and Cochrane Database of Systematic Reviews from the date of their establishment until August 2012. Studies reporting test results allowing the calculation of the sensitivity and specificity with respect to clinical risk factors (previous TB contact, history of TB, and/or suggestive chest X-ray) of the TST, QFT-G, and/or QFT-G in the KF population were included. Data was extracted by two investigators with disagreements resolved by consensus.

Results: Our search strategy retrieved 1780 citations for screening. Of these, 92 articles were selected for full-text review and 15 met criteria for inclusion. The TST had a pooled sensitivity of 0.22 across 11 studies and a pooled specificity of 0.65 across 10 studies. The QFT-G test had a pooled sensitivity of 0.58 across 8 studies and a pooled specificity of 0.69 across 8 studies. The T-SPOT.TB test had a pooled sensitivity of 0.50 across 3 studies and a pooled specificity of 0.67 across 3 studies.

Conclusions: The QFT-G and the T-SPOT.TB tests were more sensitive and specific than the TST for diagnosis of LTBI in the hemodialysis population. This systematic review calls into question the current practice of using the TST to screen for LTBI due to the low sensitivity of this test.

FR-PO463
Age, Race-Ethnicity and Dialysis Patient Mortality Using Competing Risks Regression
Connie Rhee, Paungpapa Lertdumrongluk, Elani Streja, Jongha Park, Hamid Moradi, Wei Ling Lau, Keith C. Norris, Allen R. Nissenson, Alpesh Amin, Csaba P. Kovessy, Kamyar Kalantar-Zadeh, Harold Simmons Center, Orange, CA; Drew Univ, Los Angeles, CA; DaVita Inc., El Segundo, CA; UCI, Orange, CA; Memphis Veterans Affairs Medical Center, Memphis, TN; Univ of Tennessee Health Science Center, Memphis, TN.

Background: Recent studies suggest the paradoxical African-American (referred to as black) survival advantage on dialysis is restricted to older ages, but did not separately consider Hispanic ethnicity from white and black racial groups. Prior studies have not examined the impact of age and race-ethnicity on dialysis mortality using competing risks regression, which estimates death risk on dialysis while considering racial-ethnic disparities in kidney transplantation (a competing risk that prevents observing the outcome of interest). We thus re-examined the hypothesis that minorities on dialysis have survival advantages using this method.

Methods: We examined associations between race-ethnicity with all-cause mortality among a 2001-2009 cohort of 130,990 adult dialysis patients within 7 age groups using competing risks regression (in which transplant and end of study were considered as competing risk and censoring events, respectively) to account for differential transplant rates in non-Hispanic whites (referred to as whites), blacks, and Hispanics.

Results: Compared to whites, blacks had similar, slightly higher, and reduced mortality within age groups of 18-30, >30-40, and >40 years, respectively, in case-mix analyses. Hispanics had decreased mortality compared to whites across all ages.

Conclusions: After accounting for racial-ethnic differences in transplantation, we observed that compared to white dialysis patients, Hispanics have greater survival across all ages, while in blacks this survival advantage is limited to patients >40 years old.

FR-PO464
Association between Depression Symptoms and Mortality in Hemodialysis Patients
Li Fan, Mark J. Samak, Hocine Tighiouart, David A. Drez, Kristina Lou, Saeed Kamran Shafii, Tammy Scott, Daniel E. Weiner. Tufts Medical Center.

Background: Depression and symptoms of depression are associated with increased risk of mortality in the general population and in people with chronic kidney disease. We evaluated the association between depression symptoms and all-cause mortality in a cohort of hemodialysis (HD) patients.

Methods: In 313 maintenance HD patients, depression symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) scale, with higher scores indicating a greater burden of depression symptoms. Cox proportional hazards models were used to evaluate the relationship between depression symptoms and mortality in univariate and multivariable analyses.

Results: Mean age was 63 ± 16 years, 53% were female and 22% black. Mean CES-D score was 10.6 ± 8.1, and 80% of participants had CES-D scores ≥16, a threshold consistent with depression in prior studies. Participants with CES-D scores ≥16 were more likely to have a history of cardiovascular disease, dialysis vintage, and lower Kt/V and serum albumin. Kaplan-Meier survival analysis and Cox proportional hazards models revealed a significant increased mortality risk [HR 1.19 (1.00-1.42)], with hazard increasing with age.

Conclusions: Symptoms of depression are associated with increased risk of mortality in hemodialysis patients. Further studies are needed to confirm these results and evaluate whether effective treatments for depression may impact mortality among HD patients.

Funding: NIDDK Support

FR-PO465
CD4+CD25+Foxp3+ Tregs and TH-17 Cells Balance in Tumor Immunity after Kidney Transplantation
Jianghua Chen. Zhejiang Univ.

Background: To find the relationship between tumor incidence of the kidney transplantation and Tregs expression, we analyzed the CD4+CD25+Foxp3+ Tregs expression and IL-17 in the cancer patients after the kidney transplantation.

Methods: Blood samples were obtained from age-matched 19 kidney transplantation patients got tumor, 19 normal kidney transplantation patients and 19 healthy controls.

Results: The highest CD4+CD25+Foxp3+ Tregs expression in the cancer group levels of cytokines IL-17 was measured using enzyme-linked immunosorbent assays.

Conclusions: These results and evaluation these results and evaluate the IL-17 expression after the kidney transplantation, they plays an important role in tumor incidence after the kidney transplantation.

Funding: Government Support - Non-U.S.

FR-PO466
An Anti-CD154 Domain Antibody Prolongs Graft Survival and Induces FoxP3+ iTreg in Both the Absence and Presence of CTLA4-Ig
David F. Pinelli; Anish Suri; Steven Nadler; Mandy L. Ford. Emory Univ; Brstol Myers Squibb.

Background: Blockade of CD40-CD154 interactions has been shown to be highly effective in inducing long-term survival of allografts in both murine and NHP models. However, the clinical potential has yet to be realized, due to the thromboembolic complications seen during clinical trials of an anti-CD154 monoclonal antibody in humans. Thus, development of novel therapies with improved safety profile is imperative for the field of transplantation.

Methods: We compared the most commonly used clone of anti-CD154 antibody, MR-1, with an anti-CD154 domain antibody with a silent Fc region (dAb). We first measured efficacy of these therapies in a fully allogeneic BALB/c to B6 model of skin transplantation. To further investigate the mechanism of action of these therapies, we used a transgenic model where OT-I CD8 and OT-II CD4 T cells were adoptively transferred to B6 mice that had undergone a skin transplantation.

Results: An antibody treated with CTLA4-Ig alone quickly rejected fully allogeneic grafts (MST=15 d) whereas treating with MR-1 or dAb in combination with CTLA4-Ig resulted in significant prolongation of graft survival (MST= 33 and 61 d, respectively). Treatment with either therapy led to a significant reduction in allospecific T cell expansion.
in the spleen (No Rx 1.64±0.55%, MR-1 1.05±0.14%, dAb 0.62±0.23%), as well as a reduction in the number of IFN-γ-producing allospecific CD8+ T cells (No Rx 31.05±5.68%, MR-1 10.9±6.7, dAb 6.67±7.80%). In addition, both treatments led to a significant increase in antigen-specific Treg conversion (No Rx 3.46±0.86%, MR-1 19.06±2.41%, dAb 14.74±1.55%), and dAb-induced Treg conversion was even preserved in the presence of CTLA-4/Ip (26.35±5.05%), a therapy known to have a negative effect on Treg.

Conclusions: Taken together, these data demonstrate that alternative means of blocking CD40-CD154 interactions may provide a safer and equally efficacious way to attenuate alloreactive responses, and suggest the potential for clinical application of this therapy in combination with existing modes of treatment.

Funding: Other NIH Support - NIAID R01 AI073707-05

FR-PO467

Myd88 Plays a Critical Role in Acute and Chronic Rejections of Kidney Allografts Nadine M. Lerrer, Ting Li, Jiaojing Wang, Xueqiong Wang, Zheng Jenny Zhang, Xun-Rong Luo. Div of Nephrology, Northwestern Univ Feinberg School of Medicine, 1Surgery, Northwestern Univ Feinberg School of Medicine, 2Microbiology and Immunology, Northwestern Univ Feinberg School of Medicine.

Background: Toll-like receptors in kidney injuries have been best studied in ischemic renal dysfunction and in autoimmune GNs. Their role in kidney transplantation rejection is less well characterized.

Methods: In the present study, we used a stringent C57BL/6 (B6) to BALB/c mouse kidney transplant model to study the role of myeloid differentiation protein 88 (MyD88) in kidney allograft survival.

Results: We found that Myd88−/− BALB/c recipients significantly protected B6 kidney allografts, with ~50% achieving graft survival >90 days, whereas majority of wild-type (WT) recipients rejected their grafts by day 30. In long-term protected Myd88−/− recipients, donor skin grafts were accepted indefinitely but third party skin grafts were rejected, demonstrating donor-specific tolerance. Interestingly, we observed that initial acute rejection (AR) manifested as tubulitis with infiltrating T cells was similar in both Myd88−/− and WT recipients at day 7 post transplant, although there was trend towards a decrease in infiltrating Gr1+ cells in Myd88−/− recipients and the infiltrates further decreased if Myd88−/− donor B6 kidneys were transplanted. However, by day 14, Myd88−/− recipients exhibited a significant decline in both graft infiltrating CD8+ T cells as well as Gr-1+ cells, accompanied by a decrease in the levels of IL-6, IL-17, IFN-γ, and CCL2. By day 90, kidney allografts in Myd88−/− recipients showed minimal cellular infiltration or interstitial fibrosis. T cells from Myd88−/− recipients exhibited diminished proliferation to donor stimulation when compared to sham operated mice (1.2±0.17 and 0.2±0.004, p<0.05).

Conclusions: This study demonstrates that Myd88 signaling plays a critical role in both acute and chronic rejection of kidney allografts, and provides a model for studying druggable targets involving Myd88 signaling in kidney transplantation.

Funding: Other NIH Support - NIAID T32 training grant

FR-PO468

Cell-Based Therapy with S1P3 Deficient Dendritic Cells Induces Prolongation of Heart Allograft Survival and Protection from Kidney Ischemic-Reperfusion Injury Amarnend Bajwa, Liping Huang, Hong Ye, Peter I. Lobo, Mark D. Okusa. Dept of Med./CJR, Univ of Virginia.

Background: The plasticity of dendritic cells (DCs) permits phenotypic modulation ex-vivo by gene expression or pharmacological agents and these DCs exert their in-vivo therapeutic immunosuppressive effects through direct interactions with T-cells by either deleting or causing anergy. Sphingosine 1-phosphate (S1P), a ligand for 5 receptors (S1P1-5Ras) and 51Rg receptors, a ligand for 5 receptors (S1P1-5Ras) and 51Rg agonists reduced kid ischemia-reperfusion injury (IRI) in mice. S1P3−/− (3KO) mice are protected from kidney and allogenic heart Tx (3KO donors) have prolonged graft function with immature DCs. Since ischemic injury contributes to transplant outcome, we tested therapeutic advantage of using bone marrow derived DCs (BMDC) from 3KO in kidney IRI and allogenic heart transplants (Tx) in mice.

Methods: WT B6DC and 3KO B6DCs from mice were adoptively transferred into Balb/c or B6 (LPS stimulated) mice 2d prior to kidney IRI and 7d prior to heart Tx (B6 heart IRI).

Results: Naïve Balb/c mice (no DC) had significant rise in creatinine (Cr; mg/dl) compared to sham operated mice (1.20±0.17 and 0.20±0.04, p<0.01) and mice pretreated with WT B6DC had Cr that were similar to mice receiving no DCs. However, 3KO B6DCs pretreated Balb/c mice were significantly protected from kidney IRI with Cr of 3.03±0.07, p<0.01. Additionally, 3KO B6DCs pretreated Balb/c mice prolonged allogenic heart allografts (6 vs 12d; sensation of heart beat) with less in-vivo cellular infiltration and in-vivo albuminuria (23.78±8.06 mg/100 mg/day vs. 62.69±28.83 mg/100 mg/day, p=0.03), increased creatinine clearance (1.02±0.13 ml/min vs. 0.07±0.02 ml/min, p=0.05) and decreased serum creatinine level (0.25±0.05 mg/dl vs. 0.33±0.04 mg/dl, p<0.01), compared with CsA toxicity group. Tubular interstitial fibrosis area (2.19±1.97 % vs. 14.65±6.54 %, p=0.008) and TGF-beta immunohistochemical stain (11.47±0.88 fold vs. 16.06±4.81 fold, p=0.05) were also decreased in anti-HMGB1 group vs. CsA toxicity group. 8 OHDG level in 24 hour urine was decreased, but was not significantly different between anti-HMGB1 group and CsA toxicity group.

Conclusions: Anti-HMGB1 group decreased 24 hour albuminuria (23.78±8.06 mg/100 mg/day vs. 62.69±28.83 mg/100 mg/day, p=0.03), increased creatinine clearance (1.02±0.13 ml/min vs. 0.07±0.02 ml/min, p=0.05), and decreased serum creatinine level (0.25±0.05 mg/dl vs. 0.33±0.04 mg/dl, p<0.01), compared with CsA toxicity group. Tubular interstitial fibrosis area (2.19±1.97 % vs. 14.65±6.54 %, p=0.008) and TGF-beta immunohistochemical stain (11.47±0.88 fold vs. 16.06±4.81 fold, p=0.05) were also decreased in anti-HMGB1 group vs. CsA toxicity group. 8 OHDG level in 24 hour urine was decreased, but was not significantly different between anti-HMGB1 group and CsA toxicity group.

Conclusions: The administration of anti-HMGB1 brought renal functional improvements and ameliorated fibrosis induced by CsA and it is thought to result from decrease in TLR4 and RAGE expressions.

FR-PO471


Background: Immunosuppressive drugs from different groups, e.g. calcineurin inhibitors, IMPDH inhibitors, or mTOR inhibitors are used to prevent rejection after kidney transplantation. The desired immunosuppressive effects are mediated by distinct molecular mechanisms. Moreover, these drugs produce a variety of nonimmune adverse effects to other tissues, and the molecular mechanisms are widely unknown. Epigenetic side-effects have been described or suggested for other pharmaceuticals, and there is growing evidence that methylation modifications are linked to a number of dysfunctions and diseases. We therefore hypothesize that immunosuppressive drugs alter epigenetic methylation patterns, representing a new molecular mechanism how adverse effects of immunosuppressive drugs are mediated.

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

Underline represents presenting author/disclosure.

473A
Method: In *in vitro* experiments we treated several epithelial kidney cells (Vero cells, the human proximal tubular epithelial cell line HK-2, and the primary human renal proximal tubular epithelial cells RTPC) with either cyclosporine, tacrolimus, everolimus or mycophenolic acid in various concentrations. For determination of relative DNA methylation levels we established a flow cytometry protocol using anti-5-meC antibody.

Results: A significant decrease of DNA methylation was observed after tacrolimus treatment in a dose dependent manner. However, tacrolimus neither cyclosporine, nor mycophenolic acid, nor everolimus induced significant changes in the DNA methylation signal. In order to identify affected genes, and for absolute quantification of the methylation status, a genome-wide screening of DNA methylation was carried out using Infinitum Human Methylation244K BeadChip. Significant methylation changes were found in 323 genes. Network analysis reveals that the top three network functions include hematological system development and function, renal and urological disease, drug metabolism, endocrine system development and function, and inflammatory response, among others.

Conclusion: Our data indicate that tacrolimus changes epigenetic patterns, and provide evidence that these changes may contribute to tacrolimus’ adverse effects (nephrotoxicity, hemolytic-uremic syndrome, post-Tx diabetes, BKV infection).

Funding: Government Support - Non-U.S.

FR-PO472

Polyoma Virus Infection Leads to Hypermethylation and Down-Regulation of Matrix Metalloproteinases in Primary Renal Tubulus Epithelial Cells

Jessica Thalhammer, Barbara Hertel, Hermann G. Haller, Annette D. Wagner. Nephrology, Hannover Medical School, Hannover, Germany.

Background: BK virus is a ubiquitous polyomavirus that persistently infects the kidney. This otherwise silent infection can reactivate in transplanted and immunosuppressed individuals leading to polyomavirus-associated nephropathy (PV-AN) with irreversible renal injury.

Methods: We found that the CpG islands of MMP-1 and MMP-2 show hypermethylation in BKV infected cells as compared to noninfected cells. Moreover, DNA methylationtransferase-1 that is known to induce DNA methylation was found to be upregulated in BKV infected cells.

Results: The mRNA expression of both MMP-1 and MMP-2 was down-regulated.

Conclusions: The down-regulation of MMPs might lead to the accumulation of extracellular matrix in the progression of PV-AN. These findings might reflect a novel mechanism how BKV infection contributes to the onset and maintenance of renal scarring and fibrosis, even when the infection is cleared.

The pathomechanisms are poorly understood. We hypothesize that BK virus infection influences host cell DNA methylation that leads to ongoing alteration of gene expression contributing to the development of PVAN. Polyoma virus infection results from an imbalance between the normal processes of gene silencing and degradation of extracellular matrix components, and kidney scarring is associated with a reduction of matrix metalloproteinases (MMP) activity.

Funding: Government Support - Non-U.S.

FR-PO473

A Novel Mouse Model for Unraveling the Mechanism behind Tacrolimus Mediated Hypertension and Hyperkalemia

Rebecca A Lazelle, Nick Meiermeier, Chao-Ling Yang, David H. Ellison. Div of Nephrology and Hypertension, Oregon Health and Science Univ, Portland, OR.

Background: Calcineurin inhibitors, such as tacrolimus (FK-506), are used to prevent organ rejection. While effective, tacrolimus causes clinically limiting side effects including hypertension, hyperkalemia, and chronic kidney disease. We have shown that the sodium chloride cotransporter (NCC), located in the distal convoluted tubule (DCT) of the kidney, is necessary for the development of hypertension, but it is unclear whether tacrolimus acts directly in the DCT to cause this pathology. We have developed a unique mouse model, which takes advantage of the fact that tacrolimus is effective in both acute allograft acceptance and allogenic tolerance. In this study, we investigated whether anti-IL-6 receptor producing minicircle(MC)-DNA, is competent to inhibit alloresponse-induced IL-6 in highly immunogenic murine skin allograft model.

Methods: We designed MC-DNA producing anti-IL-6R and verified in vitro system. One day before skin allograft modeling, systemic MC-DNA exposed via hydrodynamic delivery(tail vein, single injection). Using GFP tagging MC-DNA, we confirmed its organ distribution. At day 5, we measured the amount of IL-6 and anti-IL-6R in serum. We evaluated survival rate, morphological changes of graft, immune cell infiltration, and population of Th1(Th17/IFN-C/Reftg) and Treg(ThF4/Fosp). We compared its alloimmunity and graft survival efficiency with the CsA-treated group.

Results: Hydrodynamic delivery of MC-DNA was mainly localized in hepatocytes. Serum IL-6 and IL-6R antibody detected in anti-IL-6RMC-DNA treated mice. At day 8.5, untreated mice completely rejected the graft confirming by daily observation of loss of graft and erosion. However, mice received either anti-IL-6R MC-DNA or CsA presented prolonged acceptance of graft until day 15 or 15.6, respectively. Morphological changes and immune cell infiltration in the graft were also consistent with survival rate. FACS results showed that IL-6RMC-DNA treatment markedly suppressed Thy1 Population compared with the untreated mice. However, there was no effect on Trepopulation. However, CsA showed the increased Th1? and decreased Treg population compared with untreated group.

Conclusions: We found that single injection of nonviral MC-DNA targeting IL-6R is effective in both acute allograft acceptance and allogenic tolerance. This suggests that simple and effective gene therapy method using antibody producing minicircle DNA may represent a powerful tool for the transplantation.

Funding: Government Support - Non-U.S.

FR-PO474

Antiproteinuric Effects of Green Tea Extract on Tacrolimus-Induced Nephrotoxicity in Mice

Byung Chul Shlp, Jong Hun Back. Dept of Internal Medicine, Chosun Univ Hospital, Gwangju, Republic of Korea.

Background: It has been reported that the proteinuria is a early useful marker in detection of tacrolimus (TAC) nephrotoxicity. Green tea extract (GTE), as an antioxidant, induces apoptosis in renal interstitial fibroblasts cells in vitro studies. The aim of this study was to investigate the anti-proteinuric effects of GTE on TAC-induced acute renal injury in mice.

Methods: The mice (n=20) were divided into 4groups (n=5/group); control group wereintraperitoneally (IP) injected 0.9% saline for 7days; TAC group were IP injected TAC1 mg/kg, INOS inhibitor group were given inaddition NG-nitro-L-arginine-methyl ester (L-NAME)12 mmol/L by subcutaneous injection. TAC group were given TAC by IP injection andGTE 100 mg/kg by subcutaneous injection.

Results: The 24 hours urine protein levels were significantly increased in TAC group (36.1 ± 9.9mg/day) compared to control group (13.3 ± 5.4mg/day, P < 0.01)and significantly decreased tacrinactors group (19.1 ± 6.9mg/day, P < 0.01) compared to TAC group. The NO production by TAC was significantly suppressed by GTE and INOS inhibitor (P < 0.01). Renal tissue MDA level was significantly increased in TAC group compared to control group andsignificantly decreased in TAC-GTE group compared that of TAC group (p<0.01).

Conclusions: This study proves that proteinuria of the TAC induced nephrotoxicity is associated with oxidative stress and nitric oxide production. GTE treatment has meaningful anti-proteinuric effects throughantioxidative effect in the kidney from TAC-inducenced renal injury in mice.

FR-PO475

Impact of Blocking Interleukin 6 Receptor with Antibody Producing Nonviral Minicircle DNA in Skin Allograft Rejection

Jian Jin,1,2 Kyung Chun Doh,3 Long Jin,3 Shang Guo Piao,1 Youngkyn Kim,2 Jihyun Ju,3 Sun Woo Lim,1 Byung Ha Chung,1,2,3 CRCID & Transplant Research Center, The Catholic Univ of Korea; 2Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea; 3Div of Rheumatology, Dept of Internal Medicine, The Catholic Univ of Korea.

Background: Blocking of interleukin-6 (IL-6) is effective in decreasing resistance to allogenic tolerance. In this study, we investigated whether anti-IL-6 receptor producing nonviral minicircle(MC)-DNA, is competent to inhibit alloresponse-induced IL-6 in highly immunogenic murine skin allograft model.

Methods: We designed MC-DNA producing anti-IL-6R and verified in vitro system. One day before skin allograft modeling, systemic MC-DNA exposed via hydrodynamic delivery(tail vein, single injection). Using GFP tagging MC-DNA, we confirmed its organ distribution. At day 5, we measured the amount of IL-6 and anti-IL-6R in serum. We evaluated survival rate, morphological changes of graft, immune cell infiltration, and population of Th1(Th17/IFN-C/Reftg) and Treg(ThF4/Fosp). We compared its alloimmunity and graft survival efficiency with the CsA-treated group.

Results: Hydrodynamic delivery of MC-DNA was mainly localized in hepatocytes. Serum IL-6 and IL-6R antibody detected in anti-IL-6RMC-DNA treated mice. At day 8.5, untreated mice completely rejected the graft confirming by daily observation of loss of graft and erosion. However, mice received either anti-IL-6R MC-DNA or CsA presented prolonged acceptance of graft until day 15 or 15.6, respectively. Morphological changes and immune cell infiltration in the graft were also consistent with survival rate. FACS results showed that IL-6RMC-DNA treatment markedly suppressed Thy1 Population compared with the untreated mice. However, there was no effect on Trepopulation. However, CsA showed the increased Th1? and decreased Treg population compared with untreated group.

Conclusions: We found that single injection of nonviral MC-DNA targeting IL-6R is effective in both acute allograft acceptance and allogenic tolerance. This suggests that simple and effective gene therapy method using antibody producing minicircle DNA may represent a powerful tool for the transplantation.

Funding: Government Support - Non-U.S.

FR-PO476

X-Linked Inhibitor of Apoptosis Protein Expression Is Not Associated with Increased Apoptosis in an In Vivo Model of Cold Ischemia

Daniel Keys1, Swati Jain1, Kameswaran Ravichandran2, Zhibin He1, Danica Lubanovic2, Charles L. Edelstein1, Alkes Jami1.1 UC Denver, Aurora, CO; 2Dubrava Hospital, Zagreb, Croatia.

Background: Delayed graft function (DGF) independently predicts delayed 5yr kidney transplant survival. Cold ischemia (CI) contributes to the development of DGF and results in tubular damage, apoptosis and brush border injury (BBI). Our published data suggests that mice subjected to CI have increased caspase-3, renal tubular cell apoptosis and BBI at 48h of CI. XIAP is the most potent inhibitor of apoptosis currently known. The purpose of this study was to evaluate the time course of XIAP, active caspase-3, caspase-3 activity and histological changes in a mouse model of CI.

Methods: C57BL/6 mice were anesthetized and right kidneys were processed at time zero as control following perfusion with cold UW solution. Left kidneys were exposed to CI for 1, 6, 12, and 24h. Active caspase-3 and XIAP proteins were evaluated by

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

Underline represents presenting author/disclosure.

474A
immunolab. Caspase-3 activity was measured using absorbance of cell lysates after incubation with substrate for caspase-3/7. Apoptosis and BBI were quantified by an independent nephropathologist.

Results: After CI, BBI occurs first and was significantly increased at 6 hours. Active caspase-3 protein levels and caspase-3 activity levels were significantly increased at 24 hours of CI. Apoptosis was significantly increased at 24 hours of CI. XIAP protein levels were not significantly different at any time point in this model of CI.

Results: In acute GVHD, at least 21 days after BMT, severe acute GVHD was developed in all Lewis rats. In transplanted recipients with normal graft histology and function (control group). miRNAs and gene expression were analyzed using real-time PCR in an independent set of patients. Results were evaluated by statistical analysis and functional pathway analysis and validated connected in the interferon-alpha (INF-alpha) network (IPA score=38). IPA assessed on the two groups. When matching miRNA data with mRNA data we identified that mediated the interstitial inflammation of liver syndecan-1 shedding (renal) transplantation.

Conclusions: Kidney is one of the target organs of acute GVHD after BMT. The pathology of acute GVHD in the kidney was the quiet similar findings of acute T-cell mediated rejection in kidney transplantation.

FR-PO477
Integrated Messenger RNA and microRNA Profiles Suggest an Interferon Alpha Signature in Chronic Antibody-Mediated Rejection (CAMR) J. F. Garcia,1 Paola Pontrelli,1 Matteo Accetturo,1 Margherita Gigante,1 Giuseppe Castellano,1 Maddalena Gigante,2 Anna Zito,1 Gianluigi Zara,1 Annarita Oranger,1 G. Stallone,3 E. Ranieri,3 Loreto Gesualdo,1 G. Grandaliano,2

FR-PO478
Acute Graft-versus-Host Disease in the Kidney after DA-to-Lewis Rat Bone Marrow Transplantation S. Schikorra,1 Y. Kajimoto,1 G. Kanzaki,2 A. Mii,2 S. Tsuruoka,2

Conclusions: Our data would suggest a key role of INF-alpha pathway during CAMR and open new perspectives for identification of therapeutic targets.

Funding: NIDDK Support

FR-PO480
Sirolimus (SIR) Induces Increases in Baseline Glomerular Permeability, but Partly Inhibits Purmeycin Anoonculose (PA) Induced Hyperpermeability in Rats Josephine Axelsson, Anna Rippe, Bengt Rippe. 1Dept of Nephrology, Clinical Sciences, Lund, Sweden.

Background: It is well established that the immunosuppressant SIR, an mTOR inhibitor, can produce de novo proteinuria in transplanted patients. On the other hand, SIR has been shown to suppress kidney disease progression in animal models. In the present study we wanted to investigate whether glomerular permeability would be altered by SIR alone and whether SIR can affect PA induced glomerular hyperpermeability.

Methods: In anesthetized Wistar rats (250-280g) the left ureter was cannulated for urine collection, while simultaneously PA infusion access was achieved. SIR was administered as a single dose i.v. 30 min before the start of the experiments in animals infused with PA or animals not exposed to PA. Polydisperse FITC-Ficoll-7000 (mol radius 10-80Å) and Cr-EDTA infusion was given during the whole experiment. Measurements of FcRn in plasma and urine were performed sequentially at start (baseline) and at 5, 15 and 60 min after the start of the experiments. Urine and plasma samples were analyzed by high performance size exclusion chromatography (HPSEC) to assess steady state glomerular sieving coefficients (φ) for FcRnuptake. Results: SIR increased baseline glomerular permeability to FcRnuptake at 15 min, but not at 5 or 60 min. 0 for FcRnuptake increased from 2.91 × 10^-4 ± 1.18 × 10^-4 at baseline to 2.27 × 10^-4 ± 5.02 × 10^-5 (p<0.01) at 15 min after SIR. PAN alone caused a rapid increase in glomerular permeability, peaking at 5 min, and again at ~60 min. SIR blunted the PA-induced permeability peak and almost completely abrogated the second one. Conclusions: mTOR inhibition with SIR induced rapid, reversible increases in baseline glomerular permeability, but also blunted PA induced glomerular hyperpermeability in rats, underpinning the complex interactions of SIR with the glomerular filtration barrier. Funding: Government Support - Non-U.S.

FR-PO481
MRI Detectable Nanoparticles to Measure the Size and Number of Glomeruli in the Human Kidney Scott Charles Beeman,1 Edwin J. Baldo,2 John F. Bertram,1 Luisa A. Cullen-McEwen, Jennifer Richardson-Charlton,1 Teresa Wu,1 Min Zhang,2 Kevin Bennett,2 1 Washington Univ in St. Louis; 2 Univ of Hawaii; 3 Monash Univ, Australia; 4 Nephrology, Univ of Virginia Medical Center, Charlottesville, VA, 5 Arizona State Univ.

Background: The number (Ngom) and volume (Vgrom) of kidney glomeruli may predict cardiovascular and renal health (Brenner, 1988; Puelles, 2012). There are currently no methods to measure these parameters in the clinic. The cationic ferritin (CF) nanoparticle has been proposed as a glomerular MRI contrast agent (Bennett, 2008; Beeman, 2011, Heilman, 2012). Here we use intravenous CF to measure Ngom and Vgrom in intact human kidneys with MRI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Methods: Four viable human kidneys (not viable for transplant but without known renal disease) were acquired within 24 hours of death though a donor network (IHAM) with IRB and informed consent. Kidneys were perfused with CF, PBS, and formalin. Control grafts were randomized and analyzed blinded by the investigator. Grafts were imaged on a Philips Achieva 3T system. The signal intensity (SI) of each glomerulus was measured from T1-weighted calibrated fast spin echo sequences. The intravoxel incoherent motion sequence (IVIM) was used to determine diffusion parameters (D and D2) and the microstructural perfusion fraction (fP).

Results: MRI images revealed an increase in microvascular perfusion and a decrease in microstructural diffusion in DCD kidney grafts as compared to normothermic control kidney grafts. The average increase in fP was 0.05 ± 0.01, with a significant decrease in D of 1.3 ± 0.5 x 10^-12 m^2/s. These changes were observed in both normothermic and normothermic control kidney grafts.

Conclusions: MRI is a promising tool for detecting ischemia-reperfusion injury in kidney grafts. The observed changes in microvascular perfusion and microstructural diffusion are consistent with the histological findings of increased microvascular perfusion and decreased microstructural diffusion in DCD kidney grafts. These findings support the use of MRI as an imaging biomarker for predicting graft function and survival in DCD kidney transplantation.

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

Underlining represents presenting author/disclosure.
FR-PO486
Increased Autophagic Flux during Extreme Cold Ischemia Followed by Warm Reperfusion Swati Jain, Daniel Keys, Charles L. Edelstein, Alkesh Jani. UC Denver, CO.

Background: AKI post transplant DGF is associated with prolonged cold ischemia (CI) of > 30 hours followed by warm reperfusion (WR) and renal tubular cell (RTET) apoptosis. We have shown that hibernating ground squirrel (GS) kidneys endure CI for >30 hours followed by warm reperfusion (WR) and renal tubular cell (RTEC) apoptosis. Since Autophagy is a survival strategy employed by cells under stress, we hypothesised that GS kidneys employed Autophagy to survive hibernation. We examined autophagic flux in: (i) in vivo hibernating GS kidneys (ii) in vitro in GS RTECs. Methods: LC3-II (an autophagosome marker) and cleaved caspase 3 (CC3) were examined: a) in vivo after prolonged CI of several days during torpor (LT), followed by WR during IBA; b) in vitro in GS RTECs subjected to cold storage (CS) in UW solution followed by rewarming (WR) in normal media to simulate in vivo CI/WR. Autophagic flux was examined using Bafloinform and Wortmannin.

Results: In vivo IBA kidneys and cells subjected to CS/WR in vitro had significantly increased LC3-II expression. Treatment of GS RTEC with Bafloinform and Wortmannin demonstrated: (a) increased autophagic flux under conditions of CS/WR (b) no increase in CC3 protein or its activity.

Conclusions: Hibernators survive WR after several days of CI during IBA that would be lethal to non-hibernators. To determine a mechanism of tolerance by CI/WR we examined the role of Autophagy, a survival strategy employed by cells. Autophagic flux inhibition with Bafloinform or Wortmannin did not increase CC3 protein or its activity suggesting that: (a) autophagic flux is employed by hibernators to withstand stress, but (b) is not required for cell survival during WR after CI in hibernators.

Funding: NIDDK Support

FR-PO487
Cold Injury Is Mediated by Loss of Ezrin In Vivo Peter Hamar,1 Csaba Imre Szalay,1 Anita A. Wasik,2 Laszlo Rosivall,1 Sanna H. Lehtonen. 2 Institutefor Pathophysiology, Semmelweis Univ, Budapest, Hungary; 1Dept of Pathology, Haartman Institute, Helsinki, Finland.

Background: Early graft injury is the most important determinant of prognosis after kidney transplantation. Although organ preservation is performed by organ storage at 4°C it was suggested, that cooling may be associated with substantial organ damage due to cytoskeleton realignment including the loss of a crucial cytoskeletal protein: ezrin.

Methods: We have investigated renal function in an orthotopic renal transplantation model in inbred male Lewis (L) and Fisher (F) rats. F-to-L allografts (A), F isografts (I) or untreated controls (C). Renal function was monitored by serum creatinine and 24 h urine analysis (ATF).

Results: Before operations GFR was 2.41±0.52 and CIPAH 11.5±2.3 ml/min in F animals. In cold perfused (A, 1 and P) rats a significantly decreased initial GFR and CIPAH improved later. In I initial GFR, and CIPAH decreased less, but remained constant later. Serum crea and urea paralleled these results. Sham and I animals did not differ significantly. An intense mononuclear infiltrate and IL-2 mRNA (RIPCR) expression indicated acute rejection only in A, but not in any other group. Light and electronmicroscopic investigations demonstrated mild glomerular and intense tubular damage in transplanted and perfused kidneys. This graft injury caused by cold perfusion was accompanied by a severe reduction of ezrin in cold perfused kidneys.

Conclusions: In summary, initial kidney function and histologic tubular damage was not determined by ischemia or acute rejection in this model, but it was severely impaired in cold perfused A, I, and Prats at day 3. In the background loss of the cytoskeletal protein: ezrin was detected. Our study draws attention to cold injury as a possibly deleterious factor in transplantation. Funding: OTKA, K 81972.

Funding: Government Support - Non-U.S.

FR-PO488
Role of Ubiquitin Proteasome System on Renal Cold Storage: A Possible Link to Mitochondrial Dysfunction? Nirmala Parajuli, Lee Ann MacMillan-Crow. Pharmacology and Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR.

Background: Renal transplantation is the treatment of choice for patients suffering from end stage renal disease (ESRD) but, due to the shortage of donor kidneys, many patients die while on the waiting list. Kidneys procured from deceased donors are stored in cold storage solutions; however extended CS leads to renal damage and poor long-term outcome following transplantation. Our published reports show that CS induces reactive oxygen species generation (ROS), mitochondrial dysfunction, and renal damage. Exciting new studies in the liver and heart suggest that the Ubiquitin Proteasome System (UPS), a proteolytic machinery that removes modified proteins, is activated during CS and appears to contribute to organ damage. Therefore, we hypothesize that CS mediated ROS triggers activation of UPS which leads to mitochondrial dysfunction and renal damage.

Methods: Male rodent kidneys were isolated and cold stored for 0-24 hr. Mitochondrial function was assessed via high resolution respirometry and ATP measurements. UPS function was monitored by specific activity assays as well as ubiquitin expression.

Results: Our data showed that CS induces altered proteasome activity, loss of total ubiquitin protein expression, and mitochondrial dysfunction (decreased ATP). Interestingly, this CS mediated ATP depletion is partially restored by a clinically relevant proteasome inhibitor (Bortezomib), suggesting that increased UPS activity contributes to mitochondrial dysfunction. Similar to ubiquitin expression, total protein expression of AMP-activated protein kinase (AMPK), a metabolic regulator that helps to maintain cellular ATP and mitochondrial turnover, is also reduced during renal CS. Interestingly, a cell permeable activator of AMPK (AICAR) partially restored renal ATP and ubiquitin expression, suggesting that loss of AMPK may play a critical role in linking altered mitochondrial and proteasomal function during renal CS.

Conclusions: These data suggest, for the first time, that renal CS leads to altered UPS and mitochondrial dysfunction. New studies designed to target the UPS with Bortezomib may have promising therapeutic implications for renal transplantation.

Funding: NIDDK Support

FR-PO489
MitoQ Blunts Mitochondrial Damage during Renal Cold Storage via Improved Mitochondrial Biogenesis Lee Ann MacMillan-Crow, Nirmala Parajuli, Akira Marine. Pharmacology and Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR.

Background: A major hurdle in the field of renal transplantation is the severe shortage of suitable donor kidneys despite the increasing number of patients awaiting transplant. Renal transplantation using living-donor organs (not exposed to cold storage) perform better when compared to deceased donor kidneys that were exposed to cold storage prior to transplant. Our published reports showed that cold storage induces mitochondrial and renal damage, and we recently reported in a porcine kidney model that a mitochondrial targeted antioxidant, MitoQ, blunted mitochondrial damage (PLOS One 7:11, 2012). However, it remains unknown what mechanisms are governing the cold-mediated mitochondrial damage or protection with MitoQ.

Methods: Male rodent kidneys were isolated and cold stored in University of Wisconsin solution for 4 to 24 hr +/- MitoQ (100 μM). Mitochondrial function was assessed using fresh renal biopsies via high resolution respirometry and ATP measurements. Mitochondrial biogenesis was monitored using immunohistochemistry and mRNA integrity assessment.

Results: Preliminary data showed that cold storage lead to decreased mRNA levels, reduced respiratory complex function, and impaired mitochondrial biogenesis. Interestingly, HIC analysis suggested that mitochondrial biogenesis was extensively impaired within proximal tubules, but induced in distal nephron cell types. We also showed that adding MitoQ increased ATP and mtDNA after cold storage (24 hr) alone, and improved renal function following cold storage (4 hr) plus transplantation (24 hr) (serum creatinine: 2.9 versus 1.5 mg/dL + MitoQ).

Conclusions: These studies suggest that MitoQ can protect against mitochondrial and renal damage during cold storage and transplantation, possibly by restoring mitochondrial biogenesis.

Supported by NIH DK089659 (LAMC).

Funding: NIDDK Support

FR-PO490
NOx4 Activation in Renal Ischemia-Reperfusion (I/R) Injury Is Complement-Dependent Simona Simonig,1 F. Rascio,1 Giuseppe Castellano,1 C. Divella,1 Paola Pontrelli,2 P. Dittono,1 Loreto Gesualdo,1 G. Pertosa,2 G. Grandaliano,2 1Dept of Emergency and Organ Transplantation, Univ of Bar, Bar, Italy; 2Dept of Medical and Surgical Sciences, Univ of Foggia, Foggia, Italy.

Background: Renal I/R plays a key role in the pathogenesis of delayed graft function after renal transplantation and is characterized by an increased of reactive oxygen species generation. The complement cascade has been suggested to play a pathogenic role in I/R-induced renal damage. Aim of the study was to investigate the activation of NADPH oxidase renal isoform, NOx4, in a pig model of renal I/R injury focusing on complement system.

Methods: Renal I/R was induced in 5 pigs by arterial clamping. The NADPH oxidase activity was assessed by chemiluminescence on renal tissue taken before ischemia (T0) and at different time after reperfusion (T15', 30', 60'). NOX4 and 8-oxo-dG, a marker of DNA damage, and we recently reported in a porcine kidney model that a mitochondrial targeted antioxidant, MitoQ, blunted mitochondrial damage (PLOS One 7:11, 2012). However, it remains unknown what mechanisms are governing the cold-mediated mitochondrial damage or protection with MitoQ.

Results: Preliminary data showed that cold storage lead to decreased mRNA levels, reduced respiratory complex function, and impaired mitochondrial biogenesis. Interestingly, HIC analysis suggested that mitochondrial biogenesis was extensively impaired within proximal tubules, but induced in distal nephron cell types. We also showed that adding MitoQ increased ATP and mtDNA after cold storage (24 hr) alone, and improved renal function following cold storage (4 hr) plus transplantation (24 hr) (serum creatinine: 2.9 versus 1.5 mg/dL + MitoQ).

Conclusions: These studies suggest that MitoQ can protect against mitochondrial and renal damage during cold storage and transplantation, possibly by restoring mitochondrial biogenesis.

Supported by NIH DK089659 (LAMC).

Funding: NIDDK Support

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

477A
We observed a significant increase in tubular NOX4 (T0 18.6±5.5, pixel/total area, p<0.03), α-smooth muscle actin (SMA) expression was assessed by confocal microscopy (in vivo model) and immunoblotting in human proximal tubular epithelial cells (HCT2) treated C3a (5*10^-7 M). Chemiluminescence assay was used to evaluate NADPH oxidase activity in HK-2 cells after C3a stimulation.

Results: NADPH-oxidase activity was significantly increased during reperfusion in a time-dependent manner with a peak at T60 (T0 3.0±0.4, T60 5.3±2.0 aU/L/Dr, p<0.03). We observed a significant increase in tubular NOX4 (T0 18.6±5.5, pixel/total area, p<0.03) and α-SMA expression at the same time point (T0 8.0±0.1, T60 4.6±0.1, pixel/total area, p=0.02). In vitro, C3a induced both NOX4 and α-SMA protein expression in HK2 cells (p=0.02) and caused a statistically significant increase in NADPH-dependent superoxide generation compared to basal conditions (p<0.01). Interestingly, Nox4 silencing by siRNA abolished both C3a-induced NADPH oxidase activation (p<0.01) and α-SMA expression (p<0.02).

Conclusions: NOX4 is activated during I/R injury. Complement and NADPH oxidase may play a pharmacological targets to prevent oxidative damage during I/R injury.

Funding: Government Support - Non-U.S.

FR-PO491
Renal Protection through CBS/H2S Pathway in Mammalian Hibernation–A Natural Model of Hypothermic Organ Preservation during Cold Ischemia and Reperfusion

George Johnson Dugbartey,1 Leo E. Deelman,1 Robert H. Henning.1

1 Clinical Pharmacology, Univ Medical Center Groningen, Groningen, Netherlands; 2 Clinical Pharmacology, Univ Medical Center Groningen, Groningen, Netherlands.

Background: Hibernation represents the most radical example of hypometabolism among mammalian species and is characterized by repetitive cycles of cooling and rewarming. It is now recognized that many hibernators exhibit very low, but functionally relevant, levels of energy consumption, which reflect an adaptive, low-oxygen, organ storage for transplantation, major surgery and ischemia-reperfusion.

Therefore mechanisms applied by hibernators to undergo hibernation without reperfusion injury or other ill effects may have potential application to human medicine. This study aimed at investigating the role of CBS enzyme and H2S in the induction of torpor and kidney preservation during hibernation.

Methods: Male Syrian golden hamsters (Mesocricetus auratus) were housed in cages in an environment-controlled chamber at 5°C under 24-hour light and dark cycles. Movements of all animals was continuously monitored with passive infrared detectors. Omnic mini-pumps filled with saline or OA0A (100mg/kg/day) were implanted i.p. before torpor following a bolus injection of OA0A (10mg/kg) under 2.5% isoflurane anaesthesia. At 4 days following implantation of pumps, hamsters that re-entered torpor were aroused by handling for 4 hours and euthanized under pentobarbitol anesthesia. Blood samples were taken and kidney of the hamsters were obtained. Summer euthermic hamsters served as controls.

Results: Torpid hamsters were aroused during pump implantation. In contrast to saline infusion, infusion of AOAA prevented hamsters from re-entry into torpor. Infusion of AOAA also induced excess renal damage as indicated by high expression of kidney injury marker as well as changes in renal morphology. In contrast, renal morphology was well preserved during hibernation in the saline and non-hibernating summer control groups.

Conclusions: Our data show that CBS/H2S pathway is essential in entrance into torpor and preservation of kidney morphology and function during hibernation.

Funding: Government Support - Non-U.S.

FR-PO492
Association of Genetic Polymorphisms of Matrix Metalloproteinases with New-Onset Diabetes after Transplantation in Renal Transplantation

Tae Hee Kim, Sunwoo Kang, Yang Wook Kim, Miseon Kang.

Internal Medicine, Univ of Inje, Busan, Republic of Korea.

Background: New-Onset Diabetes After Transplantation (NODAT) is a serious metabolic complication that may follow renal transplantation. Excess fat deposition requires space, created by adipocyte (hypertrophy and hyperplasia) and extracellular matrix (ECM) remodeling. This process is regulated by several factors, including adipocyte-derived Matrix metalloproteinases (MMPs) and the adipokine cathepsin, which degrades fibronecin, a key ECM protein. Excess fat, also deposited in visceral organs, generates inflammation that eventually triggers insulin resistance and the associated diabetes. Therefore, we investigated the association between NODAT development and 11 single nucleotide polymorphisms (SNPs) which might be related with NODAT.

Methods: A total of 309 renal transplant recipients were included without a history of diabetes. We analyzed the association between NODAT development and a panel of 11 SNPs within 3 genes (MMP1, MMP2, MMP3) of MMPs.

Results: Two SNPs among 11 (18.1%) were significantly associated with the development of NODAT in the codominant and recessive or, codominant and dominant models, respectively.

Conclusions: The data suggest that excess fat deposition and ECM remodeling might play a role in the pathogenesis of NODAT in renal transplantation recipients. In particular, significant variations of MMP2 might confer susceptibility to NODAT in patients who receive renal transplants.

Funding: Private Foundation Support

FR-PO493

Carlos Eduardo Neves Amorim,1 Alvaro Pacheco-Silva,2 Niels O.S. Camara,1 Ronaldo Araujo.1

1 Nephrology, UNIFESP, Sao Paulo, Brazil; 2 Medicine, Univ of Sao Paulo, Sao Paulo, Brazil; 3 Hospital Israelita Albert Einstein, HIAE, Sao Paulo, Brazil.

Background: There is a consensus in the scientific literature that supports the importance of the kalikrein kinase angiotensin system in renal physiology, but few studies have investigated clinically important polymorphisms.

Methods: The aim of this study was to investigate the clinical effects of the insertion/deletion polymorphism in the angiotensin I-converting enzyme (ACE) gene and the -9/-9 polymorphism in the kinin B2 receptor (B2R) gene in kidney-transplanted patients (n = 218; ACE = n = 203 B2R) compared with 443 healthy individuals.

Results: Demographic results showed that there is a higher frequency of the D allele (high plasma ACE activity) and +9 allele (lower B2R expression) in transplant patients compared with control individuals. We also observed a higher frequency of these alleles in transplant patients who had an elevated level of plasma creatinine. At day 7 post-transplantation, we found a higher prevalence of individuals with the DD genotype with elevated plasma creatinine level. Furthermore, individuals with the DD genotype had a higher chronic and acute rejection and graft loss compared with the H1 patient genotype, which showed no loss of graft. We also found that transplantation performed between a patient DD and a donor II or II presented a higher chance of acute rejection than the opposite way. In the analyze of the prescription drug, 161 Individuals were medicated with some type of antihypertensive, and 44 were taking ACE inhibitor, 36% of transplanted group, and was observed that ACE inhibitors were renoprotective.

Conclusions: Taken together, our data suggest that the genotyping of these individuals for ACE polymorphism could be clinical relevant.

Funding: Government Support - Non-U.S.

FR-PO494
Established Renal Trait SNPs and Allograft Function in a Kidney Transplant Population

Paul J. Phelan,1 Robert P. O’Brien,2 Gianpietro Cavalleri,2 Peter J. Conlon.1

1 Nephrology, Beaumont Hospital, Dublin, Ireland; 2 Molecular Medicine, Royal College of Surgeons of Ireland, Dublin, Ireland.

Background: Recent large scale genome-wide association studies (GWAS) in individuals of European ancestry have demonstrated several SNPs associated with estimated glomerular filtration rate (eGFR) and Chronic Kidney Disease (CKD). We recently completed a GWAS in an Irish renal transplant population. Twenty of the previously associated renal-function SNPs were captured by the Illumina Bead Chip we employed for our genotyping. We tested these SNPs for association with eGFR at 5 years post transplant.

Methods: Patients were adult, first, deceased donor, kidney-only transplants, on calcineurin inhibitors between 1993 and 2002. We had data on 263 patients with a functioning graft and eGFR data at 5 years post transplant (median MDRD eGFR 43.5 ml/m^2/1.73m^2). One-third of patients were female and mean age was 47.6 years. Principal components analysis showed our cohort to cluster with other northern European populations.

Results: Our results show that while 2 variants approached statistical significance for eGFR in our cohort, none had a p value of <0.05. Our most significant SNP (rs6036478; p=0.05415) was in full LD with rs911119, an intergenic variant on chromosome 20 with strong linkage disequilibrium (LD) in the transplant cohort. The second most significant SNP was rs6465825 (p=0.0629; chromosome 7), another intergenic variant which was associated with eGFR (creatinine) in the original study. No other SNPs approached significance. Additionally, if Bonferroni correction is applied to correct for multiple testing, the 2 borderline significant SNPs do not approach significance.

Conclusions: While we believe that there is an important role for association studies in finding susceptibility genes, our results are not sufficient to support the use of these genetic variants in medical practice.

Funding: Private Foundation Support

FR-PO495
Genetic Predispension of Donors Affects the Allograft Outcome in Kidney Transplantation; Single Nucleotide Polymorphism of Aquaporin-11

Jin Park,1 Jung Pyo Lee,2 Seung Hee Yang,2 Yon Su Kim.1

1 Dept of Internal Medicine, Seoul National Univ College of Medicine, Seoul, Republic of Korea; 2 Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Republic of Korea; 3 Kidney Research Institute, Seoul National Univ, Seoul, Republic of Korea.

Background: Aquaporin-11 (AQP11) is a novel aquaporin family member. Disruption of the murine AQP11 gene causes severe proximal tubular injury and renal failure. The rs2276415 (G>A) single nucleotide polymorphism (SNP) in the human AQP11 gene results in a functional gain-of-function and its importance in renal transplantation.

Methods: A total of 206 pairs of donors and recipients were enrolled. Long-term graft survival was traced and clinical parameters that could have influenced graft outcome were collected by reviewing electronic medical record system.

Results: The frequency of the A allele was higher in recipients of donors with an elevated level of plasma creatinine. In patients who had an elevated level of plasma creatinine, the DD genotype was more prevalent in recipients. At day 7 post-transplantation, we found a higher prevalence of individuals with the DD genotype with elevated plasma creatinine level and a lower B2R expression. Furthermore, individuals with the DD genotype had a higher chronic and acute rejection and graft loss compared with the H1 patient genotype, which showed no loss of graft. We also found that transplantation performed between a patient DD and a donor II or II presented a higher chance of acute rejection than the opposite way. In the analyze of the prescription drug, 161 Individuals were medicated with some type of antihypertensive, and 44 were taking ACE inhibitor, 36% of transplanted group, and was observed that ACE inhibitors were renoprotective.

Conclusions: Taken together, our data suggest that the genotyping of these individuals for ACE polymorphism could be clinical relevant.

Funding: Government Support - Non-U.S.
Results: Despite similar allele frequencies between donors and recipients, minor allele of AQP11 rs2276415 (GA/AA) from donor, not from recipients, has a harmful effect on the graft outcome. The association was significant after adjusting for several risk factors including age, sex, HLA mismatch, donor type, hypertension, and diabetes mellitus (P=0.032). In immunohistochemistry staining, AQP11 was differently expressed according to genetic variations of donor rs2276415 showing higher expression in the grafts from GC donors.

Conclusions: In conclusion, a donor-derived, not recipient derived, genetic AQP11 polymorphism has different effects on graft outcome. Thus, the genetic influence from donors should be carefully considered for the proper management of allografts after kidney transplantation.

FR-PO496
Prospective Randomized Study of Tolerability and Efficacy of Combination Therapy on Hypertensive Chronic Kidney Disease (CKD) Matsuhiro Hayashi,1 Shunya Uchida,2 Tetsuya Kawamura,3 Michio Kuwahara,4 Masaoi Nagakura,5 Yasuhiro Iino.6

Background: In the treatment of hypertension in CKD patients, angiotensin receptor blocker (ARB) and calcium channel blockers (CCB) are the two mainstays, although it is not clear which second-line drug is beneficial for CKD patients.

Methods: In a randomized, open-label trial, the patients with CKD defined by K/DOQI guideline and hypertension (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg) in spite of usual doses of ARB were randomly assigned to receive losartan 50mg plus either 5mg of amlopidine (CCB group, n=27), or 25 mg hydrochlorothiazide (HCTZ group, n=30). The primary endpoints were changes in blood pressures, ratio of urinary excretion of protein to creatinine (uP/C ratio), and eGFR during 12 months study period. The secondary endpoints were changes in biochemical parameters and side effects.

Results: Systolic and diastolic blood pressures were not significantly different between three groups throughout the study period. The percent changes in uP/C ratio was significantly different between HCTZ group (>25.8±19.8%, mean±SE) than that in CCB group (26.7±3.3%, p<0.05) at 12 months after the assignment to each therapy, while eGFR was significantly lower in HCTZ group than ACEI and CCB groups between 14 months but not at 12 months study period. Serum uric acid levels were significantly higher in HCTZ group than CCB and ACEI groups during the entire period of the study. By logistic analysis, 25% decrease in uP/C ratio was more likely in HCTZ group (odds ratio 5.78, CI 1.14 to 37.8, p=0.03) compared with CCB group.

Conclusions: Addition of diuretics to ARB is though to be beneficial combination therapy for the control of hypertension in CKD in terms of urinary excretion of protein compared with addition of CCB or ACEI, while the effects of increased serum uric acid levels in HCTZ group on the progression of CKD should be determined by long-term study in the future.

Funding: Pharmaceutical Company Support - MSD Co. Ltd., Government Support - Non-U.S.

FR-PO497
Genetic Profile of Salt Sensitivity in Essential Hypertension Chiara Lanzani, Marco Simionini, Elena Brioni, Simona Delli Carpini, Lorena Citterio, Laura Zagato Villa, Stefano Tentori, Paolo Manunta. San Raffaele Scientific Institute, Milan, Italy.

Background: Blood pressure (BP) is controlled primarily by Na and water balance because of the infinite gain property of the kidneys to rapidly eliminate excess fluid and salt. Up to 50% of patients with essential hypertension are salt-sensitive, as manifested by increased systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels in response to a dietary Na load. The Genetics of Salt Sensitivity in Essential Hypertension (GSSENS) project aimed to identify genetic determinants of salt sensitivity in patients with essential hypertension.

Methods: In a prospective study, 434 participants underwent a salt load protocol, which consisted of eating a low-Na diet for 7 days followed by a Na load period of 1 week. Blood pressure was measured every 2 hours during the Na load period. The genetic associations were studied using a genome-wide association study (GWAS) approach.

Results: A total of 12 SNPs were found to be associated with salt sensitivity. The most significant SNP was rs1077635, located in the angiotensinogen (AGT) gene. This SNP was associated with a 2.2 mmHg increase in SBP and a 0.9 mmHg increase in DBP for every 10 mmol Na consumed. In a multivariable model, a doubling of SBP was associated with increased odds of WCH, MI, and SH by 52.7%, 5.5%, 24.5%, and 17.2%, respectively.

Conclusions: These results indicate that cilnidipine is beneficial for the suppression of pathological cardiac remodeling through an inhibitory modulation of cardiac sympathetic nerve activity in hypertensive CKD patients.

Funding: Government Support - Non-U.S.

FR-PO499
White-Coat, Masked, and Sustained Hypertension in Chronic Kidney Disease—The CRIC Study Paul E. Drawz,1 Arnold B. Alper,2 Amanda Hyre Anderson,3 Denise C. Babineau,4 Carolyn S. Brecklin,5 Jeannie Charleston,6 Jing Chen,7 Yonghong Huan,8 Susan P. Steigervalt,9 Jonathan J. Taliercio,10 Raymond R. Townsend,11 Matthew R. Weir,12 Mahboob Rahman.7

Background: The goal of this prospective study was to evaluate whether elevated proteinuria and low eGFR are associated with increased odds of white-coat (WCH), masked (MH), and sustained hypertension (SH) in a large cohort of participants with CKD.

Methods: In the Chronic Renal Insufficiency Cohort (CRIC) study, 24-hour ambulatory blood pressure (ABP) was measured between 2006 and 2012. Clinic blood pressure (BP) was measured in triplicate by study staff. WCH was defined by a clinic BP ≥140/90 mmHg and daytime ABP ≥135/85 mmHg; MH by a clinic BP <140/90 mmHg and daytime ABP ≥135/85 mmHg; and SH by a clinic BP <140/90 mmHg and daytime ABP ≥135/85 mmHg. Urine protein was measured in a 24 hour sample at baseline. Creatinine was measured annually.

Results: ABP was obtained in 1439 CRIC participants. The average time from the baseline visit to ABP was 5.1 years. The percent of participants with controlled BP, WCH, MH, and SH was 52.7%, 5.5%, 24.5%, and 17.2%, respectively. In a multivariable model, a doubling of urine protein was associated with increased odds of WCH, MI, and SH. In a separate multivariable model, a decrease in eGFR of 10 ml/min/1.73m² was associated with increased odds of MH but not WCH or SH.
FR-PO50

Renal Denervation Halts the Decline of Renal Function in Patients with Chronic Kidney Disease and Treatment Resistant Hypertension

Background: Hypertension is a predominant risk factor of renal function decline over time and achieving blood pressure (BP) targets preserves renal function. Renal denervation (RDN) emerged as an intervention before hypertension therapy was initiated in patients with treatment-resistant hypertension (TRH) and we asked whether reducing BP by RDN preserves renal function by reducing BP and increasing sympathetic activity.

Methods: 12 patients with TRH (office BP ≥140/90 mmHg and confirmed by 24-h ABPM ≥130/80 mmHg) and chronic kidney disease (CKD) stage 3 and 4 underwent RDN using the Symplicity catheter (Medtronic Inc., Santa Rosa, CA, USA). The study was registered at http://www.clinicaltrials.gov (ID: NCT01246983).

Results: RDN was evaluated up to 3 years prior and till 1 year after RDN. Estimated glomerular filtration rate (eGFR) was calculated using MDRD formula and the change in eGFR over time was calculated by regression slope individually for each patient.

Conclusions: RDN decreases decline in renal function and improves renal function compared to the control group. RDN preserves renal function by reducing BP and increasing sympathetic activity.

FR-PO501

Mindfulness Meditation Lowers Muscle Sympathetic Nerve Activity and Blood Pressure in Chronic Kidney Disease Patients

Background: Chronic kidney disease (CKD) is characterized by chronic sympathetic nervous system (SNS) overactivity that contributes to hypertension and mortality. Prior studies have shown that mindfulness meditation (MM) lowers blood pressure (BP) and heart rate (HR) in hypertensive individuals. We hypothesized that MM acutely lowers BP and HR in hypertensive patients with chronic kidney disease (CKD), and that these hemodynamic changes are mediated by a reduction in sympathetic nerve activity (SNA).

Methods: 13 patients with CKD Stage III and hypertension were studied at two separate study visits to eliminate carryover effects, in a randomized, cross-over design. We measured continuous arterial BP, HR via continuous electrocardiography, respiratory rate (RR), and muscle sympathetic nerve activity (MSNA) using microneurography, at baseline, and during: 1) 14 minutes of guided MM during one study visit, and 2) 14 minutes of BP education (control condition) during the other study visit. Data were analyzed using mixed models for linear modeling.

Results: Linear modeling revealed that the rate of change in systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and MSNA was significantly greater over time during MM compared to the control condition. At the 14-minute time point, there was a significantly greater reduction in SBP (-10.2±2.9 vs. -8.8±1.3 mm Hg, p<0.007), DBP (-6.0±4.8 vs. -1.4±6.8 mm Hg, p=0.002) during MM versus the control condition, respectively, but no difference in HR. Concomitantly, there was a significantly greater reduction in MSNA during MM compared to the control condition (-10.7±1.6 vs. -1.9±2.8 bursts/min, p<0.02).

Conclusions: These data are the first to demonstrate that MM may lower BP in hypertensive patients with CKD, and the reduction in BP may be mediated by an acute reduction in SNS activity. MM may have real physiological effects on autonomic control, and may be a useful complementary therapy in CKD patients.

FR-PO502

Sex Dependent Association between Heart Rate Variability and Pulse Pressure in Hemodialyzed Patients

Background: Elevated Pulse Pressure (PP) is associated with increased cardiovascular mortality in hemodialysis (HD) patients. Autonomic imbalance is common in HD patients but its relationship to PP is unknown. We investigated the relationship between cardiac autonomic status assessed by heart rate variability (HRV) spectral analysis and PP in HD patients.

Methods: In stable HD patients, continuous electrocardiograms were obtained during HD and repeated 5 times at 2-weeks intervals. The high- (HF) and low-frequency (LF) components and the LF/HF ratio of HRV were calculated every 5 minutes in absolute values and averaged during the first and last hour of each recording. The coefficient of variation of the corresponding pre and post-HD systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were averaged in repeated recordings of each patient.

Results: We investigated 80 patients aged 60±14 years, 32% females and 37% diabetics. All blood pressure and HRV indices showed intra-subject stability (repeated measures ANOVA). LF and HF decreased while the LF/HF ratio increased inversely with pre and post-HD PP (r=-0.369, p=0.007 and r=-0.546, p=0.000 respectively), positively with pre and post-HD DBP (r=0.358, p=0.009 and r=0.308, p=0.028 respectively) and inversely with post-HD SBP (r=-0.422, p=0.040). The LF/HF did not correlate with PP or DBP and correlated positively with post-HD SBP (r=0.422, p=0.040) in female patients.

Conclusions: Strong association between PP and spectral HRV parameters was found in male but not in female HD patients. The sex differences in autonomic cardiovascular regulation during HD may contribute to the differences in cardiovascular risk between sexes.

FR-PO503

A Urinary Peptide Score That Predicts Albuminuria Progression During the Presence or Absence of RAAS Blockade

Background: Previous studies have shown that a urinary proteomic-based risk score (CKD273) predicts albuminuria progression. We assessed whether CKD273 scores differ in hypertensive subjects treated with or without RAAS blockade.

Methods: We performed a case-control study using data from the prospective, general population-based PREVEND Study (The Netherlands). We identified 75 hypertensive cases who progressed in albuminuria stage (from normo- to microalbuminuria or from micro- to macroalbuminaria). We matched these subjects for age, gender, baseline albuminuria stage, and CKD stage 2 (CKD273) predicts albuminuria progression. We assessed whether CKD273 scores differ in hypertensive subjects treated with or without RAAS blockade.

Results: A Urinary Peptide Score That Predicts Albuminuria Progression During the Presence or Absence of RAAS Blockade

Conclusions: A Urinary Peptide Score That Predicts Albuminuria Progression During the Presence or Absence of RAAS Blockade

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Conclusions: Higher CKD23 scores observed in hypertensive subjects treated with RAAS blockade may reflect more advanced renal/microvascular damage despite similar blood pressure and albuminuria levels. This likely reflects indication bias and suggests that RAAS blockade should be accounted for as a confounder in proteomic studies.

FR-PO504
Rapid Test to Identify the Salt Sensitivity
Andrea Pio de Abreu, Giovanio Vieira Du Silva, Isaac De Castro, Katia Ortega, Decio Mion Junior. Nephrology, Univ of Sao Paolo School of Medicine, Sao Paulo, Brazil.

Background: Salt sensitivity, defined as the variation of blood pressure with the intake of different amounts of salt, has both clinical and prognostic implications. Nevertheless, the gold standard test for this diagnosis is hardly used in clinical practice, mainly due to difficulties in patients. The objective of study was to evaluate whether the use of fludrocortisone, which causes sodium retention, is accurate compared to the dietary cycle. Until the moment, there is no practical test with an good accuracy.

Methods: A crossover design study was conducted with thirty unmedicated hypertensive patients. The dietary cycle consisted of one week with a low-sodium diet (40 mmol/day) and one week with a high-sodium diet (200 mmol/day). After one month, the fludrocortisone test was performed by administering 0.4 mg/day for 4 days, maintaining the usual food ingestion. BP was measured at the end of each dietary cycle and on the first and fourth day of fludrocortisone intake.

Results: The 30 volunteers (60% female), whose mean age was 53.7 ± 7.6 years, had a mean systolic blood pressure (SBP) of 146 ± 12 mmHg and diastolic of 91 ± 10 mmHg. The mean NaU values for the low and high-salt-diet cycles were, respectively, 40 ± 25 mmol/d and 212 ± 44 mmol/d. During the administration of fludrocortisone, the mean SBP values for the low and high-salt-diet cycles were, respectively, 172.7 ± 18.1 and 213.7 ± 18.1 mmHg.

Conclusions: The Rapid Test To Identify the Salt Sensitivity, which consists in the administration of 0.4 mg / day of fludrocortisone for four days, has good accuracy to identify salt-sensitive hypertensive patients.

Funding: Government Support - Non-U.S.

FR-PO505
The Impact of Renal Denervation on Ambulatory Blood Pressure in Two Specialist Hypertension Units in the United Kingdom
Alison H.M. Taylor,1 Patrick B. Mark,4 Alan G. Jardine,1 Jonathan S. Freedman,2 Indranil Dasgupta.3
1BHF Glasgow Cardiovascular Research Centre, Univ of Glasgow, Glasgow, United Kingdom; 2Dept of Radiology, Birmingham Heartlands Hospital, Birmingham, United Kingdom; 3Dept of Nephrology, Birmingham Heartlands Hospital, Birmingham, United Kingdom.

Background: Percutaneous renal artery denervation (RDN) is a novel technique for treatment of resistant hypertension, which has been shown to have major effects on clinic blood pressure (BP). We studied ambulatory BP (ABP), a more accurate representation of BP, in patients undergoing RDN out with a specific clinical trial.

Methods: Patients with systolic BP ≥160/90mmHg despite compliance with ≥3 antihypertensive agents and no secondary cause for hypertension were treated with bilateral RDN. All patients underwent ABP monitoring and laboratory tests prior to and 6 months following RDN.

Results: 20 consecutive patients (55% female, mean age 50.1 years) were studied. At baseline, the median time since diagnosis of hypertension was 8.5 years (range 1-32 years), 20% of patients had diabetes mellitus and 35% had a history of vascular disease. The median serum creatinine was 0.83mg/dl (range 0.61-3.60). Mean clinic BP was 189/110mmHg (±26/17) and mean ABP 173/100mmHg (±18/15). The mean number of antihypertensive agents prescribed was 5.65 (±1.3). At six months following RDN there was a significant fall in both ambulatory (–9.9mmHg, p<0.02) and clinic (–18.9mmHg, p<0.02) systolic BP. There was a non-significant fall in diastolic BP using both measurements. The mean reduction in number of medications prescribed was 1.6 (±2.1, p=0.003). There was no significant change in renal function at six months.

Conclusions: RDN does lead to reduction in ABP in ‘real world’ patients with resistant hypertension, although the magnitude of effect is less than previously demonstrated.

FR-PO506
Comparison of Sleep Apnea Rates and Characteristics in Resistant and Non-Resistant Hypertension
John J. Sim, Jiaxiao Shi, Glory Tseng. Nephrology & Hypertension, Kaiser Permanente Los Angeles Medical Center.

Background: Sleep apnea is associated with hypertension and is a risk factor for resistant hypertension (RH) but the degree to which it is more prevalent in RH is largely unknown. We sought to compare rates and characterize sleep apnea in RH and non-RH within a large ethnically diverse hypertension population.

Methods: Cross sectional study during 1/1/2006- 12/31/2007 of hypertensive individuals within the Kaiser Permanente Southern California health system. Resistant hypertension defined as uncontrolled blood pressure on 3 meds or requiring ≥4 meds. Sleep apnea identified by ICD-9 coding and CPT coding for dispensation of cpap/bipap. Rates of sleep apnea in RH and non RH determined. Demographic, co morbidity and laboratory information extracted from the electronic medical records. Multivariable logistic regressions performed to calculate odds ratios (OR) for sleep apnea.

Results: Among 470,386 individuals with hypertension, sleep apnea was identified in 23,184 (4.9%). RH individuals had a sleep apnea rate of 7.1% (4,007) compared to 4.9% (19,177) in non RH (p<0.001). Among the entire hypertension cohort, adjusted OR for sleep apnea were greater in those with RH, BMI>29, male gender, and diabetes. Whites were more likely to have sleep apnea compared to blacks, Hispanics, and asians.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant Hypertension</td>
<td>1.08</td>
<td>1.04-1.12</td>
</tr>
<tr>
<td>BMI&gt;29</td>
<td>1.08</td>
<td>1.04-1.12</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.08</td>
<td>1.04-1.12</td>
</tr>
<tr>
<td>Race (white)</td>
<td>1.08</td>
<td>1.04-1.12</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.08</td>
<td>1.04-1.12</td>
</tr>
<tr>
<td>Black</td>
<td>1.08</td>
<td>1.04-1.12</td>
</tr>
<tr>
<td>Asian</td>
<td>1.08</td>
<td>1.04-1.12</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.08</td>
<td>1.04-1.12</td>
</tr>
</tbody>
</table>

Conclusions: Hyper tension, although the magnitude of effect is less than previously demonstrated.

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

481A
Conclusions: Within a large ethnically diverse hypertension population, we observed a modest increase in rate and risk for sleep apnea in RH compared to non RH. Among the traditional risk factors, BMI>29 had the greatest risk for sleep apnea within our hypertension population.

Funding: Private Foundation Support

FR-PO507

Disturbed Circadian Rhythm of the Intrarenal Renin-Angiotensin System: Relevant to Nocturnal Hypertension and Renal Damage

Shinsuke Isobe, Naro Ohashi, Hideo Yasuda, Yoshhide Fujigaki

Background: The intrarenal renin-angiotensin system (RAS) plays an important role in the development of hypertension and renal damage. Disruption of diurnal blood pressure (BP) variation is an additional risk factor for renal damage. However, little is known regarding whether intrarenal RAS circadian rhythm exists or if it influences the disruption of diurnal BP and renal damage.

Methods: We investigated the circadian rhythm of urinary angiotensinogen that reflects intrarenal RAS activity, albuminuria, proteinuria and urinary sodium excretion every hour (Na+/h) in 10 healthy individuals and 33 chronic kidney disease (CKD) patients classified according to circadian BP rhythms.

Results: BP values were higher during the day than during the night in healthy individuals and CKD patients. Urinary angiotensinogen levels were not different between the day and night in healthy individuals, but were significantly higher in the daytime in CKD patients (log urinary angiotensinogen/creatinine: daytime, 2.48 ± 0.99; nighttime, 2.31 ± 1.08; p = 0.001). Furthermore, in CKD patients showing a riser pattern of circadian BP, urinary angiotensinogen levels did not decrease during the night compared with those in the day (log urinary angiotensinogen/creatinine: daytime, 2.50 ± 0.65; nighttime, 2.52 ± 0.71; p = 0.092). Circadian fluctuation of albuminuria and proteinuria occurred parallel to that of the urinary angiotensinogen levels. Urinary angiotensinogen levels were significantly and positively correlated with the degree of hypertension and circadian fluctuation of urinary angiotensinogen were correlated with diurnal BP changes.

Conclusions: These data suggest that the circadian rhythm of intrarenal RAS activation may lead to renal damage and hypertension, which are associated with diurnal BP variation.

FR-PO508

Variables Indicative of Kidney Injury Are Related to the BP-Lowering Effect of Renal Denervation

Eva Vink, Willemien Verloop, Wilko Spiering, Michiel Voskuil, Evert-Jan Vonken, Michiel Bots, Peter J. Blankstijn

Background: Renal denervation (RDN) is a promising treatment for resistant hypertension. However, there is a wide range in the BP-lowering effect. Evidence on factors that determine BP-lowering effect after RDN is limited. Aim of current study was to further explore these factors.

Methods: Patients from a prospective cohort of patients treated with RDN with available 6months follow-up data, were included in current analysis. Data collected during routine clinical standardized work-up before RDN were used in present analysis (urine collected during 24-h, blood samples, ambulatory BP monitoring and a captopril challenge test).

Results: BP values were higher during the day than during the night in healthy individuals and CKD patients. Urinary angiotensinogen levels were not different between the day and night in healthy individuals, but were significantly higher in the daytime in CKD patients (log urinary angiotensinogen/creatinine: daytime, 2.48 ± 0.99; nighttime, 2.31 ± 1.08; p = 0.001). Furthermore, in CKD patients showing a riser pattern of circadian BP, urinary angiotensinogen levels did not decrease during the night compared with those in the day (log urinary angiotensinogen/creatinine: daytime, 2.50 ± 0.65; nighttime, 2.52 ± 0.71; p = 0.092). Circadian fluctuation of albuminuria and proteinuria occurred parallel to that of the urinary angiotensinogen levels. Urinary angiotensinogen levels were significantly and positively correlated with the degree of hypertension and circadian fluctuation of urinary angiotensinogen were correlated with diurnal BP changes.

Conclusions: These data suggest that the circadian rhythm of intrarenal RAS activation may lead to renal damage and hypertension, which are associated with diurnal BP variation.

FR-PO509

BP-Lowering Effect of Renal Denervation in Patients with Multiple Renal Arteries

Eva Vink, Willemien Verloop, Wilko Spiering, Michiel Bots, Evert-Jan Vonken, Michiel Voskuil, Peter J. Blankstijn

Background: In contrast to previous studies investigating safety and efficacy of renal denervation (RDN), we decided not to exclude patients with multiple renal arteries from treatment with RDN. The aims of present study were: to determine the prevalence of multiple renal arteries in patients referred for RDN, to investigate the relation between presence of multiple renal arteries and blood pressure (BP)-lowering effect of RDN.

Methods: Patients referred for treatment with RDN who underwent non-invasive imaging of the renal arteries before treatment, were included in present analysis. Eligible patients underwent RDN, BP and renal function were evaluated 6 months after treatment.

Results: 179 patients underwent imaging in the work-up. Thirty-five percent had multiple renal arteries. No differences in baseline characteristics were found between those with and without multiple arteries. Out of 179 patients, 109 underwent RDN, of which 60 patients completed six months follow-up. Office BP significantly changed in these patients from 206(±25)/108(±14) mmHg to 168(±24)/96(±14) mmHg (P<0.001). The change in BP was not different in patients with multiple compared to patients with solitary arteries. Renal function at 6 months did not differ from baseline in both subgroups. A classification of eligibility of the renal arteries for treatment with RDN is proposed.

Conclusions: Current analysis suggests that RDN is effective in patients with multiple renal arteries referred on the request of this present study. A high prevalence of multiple arteries, it seems reasonable not to exclude patients with multiple renal arteries from RDN.

Funding: Government Support - Non-U.S.

FR-PO510

The Impact of Sodium, Fructose Restriction and Allopurinol on Blood Pressure amongst Overweight and Prehypertensive Subjects


Background: Fructose causes hypertension partly through rising intracellular and serum uric acid (UA). The objective of this study was to compare the effect of sodium and fructose restriction in addition to allopurinol on blood pressure and metabolic syndrome components.

Methods: Randomized trial that included overweight and prehypertensive or hypertensive adults not on antihypertensive meds. The trial consisted of two phases: 1) Wks 1-4 patients were randomized to either isocaloric (with respect to baseline caloric intake) low sodium- low fructose diet (LS-F) or isocaloric low sodium diet (LS) during 4 wks. 2) Wks 4-8 the groups continued with the same diet prescriptions and were further randomized to either placebo or allopurinol 300 mg/d. Clinic and 24h ambulatory BP, anthropometric measures, laboratory data, were determined at weeks 0, 4 and 8.

Results: 72 patients were included in the trial. Compared to Wk0, at Wk8 clinic SBP and DBP were significantly lower in the LS-F group but not in the LS group. Both diets were associated with a significant day and global ABPM reduction. There were no between group significant differences with diet interventions at Wk4 or 8. Compared to placebo, at Wk8 subjects in the A group had a lower clinic SBP and this was significant within and between group comparisons. The % of dippers was also significantly higher in the A group. In addition weight was significantly reduced in the LS-F and A groups.

Table1

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>Weight (kg)</th>
<th>% Dippers</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS</td>
<td>44/4</td>
<td>150/90</td>
<td>70/70</td>
<td>80/60</td>
<td>65%</td>
</tr>
<tr>
<td>LS-F</td>
<td>46/4</td>
<td>148/90</td>
<td>70/70</td>
<td>80/60</td>
<td>70%</td>
</tr>
<tr>
<td>LS</td>
<td>44/4</td>
<td>148/90</td>
<td>70/70</td>
<td>80/60</td>
<td>75%</td>
</tr>
<tr>
<td>LS-F</td>
<td>46/4</td>
<td>148/90</td>
<td>70/70</td>
<td>80/60</td>
<td>80%</td>
</tr>
</tbody>
</table>

Conclusions: Both LS and LS-F diets are efficient to lower BP. Allopurinol significantly reduced clinic SBP and increased the percentage of dippers. Both LS-F and A were associated with weight loss despite the absence of caloric restriction.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author/disclosure.

482A
Type 2 Diabetic Patients with Treatment-Resistant Hypertension Display Urine Plasmin Excretion That Correlates with Blood Pressure and Activates ENaC

In Vitro Kristian B. Buhl,1 Christina Stolzenburg Oxlund,2 Ulla G. Fris,1 Per Svenningsen,1 Claus Bistrup,1 Ib A. Jacobsen,1 Boye Jensen,1 1Univ of Southern Denmark, Denmark; 2Univ Hospital of Odense, Denmark.

Background: Ablation filtration of plasminogen from plasma and subsequent activation to plasmin in the urinary space may potentially activate the epithelial sodium channel, ENaC. In conditions with chronic albuminuria this may cause hypertension. It was hypothesized that patients with type 2 diabetes mellitus (T2DM) and treatment-resistant hypertension (RHTN) excrete plasmin(ogen) in urine in proportion to albumin and that plasmin confers to urine the ability to activate ENaC.

Methods: A Cross-sectional design of 113 patients with T2DM and RHTN (systolic BP > 130mmHg and diastolic BP > 80mmHg despite use of at least three drugs with one diuretic and one renin-angiotensin system inhibitor). 24 hour blood pressure measurements were obtained and urine was analyzed for albumin, creatinine, plasmin(ogen), protease activity and ability to activate inward current in single collecting duct cells.

Results: Mean ambulatory blood pressure was 143 ± 17/77±7 mmHg; HbA1c 7.35%; eGFR 81.4 ml/min/1.73m² (geometric means). Micro- (39%) and macroalbuminuric (13%) T2DM patients with RHTN displayed significantly elevated levels of urinary plasmin(ogen) normalized to urine creatinine (plg/crea) compared to normo-albuminuric-T2DM-RHTN patients (48%). Urinary plg correlated significantly to urine albumin. Western immunoblottning and gelatin zymography confirmed active plasmin in urine samples from T2DM-RHTN patients with micro- and macroalbuminuria. Single collecting duct cells showed significantly increased, amiloride-sensitive, inward current when superfused with urine from albuminuric T2DM-RHTN compared to normalalbuminuric T2DM-RHTN. Urinary plg/crea correlated significantly to 24 hour ambulatory blood pressure.

Conclusions: Ablent presence of plasmin in pre-urine may inappropriately activate ENaC in patients with type 2 diabetes and microalbuminuria. This may contribute to treatment-resistant hypertension.

Funding: Private Foundation Support

Effects of Renal Denervation with a Standard Irrigated Cardiac Ablation Catheter on Blood Pressure and Renal Function in Patients with Chronic Kidney Disease and Resistant Hypertension

Jecemir R. Lugo,1 Maria A. Carreira,1 Miguel Luis Graciano,1 George Luis Marques Maia,1 Marcio Galindo Kiuchi,1,2 Tetsuki Kiuchi.1 1Nephrology, Universidade Federal Fluminense, Niterói, RJ, Brazil; 2Vascular Surgery, Hospital Regional Darcy Vargas, Rio Bonito, RJ, Brazil.

Background: Recently, transcatheter renal sympathetic denervation (RSD) has proved effective in lowering refractory blood pressure (BP). We evaluated the safety and efficacy of this procedure using a standard irrigated cardiac ablation catheter (SICAC) in 24 chronic kidney disease patients (stages 2-4) with refractory hypertension.

Methods: Twenty four patients were included and treated with a SICAC. Denervation was performed by single operator following standard technique. Patients included with CKD were on stages 2 (n=16), 3 (n=4) and 4 (n=4). Data were obtained at baseline and monthly until 180th day of follow up.

Results: Data were obtained at baseline and monthly until180th day of follow up. Baseline characteristics of the population were: (Mean±SD): 48±19 years of age, 60±12% male, 151±18 mmHg / 92±11 mmHg by 24 hour ambulatory blood pressure monitoring (ABPM). Office blood pressure values at 180th day after procedure were 135±13 mmHg/88±7 mmHg (P=0.0001, for both comparisons). Mean ABPM decreased to 132±15 mmHg/85±11 mmHg at the 180th day after the procedure (P<0.0001 for systolic and P=0.0015 for diastolic). Estimated glomerular filtration (Mean±SD) increased from baseline (64±23.9 ml/min/1.73m²) to the 180th day (85±34.9 ml/min/1.73m², P=0.001) of follow-up. Median urine albumin/creatinine ratio decreased from baseline (48.5, IQR 35.8-157.2 mg/g) to the 180th day after ablation (ACR = 15.7, IQR 10.3-34.2 mg/g, P=0.0017). No major complications were seen.

Conclusions: The procedure using SICAC seemed to be feasible, effective and safe resulting in better control of BP, a short-term increase in GFR, and reduced albuminuria. Although encouraging, our data are preliminary and need to be validated in the long term.

Dietary Sodium Reduction and Aldosterone Acutely Alter the Urine Exosome Proteome in Humans

James M. Luther,2 Ying Qi,1 Bing Zhang,1 Kristie Rose,1 Xiaojing Wang,1 Kevin Schey,1 1Biochemistry, Vanderbilt Univ, Nashville, TN; 2Medicine, Vanderbilt Univ, Nashville, TN; 3Pharmacology, Vanderbilt Univ, Nashville, TN.

Background: Urinary exosomes are a potential biomarker source for human disease, but their physiologic relevance remains uncertain.

Methods: To test the hypothesis that the urinal urine proteome is regulated by endogenous and exogenous hormones, we analyzed urine exosomes in 14 healthy control subjects in a cross-over study during high (HS, 160mmol/d) and low salt (LS, 20mmol/d) diet to activate the endogenous renin-angiotensin-aldosterone system (RAAS). In a separate cohort during HS diet, we collected urinary exosomes after vehicle and aldosterone infusion (0.7 µg/kg/hr for 10 hrs).

Results: LS diet increased renin activity (5.9±3.1 vs 0.8±0.3 ng Ang/ml/hr; P=0.01) and aldosterone (16.4±2.7 vs 7.5±1.1 ng/dL; P<0.001), and aldosterone infusion increased plasma aldosterone (55.9±5.5 vs 78±1.5 ng/dL; P<0.001). Urinary exosome peptide analysis by Multidimensional Protein Identification Technology (MudPIT) detected 2,892 unique proteins, 1,342 were significantly altered during LS diet (117 up, 717 down) after correction for multiple testing. In a separate validation cohort, proteins including NCC, ENaC-alpha, and ENaC-gamma were validated using targeted multiple reaction monitoring mass spectrometry (MRM MS). Dietary sodium restriction and acute aldosterone infusion similarly increased urine exosome ENaC-gamma excretion (Figure A), which correlated positively with plasma aldosterone (Figure B). R²=0.56, P<0.001. Urinary Nk concentration during LS diet corresponded similarly.

Conclusions: The urinary exosome content is dynamically altered by the RAAS and corresponds with anticipated physiologic changes. Furthermore, exosomal ENaC gamma may provide a useful biomarker of sodium channel activation in clinical studies.

Funding: NIDDK Support, Other NIH Support - HL100106, UL1 TR000445

Microvascular/Hypertensive Disease Is Increased in Patients with Obstructive Sleep Apnea

Sky K. Chew, 1 Deb J. Colville, 1 Ecosse L. Lamoureux,1 Judith A. Savige.1 1Dept of Medicine (Royal Melbourne Hospital), The Univ of Melbourne, Melbourne, VIC, Australia; 2Centre for Eye Research Australia, The Univ of Melbourne, Melbourne, VIC, Australia.

Background: Microvascular/hypertensive abnormalities in the retina reflect systemic small vessel disease. This study used retinal examination to compare the prevalence of microvascular/hypertensive disease (severity of changes and calibre) in patients with Obstructive sleep apnea (OSA) or Chronic obstructive pulmonary disease disease (COPD).

Methods: Patients were recruited from the Respiratory clinic and wards of a metropolitan teaching hospital. All participants underwent retinal photography using a non-mydriatic camera (KOWA, KOWA Japan). Images were graded for microvascular/ hypertensive retinopathy (Wong and Mitchell classification) by an ophthalmologist and a trained observer. Images were sent to the Centre for Eye Research Australia for measurement of the retinal arteriole and venular calibre by a grader using Knudsson’s revised version (the Harris-Hubbard formula). Statistical analysis was performed using Stata 11.2 software (StataCorp).

Results: Seventy-nine patients with OSA and 132 with COPD were recruited. Patients with OSA alone were younger (p<0.01), had a higher BMI (p<0.01), and were less likely to be smokers (p<0.01) than those with COPD.

Patients with OSA had more microvascular disease than those with COPD (OR 9.90, 95%CI 2.29 to 42.90, P <0.01). In addition, their arterioles (mean difference 18.00µm, 95%CI 12.88 to 23.08, P <0.01) and venules (mean difference 25.30µm, 95%CI 17.09 to 33.51, P <0.01) were narrower. These changes were not worse with more severe OSA and were not reversed with the use of CPAP. Microvascular/hypertensive retinopathy was still more common and the arteriolar and venular narrowing persisted in patients with OSA after adjusting for age, BMI, hypertension, smoking and dyslipidemia.

Conclusions: Patients with OSA have increased small vessel disease compared with patients with COPD, with worse microvascular/hypertensive retinopathy and narrower vessels. This narrowing was not related to OSA severity and was not reversed with CPAP treatment.

Night-Time BP of <120/70 Can Improve the Renal Outcomes in Patients with CKD

Shuichi Watanabe,1 Hiroyuki Togawa,2 Daisuke Fuwa,1 Yukoko Ito,1 Yoshikiyo Ogiyama,1 Toshiyuki Miura,1 Tadasu Ichikawa,1 Shirasawa Yuichi,1 Michio Fukuda,1 Genjiro Kimura,2 1Cardio-Renal Medicine and Hypertension, Nagoya City Univ, Japan; 2Asahi Rosai Hospital, Japan Labour Health and Welfare Organization.

Background: ABPM has been already widely adopted for the diagnosis and classification of patients, some reports, optimal blood pressure was proposed to prevent hypertensive organ damage especially heart diseases and cerebrovascular diseases. However, the evidence of optimal blood pressure for the renal dysfunction still unclear.

Methods: Two hundred and five patients with chronic kidney disease (CKD) (male 106, female 99, age 49±19 year-old, eGFR 57±35 ml/min/1.73m², mean follow-up 202days), who have undergone 24-h ABPM, were studied. The subjects were grouped into 2 according to the presence or absence of the night-time high blood pressure (night time systolic blood pressure≥120 mmHg or <120 mmHg). The primary end-point was the composite of a doubling of the base-line serum creatinine concentration, or end-stage renal disease. Analysis was by intention to treat.
Results: Fifty out of 80 subjects with night time systolic hypertension subjects reached the primary endpoint, whereas 13 out of 125 subjects without night-time systolic hypertension (SBP) reached the primary endpoint (Crude HR 4.68, 95%CI 2.00-11.0, p=0.0004, Adjusted HR 3.68, 95%CI 1.28-10.6, p=0.02), whereas, presence of day time hypertension (≥135/85 mmHg) didn’t become the major risk factor for the renal outcome. Interestingly, ROC analysis also indicated that the optimal day time blood pressure value to prevent the renal dysfunction was 120/70 mmHg (positive likelihood ratio, 3.2; 95%CI 1.6-6.2).

Conclusions: The presence of night-time hypertension was a strong predictor of renal dysfunction. Since day time blood pressure was also plays an important role for hypertensive organ damages, further studies are needed to determine the optimal day time blood pressure goal for prevention of the CKD progression.

FR-PO516
8-Week Study on Effects of Chlorthalidone in Hypertensives with Low eGFR Massimo Cirillo, Fabiana Marcharelli, Alessandra Antonia Mele, Massimo Romano, Cinzia Lombardi, Giancarlo Bilancio. Dept of Medicine. Univ of Salerno, Baronissi, (SA), Italy.

Background: Efficacy of chlorthalidone (CT) and thiazides is considered low in low kidney function (LF). Methods: A parallel-arm, non-inferiority study was done on CT effects in hypertensives with LF and hypertensives without LF (Italian Drug Agency Registry ID#671). Study design included: screening visit, baseline visit, 8-week CT treatment with visits at weeks 1, 2, 4, and 6. The screening visit selected patients on antihypertensive treatment with uncontrolled hypertension (SBP≥140 or DBP≥90), ages 25-75, completed diagnostic work-up. Subjects were treated as prescribed by their attending physicians and re-examined 1-2 weeks later (baseline). Exclusion criteria were treatment with diuretics, CT contraindications, refused consent, SBP≥180 or DBP≥110, severe co-morbidities. At baseline, 25 mg CT was prescribed on the day of the baseline to the patients on top of ongoing treatments to 60 patients with LF (Control, eGFR stably ≥60 mL/min) and 60 patients without LF (Control, eGFR ≥60 mL/min). Blood pressure was measured at each visit by blinded trained physicians according to WHO guidelines. Lab evaluations were repeated at visit 8. Study power was 80% (n=90, one sided test, ε=0.05, difference in SBP reduction = 8).

Results: LF and Control were similar for men’s (70.2% and 64.2%), age (mean = 57 and 53), baseline blood pressure (SBP/DBP=150/90 and 190/95) but differed for eGFR (mean = 39 and 76, range=15-59 and 60-104). Changes over baseline were significant at week 8 in LF and Control for SBP (mean = -20 and -23, 95%CI =-22/-18 and -26/-19) and DBP (90% and 10% and -11/-7 and -13/-8). Differences between groups were not significant for changes in SBP (3/-7/-1) and DBP (1/-4/-2). Baseline eGFR did not predict SBP/DBP changes in either groups (R=0.18, P=0.17). Weak 8 changes were significant for eGFR (LF and Control, mL/min= -2 and -5, -4/-1 and -7/-5), serum potassium (mmol/L= -0.2 and -0.2, -0.3/-0.1 and -0.3/-0.1), serum uric acid (mg/dL= +0.8 and +0.9; +0.5/+1.1 and +0.7/+1.1). Adverse events incidence was 13.3% in both the groups. The commonest events were serum sodium <135 mmol/L and SBP/DBP ≥110/90.

Conclusions: Data do not support the idea of reduced CT efficacy in low kidney function. Funding: Government Support - Non-U.S.

FR-PO517
Association of Renin and Aldosterone Concentrations with Race/Ethnicity and Blood Pressure in Community-Living Individuals: The Multi-Ethnic Study of Atherosclerosis Dena E. Rifkin,1 Ali Khaki,2 Nancy Jenny,2 Robyn L. McClelland,3 Matthew Jay Budoff,4 Karol E. Watson,4 Joachim H. Ix,1 Matthew Fujii,1 Kentaro Nakai,1 Shunsuke Goto,1 Shinichi Nishi.1 1Div of Nephrology and Kidney Center; Kobe Univ Graduate School of Medicine, Kobe, Japan; 2Div of Nephrology, Akashi Medical Center, Akashi, Japan.

Background: Hypertension (HT) is a common complication in chronic kidney disease (CKD) patients. It has been reported that CKD patients often have circadian rhythm disorder of blood pressure (BP), which is known to be an independent risk factor for CKD progression. However, the relationship between 24-h ambulatory BP (24-h ABP) pattern and renal tissue damage remains unclear, and thereby we investigate their relationship in biopsy proven glomerulonephritis.

Methods: Thirty-seven patients with glomerulonephritis were included in this study. The patients with diabetes mellitus, malignancy, acute kidney injury and vasculitis, were excluded. Clinic BP (CBP) and 24-h ABP measurements were performed in all the study patients. HT was diagnosed from CBP and/or 24-h ABP recordings. Moreover, we calculated nocturnal BP fall (%), after which the patients with HT were divided into three groups (non-dipper, moderate and riser). We also evaluated the percent of sclerotic glomeruli and interstitial fibrosis, and interstitial thickening of intra-lobar arteries and arterial hyalinization were classified into four grades (none, mild, moderate and severe) in each biopsy specimen.

Results: Twenty-six patients (70%) who have had normal blood pressure based on CBP recordings. Of these, nine patients (24%) were diagnosed as HT according to 24-h ABP recordings. When dividing into three nocturnal BP groups in twenty patients who have had HT based on CBP and/or 24-h ABP recordings, the grade of arterial hyalinization was significantly higher in the non-dipper and riser groups compared to the normotensive and dipper groups (p=0.05). Furthermore, the percent of interstitial fibrosis was significantly higher in the riser group compared to the normotensive and dipper groups (p<0.05).

Conclusions: Our findings suggest that nocturnal BP elevation develops renal tissue damage potentially through the progression of arteriolar sclerosis. Careful ABP control should be performed for protecting against renal tissue damage in CKD patients.

FR-PO520
Effects of Oral L-arginine Supplementation and Acute Resistance Exercise on Blood Pressure and Nitric Oxide in Hypertensive Patients Elisa MS Higa,1,2 Margaret Mouro,1,2 Giovana R. Punaro,1 Marco Túlio Mello,1 Sérgio Tufik,1 Marcos A. Nascimento.1 1Nephrology, UNIFESP; 2Translational Medicine, UNIFESP; 3Psychobiology, UNIFESP, Brazil.

Background: High blood pressure (BP) is a world health problem and a risk factor to cardiovascular disease. This study examined the effects of oral L-arginine supplementation and acute resistance exercises on blood pressure and nitric oxide in hypertensive men.

Methods: Sixteen hypertensive men (45.9±7 yrs, 92.46±12.99 kg, body weight and 31.03±3.76 kg/m², body mass index) volunteered to be in this randomised, double-blind, and repeated-measure study; control placebo (CTL-PLA), control arginine (CTL-ARG), exercise placebo (EXE-PLA) and exercise arginine (EXE-ARG). The supplementation period was (6/7 days of placebo or L-Arg for 7 days) separated by a 7-day washout. The
acute resistance exercises (ARE) comprise 8 exercises, with an intensity of 60% of 1 maximum repetition. Each session was performed at the beginning and at the end of the supplementation groups. More specifically, the systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), double product (DP) and heart rate (HR) were determined at rest, immediately after ARE and 5, 10, 15, 30, 45 and 60 minutes after ARE; the nitric oxide (NO) was determined at rest, immediately after ARE and 1 hour after ARE.

Results: BP decreased at all periods after ARE in the EX-EPLA and EX-ARE, but not significantly (P>0.05). DBP decreased at 45' comparing CTL-ARE to EX-EPLA and EX-ARE (83±2.31 vs 76±2.23 and 75±1.25, P<0.05, respectively), and at 60' comparing CTL-PLA to EX-EPLA and EX-ARE (85±2.90 vs 79±1.87 and 78±1.09, P<0.05, respectively). DP was increased immediately after ARE, and at 5, 10, 15, 30, 45 and 60' comparing exercises to control groups, with P=0.05 as well as HR, which showed the same result. MBP and NO levels did not show differences (P>0.05).

Conclusions: In summary, ARE reduced DBP, and maintained SBP and MBP in lower levels than placebo groups; however, NO was lower in the ARE group, but not significant. HR and DP increased, but into safety levels; NO did not show changes. These results suggest that ARE could be a powerful tool to control the blood pressure in hypertensive men.

Funding: Government Support - Non-U.S.

---

**FR-PO521**

T/L-Type Calcium Channel Blocker Reduces the Composite Ranking of Relative Risk According to New KDIGO Guidelines in Patients with Chronic Kidney Disease

**Background:** Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) group recommended that patients with chronic kidney disease (CKD) be assigned according to stage and composite relative risk on the basis of glomerular filtration rate (GFR) and albuminuria criteria. The aim of this post-hoc analysis was to investigate the effects of add-on therapy with calcium channel blockers (CCBs) on changes in the composite ranking of relative risk according to KDIGO guidelines. Benidipine, an L- and T-type CCB, and azelnidipine, an L-type CCB to angiotensin II receptor blocker (ARB), were examined.

**Methods:** Patients with blood pressure (BP) > 130/80 mmHg, an estimated GFR (eGFR) of 30–90 mL/min/1.73 m², and albuminuria > 30 mg/gCr, despite treatment with the maximum recommended dose of ARB, were randomly assigned to two groups. Each group received one of two treatments: 2 mg benidipine daily, increased to 8 mg daily (n=52), or 2.5 mg azelnidipine daily, increased to 10 mg daily (n=52).

**Results:** After 6 months of treatment, a significant and comparable reduction in systolic and diastolic BP was observed in both groups. The eGFR was significantly decreased in the azelnidipine group, but there was no significant change in the benidipine group. The decrease in albuminuria in the benidipine group was significantly lower than in the azelnidipine group. The composite ranking of relative risk according to the new KDIGO guidelines was significantly improved in the benidipine group; however, no significant change was noted in the azelnidipine group. Moreover, significantly fewer cases in the benidipine group that the azelnidipine group showed a reduced risk category score.

**Conclusions:** The present post-hoc analysis showed that compared to amlodipine benidipine results in a greater reduction in albuminuria accompanied by an improved composite ranking of relative risk according to the KDIGO CKD severity classification.

---

**FR-PO522**

Azelnidipine Attenuates the Non-Gaussian Heart Rate Variability in CKD Patients with Preceding Treatment with ARB

**Background:** Sympathetic nervous activity is the matter of importance, and 3) azelnidipine can suppress the sympathetic overactivity.

**Conclusions:** These findings suggested that 1) in patients of post-myocardial infarction, both sympathetic and parasympathetic nervous system can be altered, 2) whereas in patients with CKD, sympathetic nervous activity is the matter of importance, and 3) azelnidipine can suppress the sympathetic overactivity.

---

**FR-PO523**

Blood Pressure Patterns during Hemodialysis According to Volume Status and Ultrafiltration Amount

**Background:** Blood pressure (BP) pattern during hemodialysis (HD) may be associated with survival. Volume status is a likely major determinant of BP change during HD along with ultrafiltration (UF) amount and/or rate. However, interrelation between body volume and UF amount hampered to evaluate an impact of volume status separately.

**Methods:** A total of 177 incident HD patients (age 56±15 yrs old, female 33.3%, diabetes 54.2%) were analyzed. BP was recorded at pre-HD, 1, 2, 3 hours after, and post-HD during the third HD session (the first 4-hr session). UF amount was calculated as pre-HD body weight minus post-HD body weight. Ratio of extracellular water to total body water (ECW/TBW) estimated by bioimpedance analysis (InBodyS30, Seoul, Korea) before just dialysis, was used as an index of volume status. Higher ratio reflects volume overloaded state.

**Results:** Patients were divided based on tertiles of UF amount (≤0.7 kg, 0.7- to 1.9 kg, > 1.9 kg) and ECW/TBW (≤0.39, 0.39- to 0.41, >0.41). We plotted change in systolic BP from pre-HD value (median, interquartile range) according to ECW/TBW tertiles in each UF stratum. In patients with UF >0.7 kg, systolic BP tended to increase similarly among ECW/TBW tertiles. In the stratum of UF >1.9 kg, systolic BP dropped at 1-hr and 2-hr then rose up in patients with ECW/TBW >0.41 (tertile 3) showed no drop in systolic BP at 1-hr and 2-hour points (Figure).

Conclusions: BP pattern during HD differs by volume status as well as UF amount. No dip in BP during HD despite of usual UF amount such as 2 - 3 kg could reflect volume overload.

---

**FR-PO524**

Elevated Marinobufagenin and Telocinobufagin Levels in Chronic Heart Failure Predict Adverse Long-Term Clinical Outcomes

**Background:** Cardiotoxic steroids such as marinobufagenin (MBG) and telocinobufagin (TCB) increase in response to volume expansion and induce inflammation, oxidative stress and fibrosis. In chronic heart failure (HF) patients, we hypothesized that elevated MBG and TCB levels are associated with poorer cardiac and renal function as well as increased oxidant stress and adverse long-term clinical outcomes.

**Methods:** In 116 chronic HF patients, we measured MBG and TCB levels and performed comprehensive clinical and echocardiographic assessment. All-cause mortality, cardiovascular death, HF hospitalization, and hospitalization for HF were recorded. MBG and TCB levels were classified into tertiles.

**Results:** We plotted change in systolic BP (mmHg) from pre-HD value (median, interquartile range) according to ECW/TBW tertiles in each UF stratum. In patients with UF >0.7 kg, systolic BP tended to increase similarly among ECW/TBW tertiles. In the stratum of UF >1.9 kg, systolic BP dropped at 1-hr and 2-hr then rose up in patients with ECW/TBW >0.41 (tertile 3) showed no drop in systolic BP at 1-hr and 2-hour points (Figure).

Conclusions: BP pattern during HD differs by volume status as well as UF amount. No dip in BP during HD despite of usual UF amount such as 2 - 3 kg could reflect volume overload.
FR-PO525
Rising Marinobufagenin and Telocinobufagin Levels during Acute Decompensated Heart Failure Admission Predict Poor Long-Term Clinical Outcomes

1 Cellular & Molecular Medicine, Cleveland Clinic, Cleveland, OH; 2 Laboratory of Cardiovascular Science, National Institute on Aging, Baltimore, MD.

Background: Cardiotoxic steroids such as marinobufagenin (MBG) and telocinobufagin (TCB) increase in response to volume expansion and induce oxidative stress and fibrosis. We hypothesized that elevated levels of MBG and TCB in acute decompensated heart failure (ADHF) patients are associated with poorer cardiac and renal function as well as increased inflammatory and oxidant stress, and adverse long-term events.

Methods: In 129 ADHF patients, we measured MBG and TCB levels and performed comprehensive clinical and echocardiographic assessment at baseline and 48-72 hours after admission. All-cause mortality was tracked for 5 years.

Results: In our cohort (age 61±14 years, LVEF 31±14%, median NTproBNP 4684 pg/mL, eGFR 72±38 mL/min/1.73m2), median MBG and TCB levels were 630 [438-903] μM and 823 [406-1392] μM, respectively, MBG and TCB were directly correlated (r=0.51, p<0.0001). Higher baseline MBG and TCB both correlated with higher plasma renin activity and aldosterone (r=0.35, p<0.003). MBG and TCB were significantly higher in patients with accelerated hypertension. Higher baseline TCB systolic function (RV s'; MBG: r= -0.26, p=0.039; TCB: r= -0.38, p=0.003) but not LV systolic function (r= 0.51, p<0.0001). Higher baseline MBG and TCB both correlated with higher plasma FR-PO526
Insufficient Sleep Is Associated with Higher Blood Pressure in Pediatric Nephrology Clinic Patients

Necna R. Gupta, Rakesh Gupta.
Pediatric Nephrology, UMass Memorial Medical Center, Worcester, MA; 3 Pulmonary and Sleep Medicine, Roger Williams Medical Center, Providence, RI.

Background: Hypertension (HTN) is a common concern in pediatric nephrology patients either as primary problem or an associated finding affecting outcomes in other disorders. While several risk factors and mechanisms such as obesity, salt intake, and renal dysfunction get most attention, insufficient sleep is not appreciated as a risk factor for hypertension. Data on sleep disorders and HTN in children are primarily restricted to association with sleep apnea. Some studies have shown sleep deprivation to be associated with higher BP. We have previously shown that weekday sleep time is inversely related to ambulatory BP parameters in children referred for evaluation of HTN (ASN 2012). We hypothesize that low weekday sleep time is likely to be associated with higher BP in all pediatric nephrology patients.

Methods: A sleep questionnaire was administered to 34 patients attending pediatric nephrology clinic. It was a sample of convenience. Demographic data, BMI, clinic BP, diagnoses were recorded. Weekday and weekend sleep times were calculated in minutes. Correlation coefficient between weekday sleep time, SBP, DBP, and BMI percentile were calculated.

Results: The baseline characteristics for 34 patients were: Age – 13.8±3.5 years, male-60%, BMI percentile 66±29.1, Weekday sleep time (WST) 527±65.75 minutes, weekend sleep time 611±84.9 minutes, SBP 118±13.1 mm Hg, DBP 74±6.8 mm Hg. Most common diagnoses were hypertension (61%), VUR (12%), Nephrotic syndrome (12%), Glomerulonephritis (6%), Vasculitis (18%) and others (24%). A significant correlation was found between WST and SBP (r= -0.29, p=0.047), WST and DBP (r= -0.35, p=0.019). A trend was noticed for correlation between BMI percentile and BP parameters.

Conclusions: Low WST was associated with higher clinic BP in pediatric clinic patients with a wide variety of diagnoses. The link between insufficient sleep and BP as a potential risk factor for HTN as well as therapeutic target needs to be explored further.

FR-PO527
Histopathological Diagnoses in Patients Presenting with Hypertension and Kidney Damage


Background: Hypertension is a recognized cause of acute and chronic kidney disease (CKD). It is also a common complication of CKD from any etiology. The underlying histopathological diagnoses have not been well described in patients who present with a clinical diagnosis of hypertensive kidney disease.

Methods: We have conducted an observational study of consecutive renal biopsies performed in a 2 year period, in patients with a clinical diagnosis of hypertensive nephropathy (HN). Outcomes were the histological presence of HN or glomerulonephritis (GN), and clinical predictors of HN or GN.

Results: 28 out of the 410 native renal biopsies were performed in patients with a clinical diagnosis of HN. Mean age was 48 years, and mean eGFR was 26 ml/min/1.73m².

Conclusions: Native renal biopsies performed in patients with a clinical diagnosis of HN showed histological evidence of HN as the primary diagnosis in only 50% of cases. Similar results were seen in the small sub-group who presented with accelerated hypertension, in whom the procedural complication rate was higher. Urinalysis and quantification of proteinuria did not predict histological diagnosis. Kidney biopsy should be considered in individuals who present with hypertension and kidney damage.

FR-PO528
Renal Artery Denervation in Patients with Chronic Kidney Disease and Hemodialysis, with Resting Arterial Hypertension – North Israeli Center Experience

Farid M. Nakhouli, Ana Roth, Yanishtan Hasin, Farber Evgeny, Ganem Diab. Nephrology, Baruch Padeh Poriya, Lower Galilee, Israel; 2 Cardiology, Baruch Padeh Poriya, Israel; 3 Faculty of Medicine, Bar Ilan Univ, Israel.

Background: A number of cardiovascular disease have been shown to be characterized by a marked increase in sympathetic drive to the heart and peripheral resistance as in essential hypertension, chronic kidney disease (CKD). CKD patients show sympathetic hyperactivity, with aggravation of HTN. In CKD and HD patients is difficult to control HTN, and need multiple drugs. Here we report our first experience on renal sympathetic nerve ablation for treatment of severe resistant hypertension in CKD patients. Our results demonstrate high efficiency of this procedure for TX of resistant hypertensive in CKD.

Methods: 33 patients- aged average between 40-79 yrs old, were treated with RAD; 60% of them were with diabetes mellitus, 64% with LVH. 24 Patients were with follow up to 3 months. 9 patients had CKD (two of them were on Hemodialysis and two with RAV). All patients were with systolic BP>160 mmHg under three drugs. Mean number of antihypertensive drugs per patient was 4.5. Patients with CKD: PI Creatinine range was 2.3-6.0 mg/dl.

Results: At Baseline: Mean SBP of the whole group was 179±19 mmHg and Mean DBP was 13±17 mmHg. Three months after RAD: Mean systolic BP = 142±16 mmHg and Mean diastolic BP = 77±11 mmHg. There was significant reduction of the systolic blood pressure an average of 36 mmHg with P <0.001 . Significant reduction in the diastolic BP by an average of 6 mmHg (P = 0.038). Subgroup analysis of patients with CKD: Mean SBP: 183±20 mmHg and Mean DBP: 79±12 mmHg. Three months after RAD: Mean SBP = 147±17 mmHg and Mean DBP = 75±10 mmHg. CKD patients had significant reduction of 36 mmHg in the systolic blood pressure (P = 0.005). There was no significant reduction in the DBP. During follow-up renal function (eGFR) was unchanged.

Conclusions: 1. Bilateral RAD is associated with significant reduction in systolic and DBP in hypertensive patients resistant to multiple drug therapy. 2. CRF patients had significant reduction in systolic BP but no significant reduction in diastolic BP.

Funding: Government Support - Non-U.S.
FR-PO529
Telmisartan Improves Blood Pressure Control, Albuminuria and Inflammation in Hypertensive Diabetic Patients Not Adequately Controlled under ACE-Inhibitor Therapy  Juan F. Navarro-Gonzalez,1,2 Mercedes Muros,1 Carmen Mora,2 Patricia Garcia Garcia,1 Maria Adela Getino,1 Ana Jarque,1 Nieves Del Castillo Rodriguez,2 Antonio Rivero,1 Javier Garcia Perez.1 1Nephrology Service, Univ Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain; 2Research Unit, Univ Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain; 3Clinical Analysis Service, Univ Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain.

Background: Renin-angiotensin system blockade is the mainstream of antihypertensive therapy in diabetic patients. The aim of this study was to evaluate the effect of the switch from angiotensin converting-enzyme inhibitors (ACEI) to angiotensin receptor blockers on blood pressure (BP), urinary albumin excretion (UAE) and inflammatory profile in diabetic patients not adequately controlled despite maximal dosage of ACEi therapy.

Methods: Twenty-seven patients with BP >130/80 mmHg and residual albuminuria were switched to Telmisartan (TEL, 80 mg/day). Serum concentrations of high-sensitive C-reactive protein (hsCRP), tumor necrosis factor-α (TNFa) and interleukin-6 (IL-6), as well as mRNA expression levels of TNFa and IL-6 in peripheral blood mononuclear cells (PBMC) were determined.

Results: After 4 months, BP decreased from 141.6±8.9/103.5±5.5 mmHg (p<0.001), and UAE decreased by 18%. Reduction in UAE correlated with change in systolic BP (-0.76, p<0.05). Serum hsCRP, TNFa and IL-6 reduced significantly by 15%, 9% and 15%, respectively (p<0.001). Urinary TNFαexcretion decreased by 13% (p=0.01), whereas mRNA expression levels of TNFa and IL-6 in PBMC also experienced a significant reduction (p<0.05). A significant association was found between change in serum hsCRP (r=0.82) and TNFa (r=0.59), and urinary TNFα (r=0.66) with reduction in UAE. Finally, multivariate regression analysis showed that age and change in urinary TNFα were independently associated with reduction in UAE (r=-0.29 and r=0.49, p<0.05, respectively).

Conclusions: In conclusion, in hypertensive diabetic patients not adequately controlled under ACEi therapy, change to TEL resulted in a significant reduction in BP and UAE, and an improvement in inflammatory profile.

FR-PO530
The Impact of Guided Deep Breathing Exercise on Hypertensive Control  Loke Meng Ong, Kum Keong Ng, Fei Ping Kow, Bakar Adlina, Dharmeny Thaairatam, Hazlinda Z. Ministry of Health, Penang, Malaysia.

Background: Hypertension (HPT) remains poorly controlled despite drug therapy. Non-pharmacological intervention may enhance control of blood pressure. We conducted a single blinded, multicentre, randomized controlled trial over 8 weeks to evaluate the impact of breathing exercise guided by the music. Training was conducted by qualified therapists. In addition the IG also practised deep breathing exercise guided by the music CD at least 15 minutes once daily. In both groups, the primary end point was reduction in Diastolic blood pressure (DBP) at 8 weeks. The Compliance was good in both groups. There was a significant difference in SBP reduction from baseline in IG (p<0.001) compared to CG (p<0.001). The SBP was 10.5mmHg in CG compared to 8.3mmHg (p< 0.001) in IG while the mean DBP reduction was 5.2 mmHg (p< 0.001) in CG and 5.6 mmHg (p< 0.001) in IG. However, there was no significant difference in DBP reduction from baseline in IG compared to CG (p=0.22).

Conclusions: Relaxation with music was associated with a clinically significant reduction in both SBP & DBP. Deep breathing exercise did not augment the benefit of music in BP control. Funding: Government Support - Non-U.S.

FR-PO531
Subclinical Aldosterone Levels Help Distinguish between Future Aldosterone Producing Adenoma and Essential Hypertension  Austin Parke,1 Kevin C. Abbott,2 Lisa K. Prince,2 Stephen W. Olson.2 1Nephrology Dept, Naval Medical Center Portsmouth, Portsmouth, VA; 2Nephrology Dept, Walter Reed National Military Medical Center, Bethesda, MD.

Background: Aldosterone and aldosterone to plasma renin activity (PRA) ratios are used for the biochemical evaluation of patients with refractory hypertension and incidentally identified adrenal adenomas. However, there is no single threshold of maximum sensitivity and specificity for the diagnosis of aldosterone producing adenoma (APA). Knowledge of subclinical aldosterone trends could improve current diagnostic capabilities.

Methods: We performed a DoD Serum Repository (DoDSR) retrospective case-control study to compare aldosterone levels months to years before the histopathologic diagnosis of 28 APA patients versus 82 age-, race-, sex-, and age-of-serum-matched control subjects with essential hypertension. We hypothesized that aldosterone levels would be elevated and rising prior to diagnosis. PRA levels could not be tested on these stored serum samples.

Results: A higher percent of APA patients had a serum aldosterone level >10 ng/dl compared to matched essential hypertension disease controls at <3 years (82% vs. 6%; p<0.001) and 3-11 years (47% vs. 11%; p=0.001) as well as >15 ng/dl at <3 years (59% vs. 0%; p<0.001) and 3-11 years (21% vs. 4%; p=0.03) prior to diagnosis. A greater percent of APA patients had a serum aldosterone rate of rise of >0.25 ng/dL/year (75% vs. 27%; p<0.001), >0.35 ng/dL/year (50% vs. 17%; p=0.001), and >1 ng/dL/year (29% vs. 6%; p=0.004).

Conclusions: Compared to control subjects with essential hypertension, APA patients more frequently have aldosterone levels >10 ng/dl that continue to rise over time in the 11 years leading up to diagnosis. Knowledge of the subclinical serum aldosterone trajectory could help to better differentiate between essential hypertension and APA for patients undergoing a secondary hypertension evaluation or with an incidentally discovered adrenal adenoma.

Funding: Other U.S. Government Support

FR-PO532
Low Glomerular Density Is a Characteristic Finding in Renal Biopsies of Hypertensive Nephrosclerosis with Massive Proteinuria  Kotaro Haruhara, Nobuo Tsuibo, Go Kanazaki, Kentaro Koike, Akira Fukui, Yoichi Miyazaki, Tetsuya Kawamura, Makoto Ogura, Takashi Yokoo. Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan.

Background: Hypertensive nephrosclerosis (HNS) is a secondary renal disease that may occur in individuals with hypertension. However, there are likely to be factors other than hypertension that contribute to the development of HNS since only a minority of hypertensive individuals manifest overt proteinuria. In this study, we explored the histological characteristics contributing to the development and progression of proteinuria in hypertensive patients.

Methods: Glomerular density (GD; glomerular number per renal cortical area) and mean glomerular volume (GV) in renal biopsies from HNS patients (eGFR<60) with mild (>1g/day) or massive (>1g/day) proteinuria were measured and compared with those in the autopsy kidneys from hypertensive patients without CKD. Renal biopsy specimens from kidney transplant donors (KTD) were also analyzed as healthy controls.

Results: The GD of HNS patients with massive or mild proteinuria was significantly lower than that from KTD. The GD of hypertensive patients without CKD was also significantly lower than that from KTD. Of note, the GD of HNS patients with massive proteinuria was significantly lower than those of HNS patients with mild proteinuria and hypertensive patients without CKD. These differences were still significant when global glomerulosclerosis (GGS) were included in the calculation of the GD. Moreover, the GD of both HNS with mild and massive proteinuria are significantly larger than that of KTD.

Conclusions: This result suggests that a low GD is a renal histological characteristic of HNS with massive proteinuria.
FR-PO533 Lipoprotein(a), an Independent Predictor of ARAS in High-Risk Patients
Yangmei Mei,1 Peng Xia,2 Ling Qiu,2 Xuejuan Zeng,3 Xuemei Li, Limeng Chen.1
1Nephrology Dept, Peking Union Medical College Hospital, Beijing, China; 2Dept of Laboratory Medicine, PUMCH, Beijing, China; 3Internal Medicine Dept, PUMCH, Beijing, China.

Background: Lipoprotein(a) [Lp(a)] has been confirmed to be a prospective cardiovascular disease risk factor through large-scale meta-analysis. In this study, we aim to explore that whether Lp(a) is associated with occurrence of atherosclerotic renal artery stenosis (ARAS) among high-risk patients.

Methods: We divided consecutive 453 patients who underwent renal angiography into ARAS group (≥ 50%, n=169) and non-ARAS group (n=284). A control group (n=177) was collected among people receiving health checkup. Data collection included the age, sex, lipid profiles, renal function, and liver function. Multivariate logistic regression analysis was applied to explore that whether the clinical and biomedical parameters were associated with ARAS in these high-risk patients.

Results: We divided consecutive 453 patients who underwent renal angiography into ARAS group (≥ 50%, n=169) and non-ARAS group (n=284). A control group (n=177) was collected among people receiving health checkup. Data collection included the age, sex, lipid profiles, renal function, and liver function. The levels of Lp(a) were higher in ARAS group in comparison with the control group (median: 172.0 vs 92.6 mg/L, p<0.001). Lp(a) was positively correlated with hsCRP and LDLr (r = 0.217 and 0.231, p < 0.001, respectively) among high-risk patients. In comparison with non-ARAS group, the ARAS patients were older (67.1±10.2 vs 65.0±10.4, p=0.002) with higher levels of uric acid (371.0±91.7 vs 333.6±98.3 μmol/L, p=0.001) and lower eGFR (60.1±19.7 vs 68.4±19.7 mL/min/1.73m2, p=0.002). Multivariate logistic regression analysis revealed that Lp(a) level (OR = 1.806, 95%CI 1.006, 3.245, p = 0.048) and uric acid (OR = 2.098, 95%CI 1.107, 3.978, p = 0.023) were independent predictors of ARAS among high-risk patients after adjustment of age and eGFR.

Conclusions: Lp(a) and uric acid are independently associated with ARAS among high-risk patients. Mei, Y and Xia, P contributed equally to this work.

Funding: Government Support - Non-U.S.

FR-PO534 Comparison of 24-Hour Blood Pressure Profile between Diabetic and Non-Diabetic Patients with Advanced Chronic Kidney Disease

Background: Blood pressure is a factor in cardiovascular-related morbidity and in the progression of kidney failure in patients with ACKD.

Methods: The objective of our study was to offer a descriptive analysis of daily blood pressure profiles of incident ACKD patients through 24-hour ambulatory blood pressure monitoring (ABPM), as well as a comparison between diabetic and non-diabetic patients.

Results: The analysis included 547 patients, 64.3 years of age, 57.8% male, 68% type 2 diabetes. Among 547 patients, 433 were diabetic patients and 114 were non-diabetic patients. Using 24-h ABPM during the last year of observation, the 24-h systolic blood pressure (SBP) and diastolic blood pressure (DBP) were analyzed in the diabetic and non-diabetic groups. In the diabetic group, the 24-h systolic blood pressure was 155±25, 145±23 and 134±21 mmHg. In the non-diabetic group, the 24-h systolic blood pressure was 145±23, 134±21 and 123±19 mmHg. The difference between the groups was statistically significant (p<0.001). Similarly, the difference between the 24-h diastolic blood pressure in the diabetic group and the non-diabetic group was also statistically significant (p<0.001).

Conclusions: Our study showed that 24-h ABPM during the last year of observation is an effective way to evaluate the 24-h blood pressure profile in diabetic and non-diabetic patients with ACKD.

FR-PO535 Percutaneous Renal Revascularization: A Long Term Follow-Up of 155 Procedures
Daniel Kushnir, Jerome Marcusohn, Alon Antebi, Tatiana Tanasichyuk, Victor Frajewicki. Dept of Nephrology and Hypertension, Carmel Medical Center, Haifa, Israel.

Background: Arterial Hypertension and Renal Insufficiency may be improved by percutaneous intervention in patients with Renal Artery Stenosis (RAS) but the clinical benefit of such therapy is still obscure. The aim of the study is to evaluate the long term outcomes after renal artery intervention.

Methods: Files of patient who underwent intervention of the renal arteries at the Carmel Medical Center were retrospectively reviewed.

Results: Date of 143 patients (79 men and 64 women, mean age 64±11 years) with RAS who had underwent 155 interventions were reviewed. Main indications were Hypertension (70%) and Renal Insufficiency (26.5%). The stenosis was bilateral in 26% and unilateral in 63%; single kidney in 9%. When atherosclerosis (90%) was the cause of obstruction, a stent was placed in 10 patients. In 10 patients with Fibromuscular Dysplasia, an angioplasty was performed without stenting. Average stenosis was 81±15%, which was ostial in 61% of cases. Overall angiographic success rate was 92%. Major complications occurred in 10% of the procedures. Patients were followed for 96±42 months. Data were analyzed before the procedure, after 36 months and at the end of follow-up. Reduction of systolic (155±25, 145±23 and 134±21 mmHg, P<0.001) and diastolic (84:12 mmHg, 78:11 and 72:9 mmHg, P=0.004) blood pressure was achieved. Blood pressure improved in 61%, was unchanged in 18% and worsened in 21% after 36 months. Serum creatinine of patients on dialysis were censored. Mean serum creatinine was unchanged (1.4±0.7, 1.5±0.8 and 1.5±0.9 mg/dL, NS). After 36 months creatinine improved in 16%, was unchanged in 70% and worsened in 14% of patients. The use of anti-hypertensive drugs was reduced from 3.2±1.3 to 2.4±1.5, P=0.0001. Fifty three patients (37%) died during the observation period, of those 94% had chronic kidney disease. Seventeen patients (12%) needed chronic renal replacement therapy.

Conclusions: Stenting of the renal arteries may be useful for treatment of hypertension in RAS without causing deterioration of renal function. Renal insufficiency patients require careful evaluation before intervention.

FR-PO536 Prevalence of Obstetric Thrombotic Thrombocytopenic Purpura within 8,908 Consecutive Deliveries: A Not to Be Missed Diagnosis
Victoria Trujillo-Rodriguez,1 Sebastian Heliot, Pierre Chaintrier,2 Anne Ryum,2 Fanny Pellerud,2 Dominique Carles,1 Jacques Horovitz,1 Paul Coppo,1 Christian Combe.

Background: Thrombotic Thrombocytopenic Purpura (TTP) defined as a Disintegrin And Metalloprotease with thrombospondin type 1 domain 13 (ADAMTS13) activity ≤10% has an unknown prevalence among pregnant women with thrombocytopenia (Tp). Its recognition can lead to efficient prevention of maternal and fetal morbi-mortality.

Methods: In a tertiary obstetrical unit, TTP prevalence was assessed retrospectively among women with Tp≤75 G/L. ADAMTS13 functional activity was measured by full von Willebrand Factor length technique. ADAMTS13 inhibitor and anti-ADAMTS13 IgG were assessed in these patients.

Results: Among 8,908 deliveries over a 2-year period, 80 women had Tp≥75 G/L. Twenty had an identified etiology of Tp (from TTP) and 11 were lost to follow-up. Among 49 remaining patients, ADAMTS13 activity was in the range of TTP in 4 patients (initially diagnosedHELLP syndrome); Tp spontaneously recovered few days after delivery in all women. Three patients had sustained ADAMTS13 deficiency without inhibitor. Two of them lost their babies due to prematurity. Prophylactic plasma infusion enabled subsequent successful three pregnancies in two constitutive TTP women with improved placental histopathology.

Conclusions: 5% of women with Tp≤75 G/L in a tertiary obstetrical unit had TTP. Platelet normalization after delivery cannot eliminate TTP. Prophylactic plasma therapy during pregnancy in constitutive TTP allows proportional placenta pathology improvement and good mother and child outcome.

FR-PO537 Angiographic Intervention for Renal Artery Stenosis – Predictors of Favourable Renal Response
Haridam Sosa Barrios,1 Parthipan Sivakumar,1 Damien Ashby,1 Wladyslaw M. Gedroyc,2 Mohamad S. Hamady,2 Neill D. Duncan.

Background: Renovascular disease is increasingly recognised as a cause of renal impairment but the role of endovascular intervention in this setting is unclear. The ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial established that revascularisation does not improve renal prognosis in the average patient, but many clinicians believe that there is a subgroup of patients who benefit.

Methods: In this retrospective single-centre cohort study we included all patients who had renal angioplasty during a 2 year period for whom 12 month follow-up data were available. Patient outcomes were defined according to median GFR in the year post intervention, compared to baseline: group A improved by 5ml/min, or stabilised after a decline of 5ml/min in the previous year; group B remained the same; group C deteriorated by at least 5ml/min.

Results: Forty-nine patients (aged 49-86, 72% male) underwent angioplasty and stent insertion which was technically successful in all cases, and bilateral in 29%. Change -2.0(-3.3 to 1.2)ml/min, and with 25.5, 59.6 and 14.9% of patients in groups A, B, and C respectively.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Group A patients tended towards higher GFR during the 12 months prior to intervention (45.0 vs 39.6 ml/min, p=0.14), but there were no differences in age or gender between outcome groups. Favorable group A outcome was observed more frequently in those with GFR-30 ml/min (29 vs 14, p=0.25), and in those undergoing bilateral intervention (33 vs 22%, p=0.30).

Conclusions: Heterogeneity of outcome can be expected after intervention for renal artery stenosis. Patients benefitting from the procedure are not clearly distinguishable from the remainder by simple clinical criteria, but higher GFR and bilateral disease were weakly associated with a favorable response.

**FR-PO538**

**Correlation between Automated Office Blood Pressure and Ambulatory Blood Pressure Monitoring in CKD**

George Thomas, Jesse D. Schold, Susana Arrigain, Joseph V. Nally, Sankar D. Navaneethan.

**Background:** Automated office blood pressure monitors (AOBP) have previously been shown to correlate with ambulatory blood pressure monitors (ABPM) in the general population. We examined the correlation of AOBP with ABPM in CKD patients seen at our institution.

**Methods:** We included 238 CKD patients who had both AOBP and ABPM measured within 2 weeks of each other. Automated office BP was measured using the BPTru device (VSM MedTech Ltd, Coquitlam, BC, Canada) and is the average of five automated consecutive readings. Ambulatory BP was measured using a 24-hour monitor (Spacelabs, Issaquah, Washington, USA). We used Linn’s concordance coefficient (6:00 AM to 10:00 PM, “awake” blood pressure) using automated BP monitors on the consecutive readings. Ambulatory BP was measured every 20 minutes during the day and awake ABPM (systolic).

BPTru and awake ABPM (systolic and diastolic pressure) were 0.65 (95% CI 0.58, 0.71) and 0.64 (95% CI 0.56, 0.71) respectively. Figure 1 shows the scatterplot of BPTru (systolic) and awake ABPM (systolic).

**Results:** We identified 238 patients who fit the above criteria; mean age was 64.2 years, with more females (62%) and more Caucasians (78%). The concordance rates between BPTru and awake ABPM (systolic and diastolic pressure) were 0.65 (95% CI 0.58, 0.71) and 0.64 (95% CI 0.56, 0.71) respectively. We are now analyzing the molecular signatures of cell dependent and independent contact to identify putative therapeutic targets.

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

**FR-PO540**

**The Reactivity of Renal Dendritic Cells for Prostaglandin E2**

Shinya Nasazaka, Toru Iwabori, Seichiro Higo, Go Kanazaki, Kayori Tsuoura, Yusuke Kajimoto, Akira Shimizu. The Dep of Analytic Human Pathology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.

**Background:** Prostaglandin E2 (PGE2) has been shown to mediate autoimmune disease to expand Th17 cells via dendritic cells in animal models of multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases and allergic skin disorders. Recently, the dendritic cell specifically localized in kidney (renal dendritic cells: RDC) was identified. Despite RDCs have been recognized as the earliest producers of pro-inflammatory cytokines in renal ischemia and experimental unilateral ureter ligation, suggesting a sentinel role against kidney injury, their role in reactivity for PGE2 on renal inflammatory disease is still incompletely understood. Here we compared the reactivity between RDCs and splenic DCs (as general DCs) in response to PGE2.

**Methods:** RDCs and splenic DCs were purified by magnetic bead-labeled anti-mouse CD11c antibodies from mouse kidney, and stimulated with 1 μg/ml of LPS in the presence or absence of 100 nM of PGE2. After LPS stimulation, the expressions of PGE2 receptors (EP1, EP2, EP3, and EP4), macrophage-derived chemokine (MDC), membrane-bound PGE synthase-1 (mPGES-1), and pro-inflammatory cytokines were measured by real-time PCR.

**Results:** The expression of EP4, one of the PGE2 receptors and IL-12p35 in RDCs were more increased in the presence of PGE2 than in splenic DCs, whereas we obtained no change of IL-12p40 expression. Furthermore, in RDCs, the expressions of Cox-2 and mPGES-1 which associated with PGE2 synthesis were up-regulated in the presence of PGE2 upon LPS stimulation.

**Conclusions:** RDCs apparently had distinct characteristics from splenic DCs. It is suggested that RDC enhances the production of pro-inflammatory cytokine in the presence of PGE2 which is synthesized in renal disease, and therefore regulates inflammatory response in kidney via autocrine loop of PGE2 through the induction of Cox-2 and mPGES-1 expression.

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

**FR-PO541**

**Cytokines Accentuate Synthesis of Galactose-Deficient IgA1 in IgA Nephropathy by Dysregulating C1GalT1 and ST6GalNAc-II Enzymes**

Hitoshi Sazuki, 1 Milan Raska, 2 Koshi Yamada, 3 Zina Moldoveanu, 4 Bruce Schold, 1 Robert J. Wyatt, 1 Michael G. Healy, 1 Andrew J. Kassianos, 1,2 Xiangju Wang, 1,2 Helen G. Healy, 1 Ray Wilkinson, 1,2,4 Conjoint Kidney Laboratory, Pathology, Queensland; 1Dept of Renal Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Australia; 2Queensland Univ of Technology, Brisbane, Australia; 3Medical School, Univ of Queensland, Brisbane, Australia.

**Background:** IgA nephropathy (IgAN) is characterized by renal immunopathology involving IgA1 with galactose (Gal)-deficient O-glycans (Gd-IgA1). IgA1-producing cells, T cells and monocytes were cultured with interferon-activated PTEC, which secrete IgAN cells and HC cells to assess whether IgA1 with galactose-deficient O-glycans (Gd-IgA1). IgA1-producing cell lines from patients with IgAN (IgAN cells), but not those from healthy controls (HC cells), secrete Gd-IgA1 with O-glycans with terminal N-acetylgalactosamine (α-GalNAc) rather than galactose (Gal). GalNAc. The aberrant glycans constitute the neoantigen that leads to formation of nephritogenic immune complexes. As clinical disease onset and activity often coincide with mucosal infections and dysregulation of cytokines was described in IgAN, we hypothesized that cytokines may affect IgA1 O-glycosylation.

**Methods:** We used IgAN cells and HC cells to assess whether IgA1 O-glycosylation is altered by cytokines. To confirm the roles of specific glycosyltransferases in the expression of Gd-IgA1, we knocked-down the C1GalT1 and ST6GalNAcII genes by siRNA. Of the eight cytokines tested, only interleukin-6 and, to a lesser degree, interleukin-4 significantly increased production of IgA1 and the degree of galactose deficiency of IgA1; changes in IgA1 O-glycosylation were robust for the IgAN cells. Both cytokines reduced galactosylation of the O-glycan substrate directly via decreased expression of the galactosyltransferase C1GalT1, and, indirectly, via increased expression of the sialyltransferase ST6GalNAcII (sialylation prevents subsequent galactosylation by C1GalT1). siRNA knock-down of the corresponding gene and in vitro enzyme reactions confirmed these findings.

**Funding:** Government Support - Non-U.S.
Conclusions: Interleukin-6 and interleukin-4 accentuated galactose deficiency of IgA1 via coordinated modulation of key glycosyltransferases. These data provide a mechanism to explain increased immune-complex formation and disease exacerbation during mucosal infections in patients with IgAN.

Funding: NIDDK Support

FR-PO542
Pathogenic Role of IgA1-Containing Immune Complexes in IgA Nephropathy
Hitoshi Suzuki1, Yusuke Suzuki,2 Kenji Satake,2 Bruce A. Julian,2 Jan Novak,2 Yasuhiko Tomino,1
1Nephrology, Juntendo Univ Faculty of Medicine, Tokyo, Japan; 2Medicine and Microbiology, Univ of Alabama at Birmingham, Birmingham, AL.

Background: IgA nephropathy (IgAN) is an autoimmune glomerulonephritis wherein immune complexes (IC) composed of galactose-deficient IgA1 (Gd-IgA1; autotigand) and anti-glycan IgA autoantibodies deposit in the glomeruli. Serum levels of Gd-IgA1 as well as anti-glycan IgA autoantibodies, responsible for the formation of ICs with Gd-IgA1, are elevated in patients with IgAN. However, the pathogenic roles of Gd-IgA1-containing IC and mechanisms of immune deposits in the mesangium are still obscure.

Methods: Polymeric Gd-IgA1 myeloma protein and recombinant anti-glycan IgG were used to form IC (Gd-IgA1-IgG IC) in vitro to inject i.v. into nude mice. After various time intervals, mice were sacrificed; blood and urine were collected to determine serum IgA1 and IgG, urinary protein and creatinine and hematuria. Also, to assess the potential capacity of these IC to activate endothelial cells, human renal glomerular endothelial cells (HRGEC) were co-cultured with Gd-IgA1 alone or Gd-IgA1-IgG IC for 72 h. Then, transcript levels of TFN-a, TGF-b1, IL-6, ICAM-1 and E-selectin in HRGEC were measured by RealTime PCR.

Results: Gd-IgA1 and anti-glycan IgG formed IC that deposited with murine C3 in the mesangium and in small amounts in the subendothelial area of the glomerular capillaries, and induced hematuria and proteinuria. In control mice injected with only Gd-IgA1 or Gd-IgA1 with IgG from a healthy control, Gd-IgA1 deposited transiently and did not cause tissue injury. After stimulation with Gd-IgA1-IgG IC in HRGEC, transcript levels of TFN-α, ICAM-1 and E-selectin were upregulated (P<0.01).

Conclusions: Our studies confirmed the role of Gd-IgA1-IgG-containing IC in the pathogenesis of IgAN and induction of proteinuria and hematuria. Furthermore, the Gd-IgA1-IgG IC may bind to glomerular endothelial cells and induce release of pathogenic cytokines and chemokines.

FR-PO543
IgA Antibodies to Glomerular Endothelial Cells in Patients with Lupus Nephritis: Correlations with Renal Injury
Kazuo Takahashi,1 Ayako Kondo,2 Daixue Hirano,2 Shin’ichi Akiyama, Hiroki Hayashi,3 Shigehisa Koide,3 Midori Hasegawa, Yoshiyuki Hiki, Shunji Yoshida, Keiji Miura, Yukio Yuzawa, Fujita Health Univ, Toyoake, Aichi, Japan.

Background: Although anti-endothelial cell antibodies (AECA) against human umbilical vein endothelial cells (HUVEC) have been detected in systemically erythematous SLE (SLE), their pathologic role remains unclear. Because antigens expressed on the endothelial cell (EC) surface are pivotal for autoimmune reactions, methods that detect antibodies only to EC surface molecules are required. Thus, we developed a solubilized cell surface protein capture enzyme-linked immunosorbent assay (CSP-ELISA) that is able to detect antibodies against membrane proteins. We also aimed to elucidate the clinical importance of AECA for tissue-specific EC.

Methods: Sera from 52 patients with biopsy-proven lupus nephritis (LN), 25 with SLE without renal involvement (non-LN SLE), 10 disease controls (DC) and 81 healthy controls (HC) were tested for IgG- and IgA-AECA to human glomerular EC (HGEC) by CSP-ELISA. Results: Titers of IgG- and IgA-AECA to HGEC were significantly higher in LN and non-LN SLE patients than in the combined DC and HC (P<0.001) groups. The level of IgG-AECA did not correlate with active lesions, but the level of IgA-AECA to HGEC did correlate with histological evidence of active lesions in LN patients (P<0.001). Immunocytochemical analysis showed AECA recognized membrane proteins on HGEC. The significant correlation of titer of AECA to both HGEC and HUVEC (R=0.95 for IgG; 0.93 for IgA-AECA, respectively) indicated AECA in LN patients recognize membrane proteins expressed on HGEC and HUVEC. To identify specific antigens against AECA, biotinylated CSPs were incubated with sera from LN patients with high titers of IgG-AECA, immunoprecipitated with immobilized protein A followed by immobilized avidin, and blotted with NeutAvdin. A 150-kDa protein band that shifted to a 55-kDa protein band under reducing conditions was detected in patients with LN, but not in HC.

Conclusions: IgA-AECA was observed to be associated with pathological activity in LN. Those EC membrane components recognized by AECA may be linked with the pathogenesis of LN.

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

FR-PO544
Enzymatic Sialylation of IgA1 Hinge-Region: Pathogenic Role of Sialic Acid in IgA Nephropathy (IgAN)
Kazuo Takahashi,1,2 Milan Raska,2 Milada Stuchlova-Horynova,1,2,3 Alena Kasperova,1,2 Stacy D. Hall,1 Yoshiyuki Hiki,2 Yukio Yuzawa,2 Zina Moldoveanu,2 Bruce A. Julian,2 Matthew B. Renfrow,2 Jan Novak,2 1Univ of Alabama at Birmingham, Birmingham, AL; 2Fujita Health Univ, Toyoake, Japan; 3Palacky Univ in Olomouc, Olomouc, Czech Republic.

Background: Patients with IgAN have high serum levels of galactose (Gal)-deficient IgA1; some hinge-region (HR) O-glycans consist of terminal N-acetylgalactosamine (GalNAc) with or without N-acetylgalactosaminic acid (NeuAc, sialic acid). Sialylation of GalNAc blocks subsequent galactosylation. IgA1-producing cells from IgAN patients have increased activity of α2,6 sialyltransferase (ST3Gal1; adds NeuAc to galactose) of IgA1 O-glycans of an asialo-IgA1 myeloma protein (Ale) that mimics the Gal-deficient IgA1 in IgAN patients. The products were assessed by high-resolution mass spectrometry and ELISA with the GalNAc-specific lectin from Helix aspersa (HAA).

Results: Changes in SDS-PAGE mobility of the IgA1 heavy chain indicated that both enzymes were active. Enzymatic sialylation of the myeloma protein generated sialylated IgA1 that mimics the circulating nephritogenic IgA1 in LN patients, characterized by α2,6-sialylated GalNAc, or the IgA1 typical for healthy controls, characterized by α2,3-sialylated Gal attached to IgA1. Lectin ELISA was used to assess binding to the IgA1 before and after the enzymatic reactions. α2,6- or α2,3-sialylation of IgA1 markedly decreased reactivity with the HAA lectin. Neuraminidase treatment (removes sialic acid) completely restored the level of lectin reactivity. Thus, lectin binding to GalNAc decreased after sialylation of a neighboring glycan in the cluster of O-glycans of the IgA1 hinge region.

Conclusions: Neuraminidase should be used to treat serum IgA1 before a lectin assay to assess the content of hinge-region Gal-deficient GalNAc. Our in vitro enzymatic sialylation model will be useful to study the biological roles of Neuac in the IgA1 HR in the pathogenesis of IgAN.

Funding: NIDDK Support, Other NIH Support - NIGMS, Government Support - Non-U.S.

FR-PO545
Proteomic Analysis of Engineered IgA1-IgG Immune Complexes Reveals Association with Activated Complement C3
Nicolas Maillard, Leeann Boerma, Stacy D. Hall, Zhi Qiang Huang, Michal Mrug, Zina Moldoveanu, Bruce A. Julian, Matthew B. Renfrow, Jan Novak, 1Univ of Alabama at Birmingham, Birmingham, AL.

Background: In IgA nephropathy (IgAN), C3 colocalizes with IgA in mesangial deposits. Deletion of CPIH1.3 genes has been recently described to protect from the occurrence of IgAN, highlighting the contribution of complement alternative pathway (AP). Using an in vitro model of polymeric galactose-deficient (Gd) IgA1 with recombinant anticylglyc IgG derived from an IgAN patient in immune complexes (ICs) formed in the presence of serum, we identified and characterized by proteomic analyses complement C3 products associated with the complexes.

Methods: ICs were formed overnight at 4°C, using purified Gd-polymeric IgA (gA1e) myeloma protein, recombinant anticylglyc IgG (r1123), and IgA- and IgG-depleted serum or healthy control. High-molecular-mass fractions (HMMFs; >700 kDa) were isolated by size-exclusion chromatography. The fractions that stimulated proliferation of cultured human mesangial cells were pooled, concentrated, and fractionated by SDS-PAGE for proteomic analysis. After silver staining, protein bands were excised, digested by tryptic, and analyzed by high-resolution tandem mass spectrometry (LTQ OrbitrapVelos; MS/MS). Identification of proteins was allowed by use of MASCOT and SEQUEST algorithms.

Results: Proteomic analysis revealed that C3 α and β chain elements were present in the active ICs and only low amount of β chain was in the corresponding fractions in negative control (serum only). Amino-acid sequence obtained by MS/MS combined with information on the molecular mass of corresponding bands from SDS-PAGE identified iC3b, C3c, and C3dg (confirmed by anti-C3 immunoblotting). The presence of these low-molecular-mass products in HMMFs can only be explained by their binding to ICs. These results thus provide evidence that biologically active IgA1-ICs activate complement C3 and associate with C3 degradation fragments. iC3b, C3c, and C3dg are the products of the action of factor H and I, suggesting a critical role of regulators in the activation of complement AP in IgAN.

Conclusions: Soluble engineered IgA1 – IgG ICs can bind C3 elements in vitro.

Funding: NIDDK Support, Private Foundation Support

FR-PO546
Prevention of Formation of IgA1-Containing Immune Complexes in IgA1 Nephropathy
Alena Kasperova,1,2 Hiroiyuki Ueda,1 Milada Stuchlova-Horynova,1,2 Tyler J. Stewart,2 Matthew B. Renfrow,2 Bruce A. Julian,1 Jan Novak,2 Jiri F. Mestecky,2 Milan Raska.1,2 1Immunology, Faculty of Medicine, Palacky Univ, Olomouc, Czech Republic; 2Univ of Alabama at Birmingham, Birmingham, AL.

Background: IgA nephropathy (IgAN), the most common primary glomerulonephritis in the world, is characterized by mesangial deposits enriched for galactose-deficient IgA1 (Gd-IgA1). These immune deposits likely originate from circulating immune complexes
consisting of Gd-IgA1 bound by IgG and/or IgA antibodies specific for terminal N-acetylgalactosamine (GanNac) in the O-linked glycans in the Gd-IgA1 hinge region. Such circulating antibodies are likely to activate mesangial cells upon glomerular deposition, thus inciting renal injury. We tested the hypothesis that a GalNAc-containing competitor will prevent formation of Gd-IgA1-IgG immune complexes.

Methods: We tested two potential competitors of immune-complex formation based on non-GalNacylated IgA1 heavy chain and its CH1-CH2 fragment. The recombinant proteins were produced in E. coli, purified, and glycosylated (GalNacylated) in vitro using recombinant GalNAc-transferase 2. The reaction products were analyzed by lectin immunoblotting and mass spectrometry. Sera of IgAN patients containing anti-glycan IgG antibodies were supplemented with Gd-IgA1, with or without a competitor, and formation of immune complexes was assessed by ELISA.

Results: Supplementation of sera of IgAN patients with Gd-IgA1 induced formation of new immune complexes. GalNacylated competitors reduced formation of such complexes by 5-20%. The inhibition was dose-dependent and glycan-specific, because non-GalNacylated inhibitors did not affect formation of new immune complexes.

Conclusions: GalNAc-containing competitors can interfere with binding of Gd-IgA1 and anti-glycan IgG to form an immune complex in vitro. This finding may offer a new approach for disease-specific therapy of IgAN.

This work was supported by grants National Institutes of the Health DK082753, DK078244, DK083663, GM098539 and NIH support.

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

FR-PO547
Clinical Impact of Tonsillar APRIL on the Severity of IgA Nephropathy
Masahiro Muto,1 Yusuke Suzuki,2 Hitoshi Suzuki,1 Kensuke Joh,2 Shozo Iizui,1 Bertrand Huard,2 Yasuhiko Tomino,1 'Juntendo Univ Faculty of Medicine, Tokyo, Japan; 2Sendai Shikaihoen Hospital, Sendai, Japan; 1Univ of Geneva, Geneva, Switzerland.

Background: A proliferation-inducing ligand (APRIL) is a critical mediator for antibody production and plasma cell survival. Because immunological disorders in mucosal immunity are recently discussed in the pathogenesis of IgA nephropathy (IgAN), we investigated the clinical impact of mucosal APRIL expression in IgAN.

Methods: In addition to clinical background and before and after tonsillectomy, the expression of APRIL and its receptors (TACI, transmembrane activator and calcium modulator cyclophilin ligand interaction, BCMA; B-cell maturation antigen) in tonsils from IgAN patients (n=56) and control patients (chronic tonsillitis, n=12) were evaluated by real-time PCR, immunohistochemistry (IHC) and flow cytometric analysis (FCM). For IHC and FCM, polyclonal rabbit anti-APRIL antibody specifically recognizing APRIL-producing cells was used.

Results: Tonsil transcript levels of APRIL and its receptors were significantly higher in IgAN than those of control (P<0.05). IHC revealed that Stalk-1 cells in IgAN were detected not only in the subepithelial area but also germinal centers (GC) much more than those in control. The percentage of Stalk-1 GC (27.4±21.3%) in IgAN patients was significantly higher than that in control (7.2±6.81%, P<0.0005) and correlated with amount of proteinuria (P=0.0017) and treatment responses, such as decrease of proteinuria (P=0.0003). Combined IHC and FCM analysis revealed that CD11c+ dendritic cells and CD19 B cells are the major cell type of APRIL-producing cells in subepithelial area and GC, respectively, in patients with IgAN. Moreover, in case of high percentage of Stalk-1 GC, serum levels of IgA containing immune complexes (IC) were decreased after the tonsillectomy.

Conclusions: Up-regulation of tonsillar APRIL impacts the disease activity in IgAN. This overexpression may involve long-term survival GC B cells responsible for the production of nephritogenic IgA/IgA IC.

FR-PO548
microRNA-155 Deficiency in Peripheral Lymphocyte Is Related to IgA Nephropathy
Xiaolei Chen, Weiqin Qin, Zi Li, Juming Fan. Div of Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China.

Background: MicroRNA-155 (miR-155) is an important immune regulator involved in lymphocyte homeostasis, which is key pathogenesis of IgA nephropathy (IgAN). miR-155 level in peripheral lymphocytes of IgAN patient was studied in this study.

Methods: Forty biopsy-proven IgAN patients and 15 unrelated healthy controls were included. Expression of miRNAs in peripheral lymphocytes was determined using Exiqon microarray microarray. Realtime RT-PCR of miR-155 was performed. The expression level of Foxp3, a regulator of miR-155, was also measured. Treg and Th17 cell ratio was measured by flow cytometry. Correlation between miR-155, Foxp3 expression level, Treg/Th17 ratio and clinical indexes, such as proteinuria, hematuria, renal function and albumin level was analyzed.

Results: Microarrayindicated that in 1035 microRNA successfully analyzed, 333 are upregulated and 499 are deregulated compared with normal controls. The expression level of miR-155 in IgAN patients was dramatically lower than normal control (fold change -6.1), which was further confirmed by realtime RT-PCR (miR-155 0.173+0.07 vs Control 0.796±0.13, P<0.01). Significantly correlation between miR-155 and Foxp3 expression level was identified (r=0.681, P<0.001). A significant inverse correlation was also observed between Treg/Th17 ratios. Further study showed that proteinuria and hematuria were significantly correlated with miR-155 level (proteinuria: r=0.594, P<0.001; hematuria: r=0.590, P<0.001). However, no apparent correlation was observed in serum creatinine, BUN,Creatin-C and albumin. Moreover, miR-155 expression level is also related to the severity of renal pathologic changes.

Conclusions: Remarkable lower expression of peripheral lymphocytes miR-155 was observed in IgAN patients, which correlates with proteinuria, hematuria and pathological grade, which suggests that miR-155 might play important roles in the pathogenesis of IgAN through a potential biomarker for the disease.

FR-PO549
Aberrant O-Glycosylation of IgA1 in IgA Nephropathy (IgAN) and the Role of Sialyl-Tn Antigen
Tyler J Stewart,1 Hitoshi Suzuki,2 Milan Raska,1 Kazuo Takahashi,1 Koshi Yamada,2 Mileda Stuchllova-Horynova,2 Bruce A. Julian,1 Matthew B. Renfrow,1 Jan Novak.1 'Univ of Alabama at Birmingham, Birmingham, AL; 2Juntendo Univ, Tokyo, Japan; 3Palacky Univ, Olomouc, Czech Republic; 4Fujita Health Univ, Toyoaka, Japan.

Background: IgAN is associated with galactose deficiency of circulating IgA1 hinge region. We previously revealed that the incidence of O-glycans in IgA1 is decreased in IgAN patients compared to controls. In this study, we investigated the role of aberrant O-glycosylation of IgA1 and the role of sialyl-Tn antigen in the pathogenesis of IgAN.

Methods: Normal human serum was supplemented with Gd-IgA1 and GalNAc-containing glycosyltransferase. Supplementation of sera of IgAN patients with Gd-IgA1 induced formation of new immune complexes. GalNAcylated competitors reduced formation of such complexes. This inhibition was dose-dependent and glycan-specific, because non-GalNAcylated inhibitors did not affect formation of new immune complexes.

Conclusions: GalNAc-containing competitors can interfere with binding of Gd-IgA1 and anti-glycan IgG to form an immune complex in vitro. This finding may offer a new approach for disease-specific therapy of IgAN.

This work was supported by grants National Institutes of the Health DK082753, DK078244, DK083663, GM098539 and NIH support.

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

FR-PO550
In Patients with IgA Nephropathy (IgAN) and Healthy Controls Cells Expressing Mucosal Homing Receptors Secret Receptor Polymeric J-Chain-Containing but Differentially O-Glycosylated IgA1
Hiroyuki Ueda,1 Zina Moldoveanu,1 Hitoshi Suzuki,2 Koshi Yamada,2 Bruce A. Julian,1 Jiri F. Mestecky,1 Jan Novak.1 'Univ of Alabama at Birmingham, Birmingham, AL; 2Juntendo Univ, Tokyo, Japan.

Background: Patients with IgA nephropathy have elevated levels of circulating IgA1 with some O-glycans that are galactose-deficient (Gd-IgA1). This IgA1 forms pathogenic immune complexes with IgG antibodies. Because IgA1 secreted by tonsillar IgA1-secreting B cells is mostly polymeric, indicating a possible mucosal origin, we investigated the origin and nature of the Gd-IgA1-producing cells not well understood. To address these questions, we developed protocols for separation of cells expressing specific mucosal homing receptors and analyses of IgA1 secreted by these cells.

Methods: Using immortalized IgA1-secreting cells derived from the circulation of IgAN patients (IgANP) and healthy controls (HC), we isolated by FACs sorting the cell populations expressing either gut- or upper respiratory tract-homing receptors, a4β7 integrins and L-selectin, respectively. Then, we characterized the molecular forms and O-glycosylation of IgA1 secreted by these cells using SDS-PAGE separation under non-reducing conditions followed by Western blotting with anti-heavy chain and anti-J chain antibodies and lectin ELISA, respectively.

Results: IgA1 secreted by cells in HC was predominantly monoclonal, whereas IgA1 from cells of IgANP was enriched for J-chain-containing polymers. IgANP-derived and HC-derived cell populations expressing mucosal homing receptors (a4β7 and L-selectin) secreted predominantly polymeric IgA1. However, only the IgANP cells produced Gd-IgA1, suggesting that the pre-existing deficiency is not an exclusive characteristic of polymeric glycans, but may be a disease-specific feature.

Conclusions: Separation of circulating IgA1-secreting cells according to specific homing receptors, combined with analyses of molecular forms and O-glycosylation of IgA1 at the molecular level, may reveal the origin and nature of the cells producing Gd-IgA1 that plays a key role in the pathogenesis of IgAN.

Support: NIDDK Support, Other NIH Support - NIGMS, Private Foundation Support

Funding: NIDDK Support, Other NIH Support - NIGMS, Private Foundation Support

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

Underline represents presenting author/disclosure.
FR-P0551
Production of Aberrantly Glycosylated IgA1 in IgA Nephropathy Is Associated with Abnormal Distribution of ST6GalNAc-II in Golgi Apparatus
Milada Stuchlova-Horynova,1,4 Zora Smrzova,5 Miroslav Oveckova,1 Zina Moldoveanu,2 Bruce A. Julian,3 Hitoshi Suzuki,5 Jiri F. Mestecky,4 Jan Novak,3 Milan Raska.1,4
1Palacky Univ Olomouc, Czech Republic; 2Veterinary Research Institute, Brno, Czech Republic; 3Juntendo Univ, Tokyo, Japan; 4Univ of Alabama at Birmingham, Birmingham, AL.

Background: Patients with IgA nephropathy (IgAN) have IgA1 with galactose (Gal)-containing O-glycans which are recognized by anti-glycan antibodies, resulting in formation of circulating immune complexes (CIC) that deposit in glomeruli. O-glycosylation of IgA1 in the Golgi apparatus is initiated by attachment of GalNAc residues to the hinge region by GalNAc-transferase, followed by attachment of Gal to GalNAc residues by galactosyltransferase C1GALT1. Selective attachment of Gal to GalNAc by o.3-sialyltransferase and/or to GalNAc by s.6-sialyltransferase (ST6GalNAc-II). Premature sialylation of IgA1 by the attachment of SA to GalNAc blocks attachment of \( \alpha \) hinge region by GalNAc-transferases, followed by attachment of Gal to GalNAc of IgA1 in the Golgi apparatus is initiated by attachment of GalNAc residues to the medical college, Luzhou, Sichuan, China. 

Methods: We generated ST6GalNAc-II-specific monoclonal antibody (mAb) to track this enzyme through the Golgi apparatus. Methods: ST6GalNAc-II-specific mouse mAb was produced by DNA vaccination with plasmid encoding human ST6GalNAc-II. Recombinant ST6GalNAc-II produced in HEK293 FreeStyle cells was used for screening mAbs by ELISA or Western blotting. Our mAb and commercial cis- and trans-Golgi markers-specific mAbs were used for localization of ST6GalNAc-II in IgA1-producing cells by confocal microscopy.

Results: Using recombinant ST6GalNAc-II, we isolated ST6GalNAc-II-specific mAb. Confocal microscopy with image analyses revealed that in IgA1-producing cells from IgAN patients ST6GalNAc-II had about 13% more protein localized in cis-Golgi compared to cells from healthy controls (P<0.05).

Conclusions: Partial relocation of ST6GalNAc-II from trans- to cis-Golgi in IgA1-producing cells may represent a new mechanism contributing to production of Gal-deficient IgA1 in IgAN. Funding: NIDDK Support, Government Support - Non-U.S.

FR-P0552
Effect of Urine Protein on Renal Intersitienal Injury of IgA Nephropathy by Interleukin-17 Pathway
Junming Pan,1,2 Jiwen Wen,1 Nan Miao,1 Zi Li,1 Man Yang,1 1Dept of Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China; 2Dept of Nephrology, Dept of Internal Chinese Medicine, Luzhou Medical College, Luzhou, Sichuan, China.

Background: IgA nephropathy is a common glomerulonephritis throughout the world. The evidence suggested the imbalance of autoimmune affected the IgA production, transformation and clearance in IgAN. Interleukin-17 (IL-17) known as a pro-inflammatory factor could promote the generation cytokines and induce T cell activation and proliferation; function in autoimmune diseases. This study is to investigate the expression of IL-17 in IgAN, and effect of IL-17 on renal interstitial injury.

Methods: The plasma and urine samples of 28 IgAN patients and 8 healthy controls were gathered. NRK-52E were cultured in medium and BSA. The concentration of IL-17 was detected by ELISA. Kidney tissue from 8 IgAN patients and 3 patients with renal tumor selecting as normal tissue as control. The expression of IL-17 in kidney cells was measured by Immunohistochemistry.

Results: IL-17 level of urine was increased in IgAN patients compared with normal controls. The urine level of IL-17 was significant positive correlation with level of proteinuria and chronic renal injury. Compared with control group, the expression of IL-17 in renal tissue was increased in IgAN patients. The number of IL-17 positive cells is filtration of CD68 positive cells in kidney. Urine protein could induced the part in pathogenesis of IgAN.

Conclusions: The higher level of urine IL-17 was related with level of proteinuria and filtration of CD68 positive cells in kidney. Urine protein could induced the secretion of IL-17 in tubular epithelial cells. IL-17 alone or collaborate with cytokine take part in pathogenesis of IgAN. Funding: Government Support - Non-U.S.

FR-P0553
The Deposition of Secretory IgA in Patients with IgA Nephropathy Are Associated with Different Clinical, Pathology and Complement Activation Pathway
Junjun Zhang, Yan Liang, Zhangsuo Liu. Nephrology, First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan Province, China.

Background: Mucosal infection associated with episodic macroscopic haematuria are observed in many patients with IgAN. Secretory IgA (sIgA) is a mainly immunoglobulin associated with different clinical manifestation and renal immunopathogenesis. Compared with IgA, sIgA may activate different renal complement pathway in IgAN.

Results: We had specimen from adult patients with distinct class III, IV, and V LN and pediatric patients with class III and IV. In a paired-sample analysis we compared miR abundance in adult and pediatric active vs inactive LN, proliferative vs non-proliferative LN, class IV vs class III LN, active class III vs inactive class III LN, active class IV vs inactive class IV LN, and adult active class V vs inactive class V LN. We found significant changes in miR-324, -320, -200c (adult), -375 (pediatric), -200c, -30a, -671, respectively. All changes had p<0.01, except for miR-30a (p=0.001).

Conclusions: We detected significant changes in miR abundance related to specific LN classes. Given that the proportion of class IV LN is significantly worse than other classes, identifying miRs that are associated with class IV LN is an important step in biomarker discovery of this particular aggressive form of LN.

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

492A

FR-P0554
Overexpression of N-Acetylgalactosaminotransferase-14 Contributes to Galactose-Deficient IgA1 Production: Relevance for IgA Nephropathy
Jana Novakova,1 Tyler J. Stewart,2 Koshi Yamada,2 Hitoshi Suzuki,3 Zina Moldoveanu,2 Bruce A. Julian,3 Jan Novak,2 Milan Raska.1
1Palacky Univ in Olomouc, Olomouc; Czech Republic; 2Univ of Alabama at Birmingham, Birmingham, AL; 3Juntendo Univ, Tokyo, Japan.

Background: IgA nephropathy (IgAN) is characterized by deposition of IgA1-containing immune complexes in the renal mesangium leading to glomerular injury; IgA1 in these deposits in enriched for galactose-deficient O-glycans (Gal/GalNAc). IgA1 O-glycosylation is initiated by attachment of N-acetylgalactosamine (GalNAc) to serine or threonine in the hinge region and is catalyzed by GalNAc-transferases (GalNAc-Ts). Among the known human GalNAc-Ts, only GalNAc-T4 is up-regulated in IgA1-producing cells from those patients compared to those from healthy controls. ST6GalNAc-II knock-down has confirmed involvement of GalNAc-T14 in the production of Gd-IgA1. Therefore, we investigated the effect of overexpression of GalNAc-T14 in IgA1-secreting cells on Gal-deficient production.

Methods: An EBV-immortalized IgA1-secreting cell line was transfected by bicistronic plasmid pT14-EGFP expressing GalNAc-T14 and enhanced-green fluorescent protein (EGFP). EGFP-positive and EGFP-negative cells were sorted by FACS. RT-PCR analysis was used for determination of GalNAc-T14 mRNA levels. ELISA with a GalNAc-specific lectin was used to determine production of Gd-IgA1.

Results: Sorting of pT14-EGFP-transfected cells based on EGFP-high positive yielded a cell population with GalNAc-T14 expression 67-fold higher than in non-transfected cells and 17-fold higher than in transfected EGFP-low positive cells. Lectin ELISA revealed that the GalNAc-T14 overexpression increased production of Gd-IgA1. Furthermore, the lectin ELISA suggested that most GalNAc-T4 attached by GalNAc-T14 was not subsequently galactosylated or sialylated.

Conclusions: FACs sorting of transfected cells is a suitable method for systems in which the transfection efficiency is low. Our data suggest that overexpression of GalNAc-T14 in IgA1-secreting cells may be associated with production of Gd-IgA1. Funding: NIDDK Support, Government Support - Non-U.S.

FR-P0555
Deep-Sequencing Reveals Class-Specific Urinary microRNAs in Lupus Nephritis
Beatrice Goilav,1 Iddo Z. Ben-Dov,2 Irene Blanco,5 Olivier Loudig,1 Dawn Wahezi,3 Chaim Putterman.5
1Dept of Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China; 2Pediatric Rheumatology, CHAM, Bronx, NY; 3Pediatric Rheumatology, Mount Sinai Hospital at Monte, NY, NY; 3Pediatric Rheumatology, CHAM, Bronx, NY; 4Epidemiology, AECOM, New York, NY; 5Department of Medicine, Juntendo Univ, Tokyo, Japan.

Background: Lupus nephritis (LN), particularly, class IV LN, is associated with significant morbidity, microRNAs (miRs) are small, non-coding RNAs that regulate translation. Previous studies report changes in miR expression in kidney tissue, urine and PBMCs that correlate with LN disease activity. However, LN class-specific miRs have not been described.

Using deep-sequencing, we aimed to identify class-specific miRs in urine from adult and pediatric patients with biopsy-proven LN.

Methods: Cell-free urine from adult (n=25) and pediatric (n=8) female patients with class III, IV (proliferative) and V LN were obtained at time of active disease and during remission. Total RNA was used to prepare small RNA cDNA libraries for sequencing. Multiplexing using sample-specific 3’ adapters was applied to limit cost. Sequence reads were mapped to the human genome and small RNA databases. miRs were quantified by relative read abundance. qRT-PCR was used for quantitative validation.

Results: We had specimen from adult patients with distinct class III, IV, and V LN and pediatric patients with class III and IV. In a paired-sample analysis we compared miR abundance in adult and pediatric active vs inactive LN, proliferative vs non-proliferative LN, class IV vs class III LN, active class III vs inactive class III LN, active class IV vs inactive class IV LN, and adult active class V vs inactive class V LN. We found significant changes in miR-324, -320, -200c (adult), -375 (pediatric), -200c, -30a, -671, respectively. All changes had p<0.01, except for miR-30a (p=0.001).

Conclusions: We detected significant changes in miR abundance related to specific LN classes. Given that the proportion of class IV LN is significantly worse than other classes, identifying miRs that are associated with class IV LN is an important step in biomarker discovery of this particular aggressive form of LN.

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

492A
FR-PO556
Tolerance Failure at the Crossroad of Innate and Adaptive Immunity in Murine Lupus Nephritis
Amy G. Clark, Melissa L. Boor, Mary H. Foster. Medicine and Research Service, Duke Univ Medical Center and DVAMC, Durham, NC.

Background: Failed immune tolerance underlies pathogenesis in lupus nephritis. To identify genetic modulators of disease, we tracked tolerance mechanisms regulating autoimmunity that destroys kidneys, which collectively model human lupus genetic complexity. We found that Tg B cells in the NZB strain, a contributor of major susceptibility loci for fulminant nephritis, uniquely display aberrant reversible anergy: they produce high levels of autoIg after toll-like receptor 4 (TLR4) stimulation, a phenotype not observed in other strains. Herein we explore the mechanistic and genetic basis of altered tolerance in NZB lupus.

Methods: Purified B cells or whole spleenocytes from NZB Tg mice (n=4-11/group) were incubated +/- ligands for TLR4 (LPS, TLR7/8, R848, and/or TLR9 (Cpg), and 8-10 d supernatants assayed for Ig production by ELISA. NZB Tg mice were bred with B6 or NZW mice to generate Tg (B6xNZB)F1 and Tg (NZBxNZW)F1 (BNF1) mice.

Results: Multiple TLR ligands induce Tg autoIg secretion from NZB Tg B cells: autotig binding OD, mean±SD, 1.233±1.30 for LPS, 0.573±0.75 for R848, 0.451±0.30 for Cpg, and 3.061±0.32 for LPS+R848+Cpg, compared to those produced by non-Tg B6 or NZW control mice. IL-17A production was readily detected in pristane treated WT mice, but not in control (WT) mice. The majority of IL-17A producing cells were innate (IL)-17A levels are increased in disease, although direct evidence of pathogenicity is lacking. To identify genetic modulators of disease, we tracked tolerance mechanisms regulating a functionally and histologically, after 7 months.

Conclusions: These results demonstrate that innate immune cells produce IL-17A, which drives autoimmune and glomerular injury in experimental SLE.

Funding: Government Support - Non-U.S.

FR-PO557
Loss of Anergy and Innate Marginal Zone Cell Enrichment in BXSB Lupus Nephritis
Amy G. Clark, Melissa L. Boor, Mary H. Foster. Medicine and Research Service, Duke Univ Medical Center and DVAMC, Durham, NC.

Background: BXSB mice develop lupus nephritis that is accelerated in males carrying the yas locus. To identify mechanisms by which BXSB genetic susceptibility modifies disease, we established a well-characterized autoantibody (autoIg) transgene (Tg) in BXSB. In contrast to stringent tolerance observed in Tg C57BL/6 (B6) and other strains, BXSB Tg disease, we established a well-characterized autoantibody (autoIg) transgene (Tg) in BXSB.

Methods: B6xBSXBXF1 mice (n=4) hyperproliferate to TLR4 ligand LPS relative to B cells from nonTg F1 littermates (n=2); % divided cells, mean±SD, 52.0±3.0 vs. 36.7±2.5, p<0.05. These results are similar to those using Tg and nonTg cells from the parental B6xNZB strain. In contrast to stringent tolerance observed in Tg C57BL/6 (B6) and other strains, BXSB Tg B cells lack hallmarks of anergy (reduced in vivo life span, hyporesponsive behaviors) and are enriched in innate-like marginal zone (MZ) B cells, a subset resistant to anti-CD20 therapy. Herein we further explore the genetic origins of altered tolerance in BXSB lupus.

Results: % of IL-17A producing cells: macrophages 41.4±6.3%, neutrophils 24.0±3.3%, natural killer cells 11.5±1.5%, gammadelta T cells 7.7±1.2% (except 13.8±1.8% were CD4+ Tcells).

Conclusions: BXSB lupus results in part from defective tolerance due to genetic disruption of coordinated TLR and B cell receptor signaling, possibly exacerbated by failure of innate MZ cell enrichment. Defects are detected in innate MZ cell enrichment and parafollicular B cell differentiation.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO558
Innate Immune Cells Produce Interleukin-17A which Drives Autoimmune and Lupus Nephritis
Shawn A. Summers, 1, Oliver M. Steinmetz, 2, A. Richard Kitching, 1, Stephen R. Holdsworth, 1 1) Dept of Nephrology and Medicine, Monash Health and Monash Univ, Melbourne, Victoria, Australia; 2) II. Med Klinik, Univ Hamburg, Hambegg, Eppendorf, Germany.

Background: Systemic lupus erythematosus (SLE) and lupus nephritis are significant causes of morbidity and mortality. Clinical studies have demonstrated that serum Interleukin (IL)-17A serum levels are increased in disease, although direct evidence of pathogenicity is lacking. We sought to define the role of IL-17A in SLE induced by pristane.

Methods: We injected pristane (500µl) intraperitoneally into C57BL/6 wild type (WT) mice and assayed IL-17A production after 6 days, using flow cytometry. Subsequently we treated WT and IL-17A-/- mice with pristane and assessed: cellular immunity (8 weeks); autoimmunity and renal injury, both functionally and histologically, after 7 months.

Results: After 6 days, IL-17A production was readily detected in pristane treated WT mice, but not in control (WT) mice. The majority of IL-17A producing cells were innate cells(% of IL-17A producing cells: macrophages 41.4±6.3%, neutrophils 24.0±3.3%, natural killer cells 11.5±1.5%, gammadelta T cells 7.7±1.2% (except 13.8±1.8% were CD4+ Tcells). In contrast to stringent tolerance observed in Tg C57BL/6 (B6) and other strains, BXSB Tg disease, we established a well-characterized autoantibody (autoIg) transgene (Tg) in BXSB.

Conclusions: Our methodology is the first to directly compare FTT and FFPTE tissue in a manner that is also applicable to clinical samples. With this, we will be able to first evaluate any differences between FFPTE and FTT in clinical samples, and then begin utilizing archived, FFPTE patient biopsy samples for LN studies.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO559
Mass Spectrometry Based Proteomics Highlights the Replicability of Results between Lupus Nephritis Formalin-Fixed, Paraffin Embedded and Fresh Frozen Tissues
Abhimanyu N. Amarnani, Joe Capri, Ivan Axel Lopez, Ram R. Singh, Julian Whitelegge. David Geffen School of Medicine, Univ of California, Los Angeles, Los Angeles, CA.

Background: Lupus nephritis (LN) progresses from mild focal inflammation, to diffuse proliferative nephritis, to fibrosis and end-stage renal disease. While current treatments are based on renal pathology, the molecular basis of LN and its progression remains obscure. There is a need to use global, data-driven research techniques for analysis of molecular changes associated with renal inflammation and progressive disease. Here we present a novel mass proteomics workflow applicable to archived, clinical tissue that has been formalin fixed, and paraffin embedded (FFPE). Working towards resolving the accessibility issue of fresh frozen biopsy tissue, our goal is to directly evaluate claims that the FFPE tissue can be ‘as good’ as ‘fresh frozen’ tissue (FFT) for the purpose of global LN proteomics.

Methods: The workflow includes comparing proteomics results from identical transverse kidney tissue cuts from NZM-2232 mice, half FFPE and the other half FTT. Tissue processing included the FASP technique, in-solution dimethyl isotope labeling, stage tip exchange filtration and the Thermo QTOF Orbitrap XL Mass Spectrometer with Eksigent Nano-LC-2dHPLC. In triplicate studies, 2 FTT groups and 1 FFPE were compared.

Results: Data analysis using MaxQuant (v1.3.0.5) resulted in identification of 1700+ proteins from both FTT and FFPE groups. More than 91% of proteins were identified in both healthy and IL-17A-/- mice, and more than 90% of proteins were consistently found between FFPE samples and identical FTT samples. Relative quantitative data among groups also presented good correlation. Our general analysis demonstrates that FFPE tissue proteomics can produce results consistent with FTT, allowing further understanding of proteome changes in LN pathogenesis.

Conclusions: Our methodology is the first to directly compare FTT and FFPE tissue in a manner that is also applicable to clinical samples. With this, we will be able to first evaluate any differences between FFPE and FTT in clinical samples, and then begin utilizing archived, FFPE patient biopsy samples for LN studies.

Funding: Government Support - Non-U.S.

FR-PO560
STAT3 Programs Th17-Specific Regulatory T Cells to Control Glomerulonephritis
Malte A. Klages, 1 Michael Mullereneizen, 1 Claudia Knobloch, 1 Hans-Lothar Schmelze, 1 Ralf A. Thiele, 1,2 Ulf Panzer, 1 Oliver M. Steinmetz, 1 1) Medizinische Klinik, Hamburg Univ, Germany; 2) Immunology, Hamburg Univ, Germany; 3) Experimental Hepatology, Hamburg Univ, Germany.

Background: Th17 cells are central mediators of glomerulonephritis. The mechanisms underlying their counter regulation are largely unknown. Recently, Th17 lineage specific regulatory T cells (Treg17) have been identified which depend on activation of STAT3. To date, not much is known about their role in inflammatory diseases. We therefore studied the function of Treg17 in crescentic glomerulonephritis.

Methods: Specific deletion of STAT3 was achieved using Foxp3Cre or CD4CreSTAT3fl/fl mice. Nephropathy (NTN) was induced at day 10 renal Treg17 were assessed. Immune responses were analyzed by FACS/EILISA. In vitro Treg suppression and in vivo Treg trafficking were assessed.

Results: Foxp3CreSTAT3fl/fl mice lacking Treg17 cells did not develop spontaneous disease. However, NTN was significantly aggravated. Renal and systemic immune responses increased towards Th17. Analyses of systemic Tregs revealed enhanced activation while numbers, proliferation and suppressive function remained unchanged. Strikingly, however, renal Treg infiltration was significantly reduced. FACS analyzes of renal Tregs from Foxp3CreSTAT3fl/fl mice revealed complete lack of the trafficking receptor CCR6 which was abundantly expressed on wildtype Tregs. In vivo trafficking was analyzed by competitive co-transfer of CD45.2 knockout and CD45.1 wildtype splenocytes into RAQ2 recipients. Renal trafficking of CD6 negative Tregs from Foxp3CreSTAT3fl/fl mice was significantly impaired. Finally we confirmed that Th17 cells are the major target of Treg17 cells as aggravation of disease was reversed in the absence of Th17 responses as shown in C57BL/6 wildtype mice lacking both Treg17 and Th17 cells.

Conclusions: Our data indicate the presence of a new subtype of regulatory T cells in crescentic glomerulonephritis which specifically targets Th17 cells and depends on STAT3-activation. One of their unique properties of action is directional migration into areas of Th17 inflammation by using the chemokine receptor CCR6.

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

Underline represents presenting author/disclosure.
B Cell Derived IL-10 Does Not Vitally Contribute to Experimental Glomerulonephritis

Malte A. Kluger,1 Annett Ostmann,2 Michael Müllenhülsen,1 Matthias C. Meyer,1 Hans-Joachim Paust,1 Rolf A. Stahl,1 Ulf Panzer,1 Gisa Tieg,1 Oliver M. Steinmetz.1

Background: IL-10 secreting regulatory B cells (B10) have recently been described as negative mediators of inflammation. Their mode of action and their impact on inflammatory renal disease is remained unclear. We therefore studied the function of B10 cell derived IL-10 in a model of crescentic glomerulonephritis particularly in the light of the potential risks associated with B cell depleting therapies.

Methods: Analyzes of systemic and renal IL-10 producing B cells during NTN were performed using IL-10 eGFP reporter mice. Specific deletion of IL-10 in B cells was achieved by generating CD19Cre x IL-10 fl/ mice. Nephrotic nephritis (NTN) was induced and renal histology and function were assessed at days 4 and 10. Immune responses were analyzed by FACS and ELISA.

Results: IL-10 producing B cells were present in low numbers in kidneys of healthy mice and their frequency increased during nephritis. Lack of IL-10 production by B10 cells, however, did not influence the clinical course of NTN at early and late time points in terms of renal function and histological damage. Renal leukocyte infiltration and cytokine expression were similar except for an increased formation of macrophages in knockout mice. Systemic immune responses, cytokine production, leukocyte composition, proliferation and activation were unaffected in nephritic knockout mice. However, we found impaired antigen specific IgG production in these animals. In line, renal immune complex deposition was slightly reduced. Last but not least, detailed analysis of systemic and renal regulatory T cells did not show any significant differences.

Conclusions: In summary, we here show that IL-10 producing B cells infiltrate the kidney during the course of crescentic glomerulonephritis. Nevertheless, specific deletion of IL-10 using B10 cells did not lead to exacerbation of renal disease. This supports that B10 cell derived therapy is safe and may be effective in B cell directed therapies as a lack of B10 cell derived IL-10 does not seem to deteriorate glomerular injury.

T Cell Epitope Spreading in Experimental Autoimmune Glomerulonephritis (EAG) in Rats

Jitendra K. Gautam,1 Anjana Gevaria,1 Reetu Mukherji,2 Kline Bolton,1 1Dept of Medicine, Div of Nephrology-CIDR, Univ of Virginia Health System, Charlottesville, Va; 2Temple Univ-School of Medicine, Philadelphia, Pa.

Background: α1(IV) NC1 domain causes Goodpasture’s Syndrome (GPS) in man and the same disease in rats. EAG. We have shown that an immunodominant T cell epitope, p13, that induces EAG, is frequently associated with antibody (Ab) B cell epitope spreading along the α1(IV) NC1 chain (intramolecular Ab spreading), and the α1(IV) NC1, (intermolecular epitope spreading). However, Ab does not occur in many rats, several other peptides were also found to induce EAG. Two regions not previously described induced EAG. Ab was deposited on GBM in all these rats demonstrating Ab cross reactivity and/or epitope spreading associated with the nephritogenic epitope. Non-nephritogenic peptides were not associated with Ab formation to GBM, although many induced Ab to themselves.

Methods: We have shown in EAG that in addition to B cell epitope spreading, T cell epitope spreading also occurs. However, only a few peptides with positive SI induce EAG, most do not. The nephritogenic new epitopes also are associated with Ab formation. Thus EAG is associated with both T and B cell epitope spreading which likely augment the severity of the disease and may be therapeutic targets.

FR-PO561

The Inflammassome-Related Molecules NLRP3 and ASC Suppress Lupus Nephritis of C57BL/6lpr/lpr Mice

Surprisingly, nlrp3- or asc- or il18- deficient C57BL/6/lpr/lpr mice displayed an aggravated autoimmune phenotype with massive lymphoproliferation, severe crescentic complex glomerular nephropathy, and autoimmune lung disease, which are usually absent in C57BL/6/lpr/lpr mice. Immune phenotyping revealed that both Nlrp3 and asc-deficiency both shifted lymphocyte apoptosis to lymphocyte necrosis, which induced multiple pro-inflammatory elements and suppressed negative regulators of innate immunity such as NLRP1a, NLRP2, NLRP6 and NLRP12. Lymphocyte necrosis and innate immune activation were associated with the expansion and activation of spleen dendritic cells, macrophages, T cells, and B cells.

Conclusions: To address this question we generated nlrp3- or asc- or il18- deficient C57BL/6/lpr/lpr mice, the latter being a model of spontaneous SLE-like autoimmunity. NLRP3- and ASC-defficient mice displayed an exacerbated lupus nephritis phenotype compared to wild-type (WT) mice within 1 month after TMPD injection, but after 4 months demonstrated severely exacerbated renal disease. The lack of nlrp3 and asc deficiency was associated with a massive increase in neutrophils, eosinophils and macrophages has been shown to mediate several adhesion-dependent processes. Recent studies have shown that the combination of NLRP3 and ASC deletion both shifted lymphocyte apoptosis to necrosis, which induced multiple pro-inflammatory elements and suppressed negative regulators of innate immunity such as NLRP1a, NLRP2, NLRP6 and NLRP12. Necrosis and innate immune activation were associated with the expansion and activation of spleen dendritic cells, macrophages, T cells, and B cells.

Results: Rats were immunized with p13. 20 mer overlapping peptides were synthesized to include the full length of α1(IV) NC1. Lymphocyte proliferation assays (LPA) were done weekly and the characteristics of the individual LPA stimulation index (SI) were examined.

Methods: Mac-1 Deficiency Protects Mice from Pulmonary Hemorrhage, whereas Exacerbates Glomerulonephritis in Experimental Model of Systemic Lupus Erythematosus

Yujin Shi, Naotake Tsuibo, Kazuhiro Furushashi, Shoichi Maruyama, Seichi Matsuo. 1Internal Medicine, Nephrology, Nagoya Univ Graduate School of Medicine.

Background: Mac-1 (CD11b/CD18), a leukocyte adhesion molecule, expressed on neutrophils, eosinophils and macrophages has been shown to mediate several adhesion-dependent processes. Recently, an association of genetic variations in Mac-1 with susceptibility to SLE has been suggested as a basis for several studies.

Methods: To determine the underlying mechanism of how Mac-1 participates in SLE, we introduced pristine (TMPD) to induce pulmonary hemorrhage and experimental lupus nephritis in Mac-1−/− mice on C57BL/6 background. Organ damage was histologically analyzed. Flow cytometric analysis and ELISA were performed for the evaluation of leukocyte infiltration and cytokine concentration in inflamed sites including the peritoneal cavity, lung and kidney.

Results: Mac-1−/− mice had reduced prevalence of pulmonary hemorrhage compared to wild-type (WT) mice within 1 month after TMPD injection, but after 4 months demonstrated severely exacerbated renal disease. The lack of Mac-1 deficiency both shifted lymphocyte apoptosis to necrosis, which induced multiple pro-inflammatory elements and suppressed negative regulators of innate immunity such as NLRP1a, NLRP2, NLRP6 and NLRP12. Necrosis and innate immune activation were associated with the expansion and activation of spleen dendritic cells, macrophages, T cells, and B cells.

Conclusions: Mac-1−/− mice promote acute inflammatory immune responses that lead to pulmonary hemorrhage but downregulates chronic immune responses to protect mice from IC-mediated renal injury in a model of experimental lupus nephritis induced by TMPD.

Funding: Government Support - Non-U.S.

FR-PO563

Mac-1 Deficiency Protects Mice from Pulmonary Hemorrhage, whereas Exacerbates Glomerulonephritis in Experimental Model of Systemic Lupus Erythematosus

Yujin Shi, Naotake Tsuibo, Kazuhiro Furushashi, Shoichi Maruyama, Seichi Matsuo. 1Internal Medicine, Nephrology, Nagoya Univ Graduate School of Medicine.

Background: Mac-1 (CD11b/CD18), a leukocyte adhesion molecule, expressed on neutrophils, eosinophils and macrophages has been shown to mediate several adhesion-dependent processes. Recently, an association of genetic variations in Mac-1 with susceptibility to SLE has been suggested as a basis for several studies.

Methods: To determine the underlying mechanism of how Mac-1 participates in SLE, we introduced pristine (TMPD) to induce pulmonary hemorrhage and experimental lupus nephritis in Mac-1−/− mice on C57BL/6 background. Organ damage was histologically analyzed. Flow cytometric analysis and ELISA were performed for the evaluation of leukocyte infiltration and cytokine concentration in inflamed sites including the peritoneal cavity, lung and kidney.

Results: Mac-1−/− mice had reduced prevalence of pulmonary hemorrhage compared to wild-type (WT) mice within 1 month after TMPD injection, but after 4 months demonstrated severely exacerbated renal disease. The lack of Mac-1 deficiency both shifted lymphocyte apoptosis to necrosis, which induced multiple pro-inflammatory elements and suppressed negative regulators of innate immunity such as NLRP1a, NLRP2, NLRP6 and NLRP12. Necrosis and innate immune activation were associated with the expansion and activation of spleen dendritic cells, macrophages, T cells, and B cells.

Conclusions: Mac-1−/− mice promote acute inflammatory immune responses that lead to pulmonary hemorrhage but downregulates chronic immune responses to protect mice from IC-mediated renal injury in a model of experimental lupus nephritis induced by TMPD.

Funding: Government Support - Non-U.S.
CD147 Ameliorates Lupus Nephritis through the Regulation of Helper T Cell 17 Differentiation
Kaya Maeda, Tomoki Kosugi, Waiichi Sato, Hiroshi Kojima, Yuka Sato, Mayuko Maeda, Shoichi Maruyama, Seichi Matsuo. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

Background: CD147/Basigin (Bsg), a glycosylated transmembrane protein, plays important roles of cell survival, invasion and metastasis. We previously demonstrated that Bsg−/− mice have activation of unique pathways that could be exploited therapeutically.

Methods: RNA expression was measured in clinical biopsy tissue by Nanostring technology. Differentially expressed transcripts identified by Statistical Analysis of Microarray were compared using ANOVA followed by Tukey’s. Controls (n=4) were pretreatment donor transplant kidney biopsies.

Results: Five patients responded well (CR) with normalization of serum creatinine (SCr) and a fall in proteinuria to <0.5g/d, while 3 patients had no response (NR) by the end of the experimental period, whereas serum C3 decreased in all patients.

Conclusions: These findings indicate that a subset of Tregs express CXCR3 and thereby have trafficking properties of pathogenic CXCR3+ T cells to suppress excessive T1l responses at tissue-specific sites. Funding: Government Support - Non-U.S.

FR-PO566
CD414 Ameliorates Lupus Nephritis through the Regulation of Helper T Cell 17 Differentiation

Kaya Maeda, Tomoki Kosugi, Waiichi Sato, Hiroshi Kojima, Yuka Sato, Mayuko Maeda, Shoichi Maruyama, Seichi Matsuo. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

Background: CD147/Basigin (Bsg), a glycosylated transmembrane protein, plays important roles of cell survival, invasion and metastasis. We previously demonstrated that Bsg−/− mice have activation of unique pathways that could be exploited therapeutically.

Methods: RNA expression was measured in clinical biopsy tissue by Nanostring technology. Differentially expressed transcripts identified by Statistical Analysis of Microarray were compared using ANOVA followed by Tukey’s. Controls (n=4) were pretreatment donor transplant kidney biopsies.

Results: Five patients responded well (CR) with normalization of serum creatinine (SCr) and a fall in proteinuria to <0.5g/d, while 3 patients had no response (NR) by the end of the experimental period, whereas serum C3 decreased in all patients.

Conclusions: These findings indicate that a subset of Tregs express CXCR3 and thereby have trafficking properties of pathogenic CXCR3+ T cells to suppress excessive T1l responses at tissue-specific sites. Funding: Government Support - Non-U.S.
Conclusions: Both Hu-HSC and Hu-PBL models permit development and expansion of human nephritogenic immunity, while posing unique opportunities and challenges for study of human disease. Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support, Government Support - Non-U.S.

FR-PO573

Hypogalactosylation and Hyposialylation of Serum IgG from Patients with ANCA-Associated Systemic Vasculitis: Relation to Disease Activity

Olivier M. Lardinois,1 Jacob Hess,1 Leesa Deterding,2 Lydia Abyar,1 Caroline J. Poulton,3 Candace Henderson,1 JulieAnne G. McGregor,1 Donna O. Bunch,1 Ronald J. Falk,1 1 Medicine, Univ of North Carolina Kidney Center, Chapel Hill, NC; 2Mass Spectrometry Group, National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Background: There is ample evidence that ANCA are primarily and directly involved in the pathogenesis of small-vessel vasculitis. In several inflammatory autoimmunity diseases, the subfamily of Fc glycans deficient in terminal sialic acid and galactose (IgG-G0 glycan form) is significantly increased. Studies have shown that this also applies to patients with active ANCA-associated vasculitis (AAV) [1] and that the high incidence of IgG-G0 glycan form in serum of PR3-ANCA patients correlates with disease activity [2]. Here we investigate whether a similar pattern of abnormal IgG glycosylation exists in the serum of MPO-ANCA patients that correlates with disease activity.

Methods: Serum or plasma samples were collected from 30 healthy controls, 29 patients with MPO-ANCA, and 21 patients with PR3-ANCA. IgGs from serum or plasma samples were affinity-purified using immobilized protein AG. Isolated IgGs were digested with trypsin, and the released glycopeptides were identified and quantified by liquid chromatography-electrospray tandem mass spectrometry. The disease activity of the MPO- and PR3-ANCA patients was evaluated by Birmingham Vasculitis Activity Score (BVAS).

Results: We found that IgG-G0 levels of MPO-ANCA patients are elevated both at the time of active disease and during disease remission and, therefore, do not correlate with disease activity. As expected, IgG-G0 levels of active PR3-ANCA patients significantly dropped during disease remission and regained glycosylation levels indiscernible from those in healthy controls.

Conclusions: Our results suggest that significant differences exist between MPO- and PR3-ANCA diseases regarding the association of aberrantly glycosylated IgG levels with disease activity. It is conceivable that these differences may contribute to significant clinical difference in the disease course, severity, or relapse rate observed between the two diseases. Funding: NIDDK Support

FR-PO574

Protease 3 and Myeloblastin Are Two Distinct Entities

Elizabeth Alderman Melnics,1 Anshul K. Badhwar,1 Akhil Muthig,1 Samuel C. Allred,1 Jia Jin Yang,1 Olivier Lardinois,1 J. Charles Jennette,1,2 Ronald J. Falk,1 Dominic J. Ciavatta. 1 UNC Kidney Center, Div of Nephrology and Hypertension, UNC at Chapel Hill; 2Dept of Pathology and Laboratory Medicine, UNC at Chapel Hill.

Background: Protease 3 (PR3) is a serine protease present in the azurophilic granules of PMNs and one of the major targets of ANCA. There are two annotated transcripts from the PR3 gene: PR3 (PR3T) and myeloblastin (MBNT). Whether the PR3 gene encodes two different protein isoforms, still remains a matter of debate. PMNs isolated from ANCA vasculitis synthesize both PR3 and MPO.

Methods: Patients enrolled in this study included 38 MPO-AAV and 7 SLE patients diagnosed and treated in Hokkaido University Hospital between January 2008 and May 2012. After acquisition of written consent, peripheral blood samples were obtained without anticoagulants, and sera were stored at -80°C until use. NETs induction rate was evaluated by reaction of patient-IgG with healthy neutrophils primed by TNF-α. ANCA affinity was determined by the competitive inhibitory ELISA method. Dnase I activity and NETs degradation ability were evaluated by ELISA and the incubation of patient serum with phorbol myristate acetate-induced NETs, respectively.

Results: IgGs eluted from sera of MPO-AAV patients induced NETs (NETs induction rate: 16.6±9.7%). This rate was significantly higher than that of SLE and healthy controls (SLE: 7.2±7.2%, Healthy control; 3.2±1.4%). In addition, the NETs induction rate was correlated with vasculitis activity and ANCA affinity. On the other hand, activity of DNase I, the important regulator of NETs in the serum, was generally low in MPO-AAV patients and many patients showed impaired degradation of NETs. Furthermore, the presence of anti-NETs antibodies, which could interfere with the degradation of NETs by DNase I, was demonstrated in some MPO-AAV sera.

Conclusions: The findings demonstrated high induction and low degradation abilities on NETs of sera in MPO-AAV patients.

FR-PO575

Gleaning B Cell Phenotype from Rituximab Panel Data: Decreased %CD5 5 Cells in Patients with ANCA Vasculitis Portend a Shorter Time to Relapse after Rituximab

Donald O. Bunch,1 JulieAnne G. McGregor, Lydia Abyar, Caroline J. Poulton, Elizabeth Alderman Melnics,1 Anshul K. Badhwar,1 Ronald J. Falk,1 John Schnitz, Patrick H. Nachman. 1UNC Kidney Center, Univ of North Carolina Chapel Hill, NC.

Background: To avoid infections and adverse events from therapy in patients with anti-neutrophil cytoplasmatic antibody (ANCA) associated vasculitis (AAV), clinicians require improved markers of disease activity and impending relapse to guide immunosuppression

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

Underline represents presenting author/disclosure.
strategies post-rituximab. CD5+ B cells, a surrogate marker of B regulatory cells, may serve as this needed biomarker but more data is required.

Methods: We examined B cell phenotype in 45 patients with AAV after rituximab therapy by flow cytometry. Immunosuppression in addition to rituximab was not an exclusion criterion. Whole blood or PBMCs were stained with antibodies to CD19, CD20, CD45 and CD5. Data from research samples was supplemented with data acquired from clinical R PRI patients.

Results: Patients who had <30% CD5+ B cells at the time of B cell repopulation (≥ 1% CD19/CD20 lymphocytes, n=5) relapsed sooner (14±1.5 mos) than patients who repopulated with ≥30% CD5+ B cells (n=40, 23±14 mos; p=0.025) after rituximab. Patients in the two groups were similar with regard to age, gender, PR3 positivity and lung involvement.

Conclusions: Our data indicate a low %CD5+ B cells correlates with a shorter time to relapse following rituximab therapy without taking immunosuppression dose into consideration. Monitoring ≥30% B cells serves as an effective biomarker to signal impending treatment failure and may guide rituximab re-dosing and/or use of other reimmunotherapy maintenance in AAV.

Funding: NIDDK Support, Private Foundation Support

FR-PO576

Genetic Regulation of CD177 – A Receptor Presenting Anti-Neutrophil Cytoplasmatic Antigen Protein 3 
Claudia Eulenberg, Sylvia Bähring, Friedrich C. Luft, Ralph Kettritt.
Experimental and Clinical Research Center, Charité Medical Faculty and the Max-Delbrück Center for Molecular Medicine; *Nephrology and Intensive Care Medicine.

Background: ANCA activate neutrophils leading to crescentic glomerulonephritis. CD177 presents the major ANCA antigen protein 3 (PR3) on the neutrophil membrane (mPR3) yielding CD177neg/mPR3low and CD177pos/mPR3high subsets. The percentage of CD177neg/mPR3low neutrophils confers a risk for ANCA vasculitis, is associated with worse clinical course and a stronger response to PR3-ANCA. We studied mechanisms that control CD177 protein expression.

Methods: We used human neutrophils, CD34+ stem cells, DNA and cDNA sequencing.

Results: We detected CD177 mRNA in CD177pos/mPR3high neutrophils, but neither full-length nor truncated mRNA in CD177neg/mPR3cells. We separated both cell populations and analyzed their DNA and cDNA. By Southern blot analysis of the CD177 gene we excluded genomic recombination with a neighboring pseudogene and copy number variations to be causes of different CD177 gene expression. Structure DNA aberrations and single nucleotide variations were excluded for both subsets by genome-wide human SNP array 6.0 from Affymetrix® suggesting no differences in the DNA sequences between both subsets. SNP array 6.0 from Affymetrix® excluding genomic recombination with a neighboring pseudogene and copy number variations as exclusion criterion. Whole blood or PBMCs were stained with antibodies to CD19, CD20, CD4, CD8, CD3, CD34, CD62L, CD45RO, CD38, CD11a, CD11b, CD14, CD15, CD16, CD20, CD40, CD45R0, CD56 and CD69. DNA sequences in exon-coding region and in exon-intron transitions of the CD177 gene did also not differ between both subsets. Haplotype analysis in 13 parent-offspring trios identified 12 informative heterozygous SNPs revealing monoallelic CD177 expression in 11/13 trios with no informative SNPs in the remaining 2 trios. We identified 12 informative heterozygous SNPs revealing monoallelic CD177 expression in 11/13 trios with no informative SNPs in the remaining 2 trios. We identified the parental-allelic origin in 8/11 trios (2x paternal, 6x maternal). Monoallelic expression was non-symmetric in 9/11 children affecting the primary CD177 protein structure. Haplotype analysis in a neutrophil-differentiated CD34+ stem cell model suggested that one allele was preferentially expressed. The second allele showed minor expression before differentiation that decreased with G-CSF treatment.

Conclusions: The findings provide novel insight into CD177 gene regulation and could facilitate studying CD177-related mechanisms in ANCA-associated vasculitis and additional neutrophil-mediated diseases.

Funding: Government Support - Non-U.S.

FR-PO577

Correlation between the CD4-CD8 Values and Responses to Treatment of Primary Glomerulonephritis

1Nephrology, Gulhane Military Medical Academy, Ankara, Etilik, Turkey; Internal Medicine, Gulhane Military Medical Academy, Ankara, Etilik, Turkey; *Nephrology, Gulhane Military Medical Academy, Ankara, Etilik, Turkey; Immunology, Gulhane Military Medical Academy, Ankara, Etilik, Turkey; Immunology, Gulhane Military Medical Academy, Ankara, Etilik, Turkey.

Background: Focal segmental glomerulosclerosis (FSGS) is a histologic diagnosis. Primary FSGS was previously considered to be largely unresponsive to immunosuppressive therapy. Several treatments, cyclosporine, and several immunosuppressive agents have been used with considerable therapeutic success. In a study conducted in patients with idiopathic membranous glomerulonephritis, CD4 +/ CD8 + ratio was found significantly lower than the control group. In this study a CD4 +, CD8 + level and the CD4 +/CD8 + ratio evaluated the importance of the response to treatment.

Methods: In the 6-month follow-up responses to the treatment of patients which as a result of renal bx FSGS (primary) reported CD4+ + CD8+ + values and CD4+ + CD8+ + ratio evaluated retrospectively. Lymphocyte subgroups were measured by flow cytometry from peripheral blood in 23 patients. In patients between two groups who do not respond and respond to treatment were compared.

Results: There was significant difference between the CD 8 values(p<0.05) &8230; 730 and 6290.03 in two groups. The CD4+ + CD8+ + T-cell ratio was significantly decreased in patients who can be treated patients compared with unresponsiveness group.

Conclusions: Regulatory T-cells confer negative regulatory effects on the immune response mediated by T-cells, and they can inhibit the proliferation of CD4+ + T lymphocytes and the secretion of cytokines (mainly IL-2). In addition, they may also suppress self-reactive T-cells (CD8+). Studies have demonstrated that regulatory T-cells inhibit the activation of helper T-cells normally induced by antigen-presenting cells, which suppresses B lymphocyte activation and reduces the production of autoantibodies by B lymphocytes, thereby resulting in the alleviation of tissue injury mediated by the immune complex. More studies need conducting in order to understand of the importance of the Lymphocyte subgroups in the primary glomerulonephritis.

FR-PO578

Detection of Anti-Phospholipase A, Receptor Autoantibodies: A Comparison of Three Different Immunosays

Astrid Behnert, Mario Schiffer, Laurence H. Brilliant, Michael Mahler, Marvin J. Fritzler. 
1Hannover Medical School, Hannover, Germany; 2Boston Univ School of Medicine, Boston, MA; 3INOTA Diagnostics, Inc., San Diego, CA; 4Univ of Calgary, Calgary, Canada.

Background: The detection of PLA2R antibodies in idiopathic membranous nephropathy (IMN), a common cause of nephrotic syndrome in adults, helps to differentiate between primary and secondary MN, it indicates whether immunosuppressive therapy is required and antibody titers are often used to monitor patients during therapy. We here compared for the first time the only commercially available immunoassay (a semiquantitative cell based assay (CBA-IIF, Euroimmun)) to an observer independent, high throughput immunoassay on an addressable laser bead immunoassay (ALBIA) platform and a recently developed ELISA.

Methods: Serum samples of 162 patients with IMN were tested on CBA-IIF and ELISA according to the manufacturer’s protocol (Euroimmun) and on ALBIA as previously described [Behnert et al., 2013].

Results: Using the cut-off values established by the manufacturer for the ELISA and in our previous study for the ALBIA, good qualitative agreements were found. The overall qualitative agreements were 78.8% for CBA-IIF vs. ELISA, 91.4% for CBA-IIF vs. ALBIA, and 75.5% for ELISA vs. ALBIA. The Spearman rho values were: 0.69 for ELISA vs. ALBIA, 0.74 for ELISA vs. CBA-IIF and 0.85 for ALBIA vs. CBA-IIF.

Conclusions: Interestingly, our ALBIA correlated better with the Euroimmun CBA-IIF than ELISA and CBA-IIF differed from the Euroimmun. The excellent interassay correlations found in the matrices utilized in these platforms. In ELISA, antigen is absorbed to plastic and reactivity of antibodies is highly dependent on sufficiently exposed epitopes. In ALBIA, the binding of antigen to spherical beads may permit binding of autoantibodies to the cognate, more stearically accessible conformational epitopes.

FR-PO579

Serological Profile of Idiopathic Membranous Nephropathy Cohort

Beina Teng, Janina Müller-Deile, Andrzej Skobner, Mario Schiffer, Marvin J. Fritzler. 1Hannover Medical School, Hannover, Germany; 2Univ of Calgary, Calgary, Canada.

Background: Idiopathic membranous nephropathy (IMN), a common cause of nephrotic syndrome, has recently been identified as an autoimmune-mediated disease [Beck et al., 2009]. Autoantibodies (aab) to PLA2R are fairly specific for IMN and only found to a small percentage in secondary MN [Hofstra et al., 2012]. The clinical outcome of IMN patients is quite diverse (spontaneous remission vs. ESRD vs. proteinuria without progression). We performed serological profiles of 162 IMN patients to compare aab profiles with aab frequencies found in normal healthy individuals (NHI) and to hopefully identify factors that help to predict disease course in IMN.

Methods: Serum samples from 162 IMN patients were assayed for a variety of aab by ELISA (DF570, ACA, B, GPI), addressable laser bead immunoassay (ALBIA; Sm, U1RNP, SS-A, Ro52, SS-B, Sc-70, Jo-1, CENP-B, PMSc, PCNA) and to dsDNA by the C. lucilliae IIF assay. PL-A, R aab were detected by a CBA-IIF (Euroimmun) and ALBIA [Behnert et al., 2013].

Results: PL-A, R aab were found in ~54% of IMN patients whereas the frequency of other aab was uniformly below 2%. Anti-DF570 were found in 16% of IMN patients.

Conclusions: The frequency of anti-PLA2R aab in our IMN cohort is consistent with what has been previously published [Qiu et al., 2011]. The frequency of the other aab, including anti-DF570/LEDGF, was comparable to what has been reported in NHI and hence do not appear to serve as biomarkers to predict disease outcome or subsets. Anti-DF570 antibodies are more prevalent in apparently NHI compared to patients with systemic autoimmune rheumatic diseases (SARD) [Mahler et al., 2012] whereas anti-Ro/
TRIM21 reactivity is often regarded as a marker for SARD. The absence of anti-Ro52/TRIM and the high prevalence of anti-DFS70 confirms that IMN is a rather organ specific autoimmune disease.

**FR-PO580**

**Invariable Natural Killer T Cells Are Depleted in Renal Impairment and Recover after Kidney Transplantation**

Konrad Peukert,1 Margit Patocki,1 Stephen E. Smoller,1 Anke Schierz,2 Hermann G. Rössler1 and Sibylle Von Vieldinghoff1

*Internal Medicine, Hannover Medical School, Hannover, Germany; 2PHV Dialysis Centre, Germany.*

**Background:** Altered immune function in patients with renal failure results in both susceptibility to infection and increased inflammatory response. Invariable natural killer T (iNKT) cells are a conserved, immunoregulatory T lymphocyte subset that responds to lipid antigens with near-instantaneous cytokine production and cytotoxicity. iNKT cells are required for antibacterial host defense. Whether chronic renal failure and renal replacement therapy alter iNKT cell abundance or phenotype has not been investigated.

**Methods:** iNKT cells were studied by flow cytometry in peripheral blood of patients with acute renal failure, chronic hemato- and peritoneal dialysis, chronic kidney disease and after renal transplantation.

**Results:** A very marked reduction in iNKT lymphocytes was found in acute renal failure before the first hemodialysis session. iNKT cells were depleted in peripheral blood of hemodialysis and peritoneal dialysis patients. This phenotype was accentuated after a hemodialysis session. Lesser degrees of iNKT cell depletion were observed in patients with chronic kidney disease. The iNKT cell phenotype was altered with lower levels of CD56 and CD161 expression. The decrease in iNKT cells and CD56 and CD161 expression were reverted within the first year after kidney transplantation.

**Conclusions:** We describe for the first time that iNKT lymphocytes are reduced in end-stage renal disease and further depleted by renal replacement therapy. iNKT cells are important for early host response including activation of other immune cells and their depletion may contribute to immune dysfunction in renal disease.

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

**FR-PO581**

*A δ-Opioid Receptor Agonist, Identified by a High-Throughput Chemical Screen, Blocks Neutrophil FcγRIIA Mediated Functions* Hiroshi Nishi,1 Toshihiko Nagashima,2 Satoshi Saito,3 Toshiyuki Itoh4 and Kazuhiro Miyake1

*1Department of Pathology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; 2Dept of Dermatology, Univ of Lübeck, Lübeck, Germany.*

**Background:** Inflammation mediated by antibody-antigen immune complexes (ICs) contributes to autoimmune diseases. Studies in mice expressing the uniquely human FcγRIIA selectively on neutrophils that lack endogenous murine FcγRs (γ-chain deficient), suggest that human FcγRIIA on neutrophils represent a critical link between IgG and tissue injury in models of glomerulonephritis, arthritis and the reverse passive Arthus (RPA) reaction. Yet, there is little understanding of how this human receptor is regulated.

**Methods:** A high-throughput chemical screen was employed using 8,483 bioactive small molecules and neutrophils from mice expressing the human FcγRIIA. The effect of top ranked compounds on IC induced reactive oxygen species generation, phagocytosis, degranulation and adhesion was evaluated in vitro. Compound effect on IgG mediated tissue injury in animal models was also assessed.

**Results:** A synthetic κ-opioid receptor (KOR) agonist was identified that potently blocked FcγRIIA-mediated neutrophil cytotoxic functions in a dose dependent manner, while cell viability and responses to the phospholipid-myristate-acetic acid were unaffected. Similar results were obtained with dynorphin A, an endogenous ligand of KOR. The KOR agonist was effective in blocking skin separation in an ex vivo model of epidermolysis bullosa acquisita and in vivo, inhibited the skin RPA reaction and K/BxN serum transfer arthritis. The effect of the KOR agonist was relatively selective for FcγRIIA, as it did not prevent thrombohemorrhagic vasculitis, which depends on the complement receptor Mac-1 (CR3). Current studies are evaluating the effect of this compound in glomerulonephritis.

**Conclusions:** A KOR agonist and ligand affects the proinflammatory functions of neutrophils activated with ICs. This raises the possibility that receptor targets of this class of opioids calibrate neutrophil responses to IgG and may be clinically beneficial in human neutrophil FcγRIIA-mediated inflammatory diseases.

**Support:** NIH HL065095 and Alliance for Lupus Research (TM), JSPS Postdoctoral Fellowship (HN).

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

**FR-PO582**

**Development of an Immunosuppressive Adverse Effects Index: Validity and Reliability Evaluation** Calvin J. Meaney,1,2 Ziad Arabi,2 Rocco C. Venuto,1 Joseph D. Consilvio,3 Gregory E. Wilding,3 Kathleen M. Tornatore,3 1Immunosuppressive Pharmacology Research Program, NYS Center of Excellence in Bioinformatics and Life Sciences; 2Pharmacy Practice, School of Pharmacy & Pharmaceutical Sciences; 3Medicine, Nephrology, School of Medicine and Biomedical Sciences; 4Biostatistics, School of Public Health, Univ at Buffalo.

**Background:** Immunosuppressive regimens (ISRs) prescribed in renal transplant recipients (RTR) are complicated by interpatient variability in response and adverse drug effects (AE). Standardized, objective monitoring approaches are not available to evaluate AE of maintenance ISR consisting of calcineurin inhibitors (CNI), either cyclosporine (CYA) or tacrolimus (TAC), with mycophenolic acid (MPA).

**Methods:** An immunosuppressive AE index (iAlex) was developed by transplant nephrologist with multi-disciplinary physician group incorporating objective AE severity in 17 clinical domains using physical exam, patient interview, laboratory and medication evaluations. This index emphasized AE associated with CNI, MPA, and steroids. Stable RTR having CYA (n=39) and TAC (n=28) with MPA were assessed with index and AE scores compared. Index evaluation included: face (inspection), content (subject matter expert opinion), and construct (ability to detect known AE) validities. Inter-rater reliability was evaluated with Kappa statistic and intra-class correlation (ICC).

**Results:** Multi-disciplinary index development and expert opinion to RTR verifies face validity. Nephrologists (subject matter experts) rated the 17 index domains as 3.1±0.75 of 4 (maximum) for clinical importance providing content validity. This index distinguished 1.75-fold greater gastrointestinal AE in TAC group compared to CYA (p<0.008). This AE difference is established between CNI ISR verifying construct validity. ICC was 0.81 (95% CI: 0.65-0.90) and Kappa statistic 0.68±0.02 for the overall index.

**Conclusions:** This novel immunosuppressive AE index demonstrated validity and reliability in RTR. Incorporation of this AE index into clinical evaluation post-transplantation may enhance nephrotherapeutic drug monitoring and quality of life.

**Funding:** NIDDK Support

**FR-PO583**

**Urinary Xist Is a Potent Biomarker in Mouse Model of Membranous Nephropathy** Chia-chao Wu,1 Yuh-feng Lin,2 Shih-Hua P. Lin.1 1Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; 2Dept and Graduate Institute of Microbiology and Immunology, National Defense Medical Center, Taipei, Taiwan; 3Div of Dermatology, Dept of Medicine, Shuang Ho Hospital, Graduate Institute of Clinical Medicine, Taipei Medical Univ, New Taipei City, Taiwan.

**Background:** Membranous nephropathy (MN) is one of the most common forms of nephritic syndrome in adults. The key to a substantial improvement of MN treatment is the identification of reliable biomarkers and targeted therapeutic methods. The long noncoding RNAs (IncRNAs) are often expressed in a disease stage-specific manner making these molecules attractive biomarker or therapeutic target. Therefore, this study shows for the first time that identification of MN-related IncRNAs in the pathogenesis of experimental MN model.

**Methods:** The membrane nephritis (MN)-related protein-coding genes, long noncoding RNAs and H3 post-translation modifications during the progression of MN including in serum and urine from experimental murine MN model at different stage were collected and checked. The biological effect and molecular mechanism of MN-related long noncoding RNAs in experimental MN model were also investigated using microarray assay, quantitative RT-PCR, and checking genome-wide binding sites in murine kidney by Chromatin isolation by RNA purification-sequencing (ChIRP-seq).

**Results:** The results indicated that Xist and NEAT1 expression levels are significantly up-regulated in experimental MN kidney. Chromatin immunoprecipitation experiments showed that decreased level of H3K27me3 targeting to NEAT1 and Xist promoter region in MN kidneys. Notably, Xist is upregulated in urine from experimental MN mice using quantification RT-PCR. Moreover, Xist are upregulated in renal biopsies with acute injury using array-based databases.

**Conclusions:** In summary, we provide the first evidence that Xist appears to be a potentially useful biomarker for evaluating kidney damage in experimental MN. These results suggested the potential use of Xist urine assay can aid MN diagnosis.

**FR-PO584**

**Increased Serum Soluble Urokinase Plasminogen Activator Receptor in HIV Patients Reduces Nephrin Expression in Human Podocytes** Joanna Mikulak,1 Massimo Alfano,2 Manuela Nebuloni,3 Guido Giusti,4 Pravin C. Singhal,5 Domenico Mavilio,1 1Laboratory of Clinical and Experimental Immunology, Instituto Clinico Humanitas, Mailan, Italy; 2AIDS Immunopathogenesis Unit, San Raffaele Scientific Institute, Milan, Italy; 3Dept of Biomedical Clinical Sciences, Univ of Milan, Milan, Italy; 4Dept of Urology, Humanitas Clinical and Research Center, Milan, Italy; 5Medicine, Hofstra North Shore LIJ Medical School, New York, NY.

**Background:** Recently increased level of serum soluble form of urokinase-type plasminogen activator receptor (suPAR) has been postulated as one of the putative causes of kidney disease in adults with primary FSGS. In a mouse model, circulating suPAR has been shown to cause foot process effacement, proteinuria and FSGS through the activation of podocyte β3 integrin. We investigated the possible role of suPAR in HIV-associated kidney damage.

**Methods:** The effect HIV-plasma (containing suPAR, from HIV patients) was studied on human podocyte nephrin expression. To confirm the effect of suPAR, HIV-plasma was pre-treated with anti-suPAR antibody and followed by evaluation of its effects on the expression of nephrin and other markers in podocytes. To confirm its role, the direct effect of recombinant suPAR was also investigated.

**Results:** HIV-plasma down regulated only nephrin expression (no change in podocin and synaptopodin) in podocytes. This reduction of nephrin expression was specific for suPAR since it was restored after treatment of HIV conditioned plasmas with the specific anti-suPAR antibody. Similar effect was observed in human podocytes with human recombinant suPAR protein. Nefrin loss was related to nephrin mRNA downregulation and was irreversible. In addition, the effect of suPAR on nephrin reduction was specific for the full length three-domain D3ΔD3 protein and not for cleaved D3 or D3ΔD3 soluble fragments.

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

Underline represents presenting author/disclosure.

---

**Poster/Friday**

**Immunochemistry of Glomerular and Tubulointerstitial Disease**


---

**498A**
Conclusions: Both recombinant and HIV-plasma suPAR were able to downregulate the expression of nephrin in human podocytes. HIV infection may be the potential factor to link increased suPAR concentration and glomerular permeability.

Funding: NIDDK Support

FR-PO585

Identification of a Human Podocyte Subpopulation Expressing Dc-Specific ICAM-3-Grabbing Nonintegrin Receptor (De-Sign) Joana Mikulak, 1 Guido Giusti, 2 Stefano Mantero, 1 Manuela Nebuloni, 1 Pravin C. Singhal, 1 Domenico Mavilio. 1

Laboratory of Clinical and Experimental Immunology, Institut Clinico Humanitas, Milan, Italy; 2Dept of Urology, Humanitas Clinical and Research Center, Milan, Italy; 2UO/IS/RBG, CNR, Milan, Italy; 1Humanita Clinical and Research Center, Milan, Italy; 2Pathology Uni, Univ of Milan, Milan, Italy; 1Medicine, Hofstra North Shore LIJ Medical School, New York, NY.

Background: HIV-associated Nephropathy is one of the clinical manifestations of AIDS. Our previous study in human podocytes has demonstrated the contribution of De- sign in HIV-1 internalization and establishment of virus reservoir. Since De-sign receptor plays a critical role in HIV pathogenesis, we attempted to confirm these findings in vivo as well as in primary podocytes.

Methods: Frozen human renal tissues from nephrectomized specimens were immunolabeled for De-sign and examined under confocal microscope; mRNA hybridization probe was also used to localize De-sign. In addition, glomeruli were isolated by laser-manipulated micro-dissection and a laser capture method. LeftMan Q-PCR assays were carried out to identify podocyte specific molecular marker transcripts. Primary podocytes cultured from the isolated glomeruli (human renal tissues) were co-probed with captured glomeruli displayed ICAM-3-Grabbing Nonintegrin Receptor (Dc-Sign) probe exhibited comparable results. TaqMan Q-PCR assays on captured glomeruli displayed expression of nephrin, podocin, synaptopodin, WT-1, and DC-sign. Additionally, confocal microscopy revealed that a small percentage of cultured podocytes also express De-sign. Twenty percent of glomeruli displayed expression of De-sign under confocal microscopic analysis. Both in situ hybridization studies and specific anti-De-sign mRNA probe exhibited comparable results. TaqMan Q-PCR assays on captured glomeruli displayed podocyte specific mRNA transcripts not only for nephrin, podocin, synaptopodin, WT-1 but also for De-sign. In vitro studies, TaqMan Q-PCR assays on podocytes, confirmed the expression of nephrin, podocin, synaptopodin, WT-1, and DC-sign. Additionally, confocal microscopy revealed that a small percentage of cultured podocytes also express De-sign. The cells expressing De-sign receptor also co-expressed other podocyte specific markers.

Results: These findings indicate that a small sub-population of podocytes able to express De-sign receptor.

Funding: NIDDK Support

FR-PO586

Angiotensinogen Copies Induce Disparate Effects during the Initiation and Progression of HIV-Associated Nephropathy (HIVAN) Xiaojuan Lan, 1 Arkrita Sagat, 1 Partab Rai, 1 Guohua Ding, 1 Ashwani Malhotra, 1 Pravin C. Singhal, 1 Medicine, Hofstra North Shore LIJ Medical School, New York, NY; 2Pathology, New York Medical College, Valhalla, NY; 3Medicine, Wuhan Univ, Wuhan, Hubei, China.

Background: Ang II contributes to the progression of HIVAN through its hemodynamic effects as well as direct cellular effects. We evaluated the effect of different copies of angiotensinogen (Agt) in the initiation and progression of HIVAN in genetically engineered HIVAN mice (Tg26/Agt).

Methods: Control and Tg26 mice with 2 (Tg26/Agt-2) and 4 (Tg26/Agt-4) copies of Agt were evaluated for severity of renal lesions, arteriosclerosis and hypertension with sirus red. RNA was extracted from renal tissues and probed for AT1, AT2, PAI-1, and molecules involved in Tert and epithelial mesenchymal transition (EMT) pathways.

Results: Tg26/Agt-4/8wks showed lower blood pressure (110/80 mm Hg) when compared to mice with Tg26/Agt-2/8 wks (140/90 mm Hg). Tg26/Agt-4/16wks displayed attenuated expression of PAI-1 vs Tg26/Agt-2/8wks; however, Tg26/Agt-4/16wks compared to mice with Tg26/Agt-2/8 wks (140/90 mm Hg). While Tg26/Agt-4/16wks displayed more advanced renal lesions which were more advanced than Tg26/Agt-2/8 wks (140/90 mm Hg). The mechanism underlying the pathogenic role of CD103+ DCs in AN mice may relate to the cross-presentation of antigen to CD8+ T cells.

Funding: Government Support - Non-U.S.

FR-PO587

Pericytes Are Critical Innate Immune Response Sentinels in the Kidney Shunsaku Nakagawa, Julia Lichtneker, Gabriela Campanholle, William Arthur Altemeier, Jeremy Stuart Duffield. Dept of Medicine, Univ of Washington, Seattle, WA.

Background: In recently published studies we showed kidney pericytes markedly activate innate immune pathway in response to kidney injury in vivo, that targeted therapies against pericytes are anti-inflammatory and that Toll-like receptor (TLR)-2/-4 and Myd88 signaling was involved with activation of inflammation and fibrosis after ischemia-reperfusion injury (IRI), but that Myd88 signaling in the myeloid lineage had little impact on macrophage activation or disease progression after IRI (Campanholle et al PLoS ONE 2013). In the following we have dissected innate immune responses to sterile kidney injury in pericytes.

Methods: Pericytes were isolated from normal kidney of wild-type, Tlr2-/-, and Myd88-/-, Nrps3-/- and Caspase -1/2-/- mice and primary cultures generated. Crude Damps were purified and characterized from IRI kidneys 24h after surgery. After stimulation with TLR ligands or Damps, pericyte cultures were analyzed for cytokine secretion and functional responses.

Results: Stimulation of TLR 1/2, 2/3, 4, 7, and 9 in pericytes resulted in secretion of a broad array of pro-inflammatory cytokines and chemokines including IL-6 and MCP-1. Myd88 deficiency in pericytes attenuated these responses. DAMPs from IRI kidney activated TLR-2/-4, Myd88 signaling in IRI pericytes but not primary tubular epithelial cells and vascular endothelial cells. Nuclear protein histones were identified as a major component DAMPs. DAMP-mediated pericyte activation resulted in secreted factors including IL-6, MCP-1 but also IL-1b, indicative of activation of inflammasome signalling. These responses were dependent on TLR-2/-4, Myd88 pathway, and the NLRP3 inflammasome. Finally transition of pericytes to myofibroblasts requires active Myd88 signaling.

Conclusions: Pericyte activation by Damps is a critical step in inflammation, recruitment of leukocytes, myofibroblast transition and progression of sterile kidney injury.

Funding: NIDDK Support

FR-PO588

Kidney CD103+ DCs Exacerbate Renal Injury through Activating CD8+ T Cells in Adriamycin Nephropathy. Qi Cao, Guoping Zheng, David C. Harris. Centre for Transplant and Renal Research, Westmead Millennium Institute, The Univ of Sydney, Sydney, NSW, Australia.

Background: CD103+ DCs, a newly described subset of DCs, display two distinct functions: induction of regulatory T cells and activation of CD8+ T cells by cross presentation of antigen. These have been demonstrated in diseases of lungs, intestine and skin. However, the characteristics and functions of CD103+ DCs in kidney remain unclear.

Methods: Adriamycin nephropathy (AN) was induced in BALB/c mice. The distribution, phenotype and in vitro function of kidney CD103+ DCs were assessed in normal and AN mice. CD103+ DCs were depleted by neutralizing CD103-saporin (SAP) antibody in AN mice to examine their role in vivo.

Results: CD103+ DCs were identified in kidney as CD45+MHC-II+/CD11c+/CD103+/F4/80+/CD11b+ cells. CD103+ DCs were distributed predominantly in cortex and normal kidney. The number of CD103+ DCs was significantly increased in kidney of AN mice compared to that of normal mice. Depletion of kidney CD103+ DCs by CD103-SAP antibody in AN mice restored renal function as evidenced by a decrease in proteinuria & serum creatinine and increase in creatinine clearance. AN mice treated with CD103-SAP antibody also had less glomerulosclerosis, tubular atrophy and interstitial expansion than did control mice. AN mice treated with CD103-SAP antibody also had less glomerulosclerosis, tubular atrophy and interstitial expansion than did AN control mice. The possible mechanisms underlying the pathogenic role of CD103+ DCs were examined. Kidney CD103+ DCs expressed high levels of Il-6 in AN mice, but not other inflammatory cytokines including Il-1beta, Il-12, Ifn-g, Tnf-alpha and Mcp-1. The co-stimulatory molecules Cd80, Cd86 and B7-H1 were highly expressed in kidney CD103+ DCs in AN mice compared to those of normal mice. Kidney CD103+ DCs displayed higher capability of cross-presenting antigen to CD8+ T cells than did CD103- DCs.

Conclusions: CD103+ DCs are present in kidney and induce renal injury in AN mice. The mechanism underlying the pathogenic role of CD103+ DCs in AN mice may relate to their ability to activate CD8+ T cells.

Funding: Government Support - Non-U.S.

FR-PO589

Characterization of Innate Lymphoid Cells in the Kidney Jan-Eric Tureg, 1 Rolf A. Stahl, 1 Ulf Panzer. 1 III. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 1ID of Molecular Immunology, MRC National Institute for Medical Research, London, United Kingdom.

Background: Innate lymphoid cells (ILC) are a recently identified cell type that is characterized by production of large amounts of the T helper cell cytokines IL-22, IL-17A, IFN-g, as well as IL-5 and IL-13 during immune responses. As cells of the innate immune system, ILC are activated independently from antigen directly by cytokine signals. So far ILC have mainly been studied in barrier organs, such as the gut, lung and skin.

Methods: We used multicolor flow cytometry to identify and characterize this novel cell type in the kidney of naive and nephritic mice (nephrotoxic nephritis) for the first time.

Results: Lineage-negative Thy1.2 IL-7R+ ILC comprised around 1% of total renal lymphocytes in naive mice. These renal ILC displayed expression of the surface markers IL-33, CD25 and Sca-1, and of the transcription factor GATA3, identifying them as IL-13 and IL-5-producing type 2 ILC (ILC2). Furthermore, we could show that repetitive injections

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
of the IL2-activating cytokine IL-33 expanded renal ILC2 in naive and nephritic mice, resulting in a shift to a protective type 2 immune response in the kidney during a mouse model of crescentic glomerulonephritis. In line with this, the course of the disease was ameliorated in IL-33 treated mice.

**Conclusions:** In conclusion, our data provide first evidence for the presence of ILC2 in the murine kidney and suggest that modulation of the renal ILC2 response can be a promising therapeutic strategy, warranting further investigation.

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

FR-PO590  
Antisense Inhibition of Renal CD40 Attenuates Adriamycin-Induced Nephropathy  
Adam F. Murlick, Aaron Donner, Karen He, Huimin Li, Gene Hung, Mark Graham, Rosanne M. Crooke. Isis Pharmaceuticals, Carlsbad, CA.

**Background:** Adriamycin nephropathy (AN) is a common experimental model of chronic kidney disease resulting in progressive podocyte depletion and tubulointerstitial inflammation, followed by the development of glomerulosclerosis. Studies have demonstrated that blockage of CD40-CD40L via administration of a CD40L antagonistic antibody was effective at mitigating AN. The promise of such inhibitors has been stymied by thromboembolic events in patients receiving CD40L antagonists, resulting in termination of their clinical development. An alternative approach would be to inhibit CD40 via antisense oligonucleotides (ASOs).

**Methods:** To test this concept, AN was established in BALB/c mice by i.v. administration of 10.5 mg/kg adriamycin. Three days afterward treatments of 25 mg/kg/wk of CD40 ASO or a mismatch control ASO were initiated. After 6 wks, kidneys were harvested and histological and transcriptional assessments of disease severity were evaluated. Additionally, kidney function was evaluated by FITC-inulin clearance following a bolus injection.

**Results:** CD40 ASO treatment resulted in an 80% reduction in renal CD40 target mRNA expression and markers of renal injury, NGAL and KIM-1, were reduced in mice receiving CD40 ASO by 65% and 50%, respectively, relative to control ASO treatment. MCP-1 and CCL5, both downstream inflammatory targets of CD40 activation, were also reduced by >50% in renal tissue from CD40 ASO treated mice. The single dose FITC-inulin test revealed a >50% reduction in residual plasma FITC-inulin after 2hrs post-injection in CD40 ASO treated mice relative to control. Glomerular pathology, as assessed in both H&E- and PAS-stained tissues, was markedly attenuated after CD40 ASO treatment.

**Conclusions:** In summary, inhibition of CD40 in established AN mitigated functional, transcriptional and histologic assessments of disease severity suggesting that antisense inhibition of CD40 could be a therapeutically attractive modality for the treatment of renal inflammation in chronic kidney disease.

**Funding:** Pharmaceutical Company Support - Isis Pharmaceuticals

FR-PO591  
Angiotensin II Receptor Blockers in Experimental Chronic Kidney Disease Model  
Sun Moon Kim, Hye-Young Kim, Han Ro, Ji Yong Jung, Yon Su Kim. 1 Internal Medicine, Chungbuk National Univ Hospital; 2 Internal Medicine, Chungbuk National University, College of Medicine; 3 Internal Medicine, Gachon Univ of Medicine and Science; 4 Internal Medicine, Seoud National Univ, College of Medicine.

**Background:** Activation of renin-angiotensin system has a detrimental effect on the progression of chronic kidney diseases (CKD). And blockade of RAS demonstrated overexpression of cmip in T cells, mice were exposed to various adenosine receptor agonists/antagonist prior to stimulation with T-cell activator. In this study, we investigated the functional consequences of cmip induction in INS T cells, we generated transgenic mice selectively overexpressing cmip in mature lymphocytes.

**Methods:** Lck-cmip transgenic (Tg) mice were constructed by a targeting system based on the constitutive expression of human cmip gene under control of Lck promoter, resulting in the generation of a new mouse model that overexpression of cmip in T cells, mice were exposed to various adenosine receptor agonists/antagonist prior to stimulation with T-cell activator. In this study, we investigated the functional consequences of cmip induction in INS T cells, we generated transgenic mice selectively overexpressing cmip in mature lymphocytes.

**Results:** Tg mice developed an altered TL phenotype with an increase of naive T cell subpopulation (CD4+ or CD8+CD44hiCD26lo), whereas effector (CD4+ or CD8+CD44hiCD26hi) memory T cell subpopulations (CD4+ or CD8+CD44hiCD26lo) were decreased, as compared with control littermates (CL).

**Conclusions:** Following CD3/CD28 (1 μg/ml each) activation, Tg T cells displayed lower proliferation and decreased expression of IL-15 and IL-15Rα chains (IL-15Rα), whereas expression of IL-15Rβ was increased. Dendritic cells (DCs) and the implication of this effect on CTL proliferation.

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

FR-PO594  
Interleukin-15-Dependent Cytotoxic T-Cell Proliferation by Adenosine  
Amos Doudevanyi,1 Hadar Einii,2 Moshe Zlotnik. 1 Clinical Biochemistry and Pharmacology, Soroka Medical Center and Ben-Gurion Univ of the Negev, Beer-Sheva, Israel; 2 Nephrology, Soroka Medical Center, Beer-Sheva, Israel.

**Background:** Dendritic cells (DCs) regulate the immune response through production of various cytokines and signaling molecules, among which is IL-15, an important NK and cytotoxic T-cell (CTL) activator and survival factor. At the site of immune reaction, adenosine is produced from ATP by CD39 and CD73, ecto-enzymes expressed on regulatory T-cells (Treg). The aim of this present study was to examine the effect of adenosine on IL-15 production by DCs and the implication of this effect on CTL proliferation.

**Methods:** Bone marrow derived DCs (BMDCs) were isolated from MCR mice. BMDCs were exposed to various adenosine receptor agonists/antagonist prior to stimulation with LPS and interferon-γ (IFN-γ). Levels of cAMP, IL-15 and IL-15 receptor α chain (IL-15Rα) were measured using QPCR and/or ELISA. To assess the effect of adenosine on DC proliferation, BMDCs were gamma-irradiated and co-cultured with CD8+ T cells, in the presence or absence of adenosine.

**Results:** Stimulation of BMDCs with LPS and IFN-γ increased IL-15 and IL-15Rα levels. The effect of stimulation of BMDCs with adenosine significantly reduced IL-15/IL-15Rα mRNA and protein levels. This down-regulatory effect was blocked by the combination of ZM 241385, an A2a, A3, and MR stimulation, and MRS1754, an A2a antagonist, while addition of only one of them separately yielded a partial inhibitory effect. Treatment of...
BMDCs with adenosine receptor agonists increased cAMP levels, and di-butril-cAMP, a stable cAMP analog, effectively reduced IL-15Rα levels. Finally, treatment of BMDCs with adenosine, before stimulation and co-culture, significantly reduced PBMC-dependent CTLL-2 proliferation.

**Conclusions:** Our data indicate that adenosine acting through A2aR and A2bR by elevation of cAMP suppresses IL-15 and IL-15Rα levels in activated DCs and restrains CTL proliferation. These findings can set a pharmacological base for CTL dependent pathologies such as graft rejection treatment.

**Funding:** Private Foundation Support

FR-PO595

**Delayed Treatment with Adenosine 2a Receptor Agonist Protects Kidneys from Long-Term Fibrosis**

**Isaiah Vincent,1 Diane L. Rosin,2 Li Li,3 Liping Huang,1 Hong Ye,1 Mark D. Okusa.1**

DCs: myeloid DC1 (mDC1), mDC2 and plasmacytoid DC (pDC). The CD14++CD16+ monocytes/macrophages and CD11b+CD11c-Ly6g+ monocytes/macrophages and CD14++CD16-, CD14++CD16+, and CD14+CD16++; and the subtypes of circulating monocytes and dendritic cells consist of 3 subpopulations: monocyte subtypes: A Pro-Inflammation has subsided, reduced osteoprotegerin (OPG). Sclerostin was measured with the TECO ELISA (TECO medical, Sissach, CH).

**Results:** The mean age of our population was 71±14 (44% of men). Mean sclerostin concentration was 1500±710 pg/mL. In univariate regression analysis, we found a significant positive relationship between sclerostin and age, height, dialysis vintage, albumin, troponin T and OPG. A significant negative relationship was found with PTH, CTX, PINP and b-ALP. In multivariate analysis, age, height, phosphorus, albumin, troponin T, PTH and b-ALP were still associated with sclerostin. Patients in the lower tertile of sclerostin were younger, smaller and had a lower dialysis vintage than those in the third tertile. They had lower levels of albumin, troponin, OPG and higher levels of PTH, CTX, TRAP-5b and b-ALP.

**Conclusions:** We confirm that the concentrations of sclerostin are high in hemodialysis patients. We did not find any association between sclerostin and mortality. Like others, we found an inverse association between sclerostin and PTH or b-ALP levels. Interaction between sclerostin and albumin or troponin levels would deserve additional studies.

**Funding:** NIDDK Support

FR-PO596

**A Pro-Inflammatory Change in Numbers of Monocyte and Dendritic Cell Subtypes Occurs Early in the Course of CKD**

**Eva Schepers, Griet LrL Glorieux, Nathalie Neirynck, Annemieke Dhondt, Raymond C. Vanholder. Internal Medicine, Nephrology, Univ Hospital Ghent, Ghent, Belgium.**

**Background:** Antigen-presenting cells play an important role in chronic inflammation associated with accelerated cardiovascular disease and immune dysfunction. Both monocytes and dendritic cells consist of 3 subpopulations: monocyte subtypes: CD14++CD16+, CD14++CD16+, and CD14+CD16++; and the subtypes of circulating DCs: myeloid DC1 (mDC1), mDC2 and plasmacytoid DC (pDC). The CD14++CD16+ monocytes are described as pro-inflammatory and for DCs the mDCs have antimicrobial activity while pDCs are mediators of antiviral immunity. No study up till now evaluated changes of these cell types in all stages of CKD.

**Methods:** This study for the first time describes the proportional distribution of monocytes and circulating DC populations in 198 patients throughout the consecutive stages of CKD and/or on renal replacement therapy in comparison to healthy controls. Flow cytometric analysis on whole blood was performed. Monocytes were identified based on the pan-monocytic CD14 and the subpopulations were distinguished based on CD14- CD16+ CD14+ CD16- CD14++ CD16+ CD14++ CD16+ For statistical analysis, an enumeration kit was applied. Both absolute number and percentage of the total leukocyte population were evaluated.

**Results:** Although no difference in total monocytes was observed vs controls, a significant increase of CD14++CD16+ monocytes was found from CKD stage 3 on, which rises further up to a 3-fold rise in HD patients. Only in HD patients a significant decrease in number and percentage of CD14- CD16- cells combined with an increase in CD14++CD16+ monocytes was found. In PD patients no changes were observed. The DCs were decreased, by more than 25% from CKD1 on which was mainly due to a decrease in pDC. The pDC group was the only population in which also the number and percentage mDC1 was decreased. An inverse correlation could be found between the CD14++CD16+ and the pDCs throughout the consecutive stages.

**Conclusions:** An increase in CD14++CD16+ monocytes and a decrease in the pDC suggest a pro-inflammatory role for these cells during progression of CKD. This points to the importance of studying these leukocyte subtypes more in depth in different stages of CKD.

FR-PO597

**Determinants of Sclerostin Concentration in Hemodialysis Patients**

**Pier Delanaye, Jean-marie H. Krzesinski, Xavier Warling, Nicole Simone Smelten, Etienne Cavalier. Nephrology-Dialysis, Univ of Liege, Belgium.**

**Background:** Sclerostin is an inhibitor of bone formation produced by osteocytes. A recent study showed that sclerostin was negatively associated with parathormone (PTH) levels and better predicted high bone turnover. Little is known about the other physiologic determinants.

**Methods:** Among the hemodialysis patients in 3 centers in the area of Liège, Belgium (n=212), we analyzed the results from 165 patients with vascular calcification score (Kaupilla method). Sclerostin was available in 164 patients. The following clinical data were considered: age, gender, height, weight, dialysis vintage, hypertension status, diabetes, smoking and previous cardiovascular disease. The following laboratory data were considered: calcium, phosphorus, PTH, 25-OH vitamin D, albumin, troponin T and CRP. Different bone biomarkers were measured: bone-specific alkaline phosphatase(b-ALP), C-terminal telopeptide of collagen type I (CTX), intact amino-terminal propeptide of type I procollagen (PINP), tartrate-resistant acid phosphatase 5b(TRAP-5b) and osteoprotegerin(OPG). Sclerostin was measured with the TECO ELISA (TECO medical, Sissach, CH).

**Results:** The mean age of our population was 71±14 (44% of men). Mean sclerostin concentration was 1500±710 pg/mL. In univariate regression analysis, we found a significant positive relationship between sclerostin and age, height, dialysis vintage, albumin, troponin T and OPG. A significant negative relationship was found with PTH, CTX, PINP and b-ALP. In multivariate analysis, age, height, phosphorus, albumin, troponin T, PTH and b-ALP were still associated with sclerostin. Patients in the lower tertile of sclerostin were younger, smaller and had a lower dialysis vintage than those in the third tertile. They had lower levels of albumin, troponin, OPG and higher levels of PTH, CTX, TRAP-5b and b-ALP.

**Conclusions:** We confirm that the concentrations of sclerostin are high in hemodialysis patients. We did not find any association between sclerostin and mortality. Like others, we found an inverse association between sclerostin and PTH or b-ALP levels. Interaction between sclerostin and albumin or troponin levels would deserve additional studies.

**Funding:** NIDDK Support

FR-PO598

**Diphosphorylated-Uncarboxylated Matrix Gla Protein Concentration Is Predictive of Vitamin K Status and Correlated with Vascular Calcification in Hemodialysis Patients**

**Pier Delanaye, Jean-marie H. Krzesinski, Xavier Warling, Nicole Simone Smelten, Etienne Cavalier. Nephrology-Dialysis, Univ of Liege, Belgium.**

**Background:** Matrix Gla protein (MGP) is a potent local inhibitor of vascular calcification. MGP must benefit from a vitamin K-dependent carboxylation. The dosage of the inactive form (uncarboxylated and diphosphorylated: dp-ucMGP) could reflect the status of vitamin K. dp-ucMGP could also be correlated with vascular calcification.

**Methods:** Among the hemodialysis patients in 3 dialysis centers in Liège, Belgium (n=212), we analyzed the results from 165 patients with vascular calcification score (Kaupilla method). 5 patients do not have MGP concentrations measured. We compared 23 patients treated with anti-vitamin K and 137 patients without this therapy. The following clinical data were considered: age, gender, BMI, dialysis vintage, hypertension status, diabetes, smoking and previous cardiovascular disease. Following laboratory data were utilized: calcium, phosphorus, PTH, 25-OH vitamin D, bone alkaline phosphatase, albumin, and CRP. We did not find any association between sclerostin and mortality. Like others, we found an inverse association between sclerostin and PTH or b-ALP levels. Interaction between sclerostin and albumin or troponin levels would deserve additional studies.

**Results:** No difference was observed between patients treated or not with anti-vitamin K regarding the clinical characteristics. We observed significant differences for dp-ucMGP (5549±2230 pM vs. 2217±1134 pM, p <0.0001) and albumin (40 mg / L [38, 41] versus 42 mg / L [38, 41] p = 0.048). In 137 patients without anti-vitamin K therapy, a slight but significant correlation was found between dp-ucMGP levels and the calcium score (r=0.17, p=0.04). Considering the tertiles of dp-ucMGP (1647 et 2404 pM), subjects in the high tertile had a significantly higher vascular calcification score than those in tertile 1: 9 ± 6 versus 11 ± 6 (p=0.0414). Tertile 3 comprised of more men whom had a higher BMI and lower albumin levels.

**Conclusions:** We confirm that the concentration of dp-ucMGP is higher in dialysis patients treated with anti-vitamin K. This confirms the interest of the dp-ucMGP as a marker of vitamin K status. We found an association between the concentration of dp-ucMGP and the level of vascular calcifications.

**Funding:** National Heart, Lung, and Blood Institute, Bethesda, MD.

FR-PO599

**Sclerostin and DKK-1 Levels across CKD Stages**

**Geert J. Behets,1 Liesbeth Viaene,2 Frank A. Blocki,3 Patrick C. D’Haese,1 Pieter Evenepoel.2**

**Background:** Causal pathways of bone formation. In dialysis patients, serum sclerostin levels are positively correlated with mineral bone density and bone volume, and negatively with bone turnover. Methods: In a cross-sectional, observational study we evaluated 169 predialysis (CKD stage 1-5), 98 hemodialysis (HD), 62 peritoneal dialysis (PD) and 78 apparently healthy subjects (HC). Serum sclerostin and DKK-1 were measured by ELISA. Other parameters included 1-84 PTH and FGF-23.
FR-PO600

Effects of a Magnesium (Mg) Based Phosphate (P) Binder on Bone Metabolism in a Rat Model of Chronic Renal Failure (CRF). Geert J. Behets, Ellen Neven, Kristina Gundlach, Sonja Steppan, Patrick C. D’Haese. University of Antwerp, Antwerp, Belgium; Fresenius Medical Care, Bad Homburg, Germany.

Background: We have previously shown that the Ca-Mg based P-binder Osvaren (CaMg) at doses of 75 and 150 mg/kg/day effectively reduces serum P levels and vascular calcification (VC) in adenine-induced CRF rats. However, due to the severe CRF and resulting hyperparathyroid bone (HPT) disease, this model is not suitable to measure dynamic bone parameters. In the current study a less severe CRF model (5/6th Nx) was used to evaluate the possible effect of CaMg on bone.

Methods: Six groups of male Wistar rats (N=12 each) underwent a 5/6th Nx. Three groups received a normal P diet (0.8%; NP); and 3 groups a high P (1.03%; HP) diet. This approach was used to differentiate between possible bone effects resulting from P-deficiency vs. a direct Mg-effect. CaMg (185 and 375 mg/kg/day) was administered orally for 8 weeks.

Results: Serum creatinine levels indicated a mild CRF developed 2 weeks after 5/6th Nx (0.48±0.16 vs 1.17±0.33 mg/dl, p<0.05), which remained stable throughout the treatment period (1.51±0.90 mg/dl after 8 weeks). Serum total and ionized Ca levels and serum P levels did not differ between groups. PTH levels were ± 4.5 times higher at week 8 compared to baseline (p<0.05) pointing to a mild HPT. After 8 weeks, the only NP 375 group showed a significant decrease in urinary P excretion (11.1±2.7 vs 52.6±6.7 mg/24h, p<0.05), while it remained stable in the other groups. Bone and serum Mg levels were not different between groups. The NP 375 group showed a (statistically non-significant) increase in osteoid area (OA) versus vehicle (2.80±1.76 vs 0.76±0.030%, p=0.28). In the HP groups, no differences between treatments were found. Osteoblast and osteoclast perimeters as well as mineralization parameters (bone formation rate, mineralization lag time, adjusted apposition rate) showed no differences between groups.

Conclusions: In this study, CaMg did not show any direct effect on bone metabolism. The observed slight increase in OA in the NP 375 group is due to a relative P depletion rather than a direct effect of Mg.

Funding: Pharmaceutical Company Support - Fresenius Medical Care, Germany

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

Underline represents presenting author/disclosure.

502A

FR-PO601

PTH, FGF-23, Sclerostin and Bone Mineral Density in End-Stage Renal Disease Liesbeth Vaene, Kathleen Claes, Pieter Evenepoel. Nephrology, Univ Hospitals, Leuven, Belgium.

Background: PTH, and the osteocyte derived hormones FGF23 and sclerostin all play an important role in bone biology. Circling levels of these hormones increase in chronic kidney disease to reach levels that are many folds higher in patients with end-stage renal disease (ESRD) as compared to healthy controls. The relationship between PTH, FGF23, and sclerostin levels and bone mineral density (BMD) in ESRD patients is incompletely understood.

Methods: We performed a cross-sectional study in 268 patients (65% M; age 52±13 years) with ESRD referred for renal transplantation. Parameters of mineral metabolism, including serum bone biomarkers (PTH, FGF23, Klotho), serum sclerostin (Teconcal), serum P, Ca, Mg, and calcitriol were determined prior to engraftment and all patients underwent dual energy X-ray absorptiometry (DEXA) at lumbar spine (LS), total hip (TH) and forearm (1/3R) within 2 weeks after the transplant procedure. DEXA results are expressed as BMD (g/cm²) and T-scores. Results: Serum levels of bone biomarker PTH (130 [67-2377] pg/ml), FGF23 (1853 [554-5184] pg/ml), and sclerostin (1.15 [0.79-1.51] ng/ml) were high and as expected in ESRD and did show significant inter-correlations. T-scores less than -2.5 were observed in 19, 8, and 29% at LS, TH and forearm (1/3R) respectively. In univariate analysis, biomarker PTH (direct), and sclerostin (directly correlated with BMD at LS (p<0.05), TH (p<0.05) and 1/3R (p=0.06, FGF23 only). Adjustment for classical BMD determinants (age, gender and vitamin D status) and dialysis vintage only attenuated associations for sclerostin and PTH. Regarding FGF23, significance was lost at TH but reached at 1/3R.

Conclusions: High sclerostin and FGF23 levels, as opposed to PTH, associate directly with BMD in ESRD. Whether sclerostin and FGF23 are part of a homeostatic feedback loop aimed at preventing excessive mineralization or whether these hormones merely reflect high osteocyte number remains to be clarified.

Funding: Pharmaceutical Company Support - Daizn Inc.

FR-PO602

The Bone-Vascular Axis and Inflammation in End-Stage Renal Disease Liesbeth Vaene, Geert J. Behets, Sam Heye, Kathelen Claes, Diethard Monbaliu, Jacques Pirenne, Patrick C. D’Haese, Pieter Evenepoel. Nephrology, Univ Hospitals, Belgium; Pathophysiology, Univ of Antwerp, Belgium; Radiology, Univ Hospitals, Belgium; Abdominal Transplantation, KU Leuven, Belgium.

Background: Vascular calcification is a common complication of end stage renal disease (ESRD) and is predictive of subsequent cardiovascular disease and mortality. Mounting evidence linking bone disorders with vascular calcification has contributed to the development of the concept of the bone-vascular axis. Inflammation is involved in the pathogenesis of both disorders. The aim of the present study was to evaluate the relationship between aortic calcification (AC), inflammation, and bone disturbances in patients with ESRD.

Methods: Parameters of inflammation and mineral metabolism, AC and bone histomorphometry were assessed in 81 ESRD patients (55±13 year, 68% male) referred for renal transplantation. Static bone histomorphometry parameters such as bone area, and osteoblast- and osteoclast-covered perimeter to total perimeter were determined on transiliac bone biopsies performed during the transplant procedure. AC was quantified on lateral lumbar X-rays using the Kaupilla method.

Results: AC, low bone turnover and low bone volume was observed in 60, 37, and 21 % of patients. The association between AC and bone histomorphometric parameters are shown in Figure 1.

Inflammatory markers were found to be independently associated with aortic calcification (hsIL-6) and low bone volume (TNFα). Low bone volume was a significant risk factor for aortic calcification, independent of age, diabetes, and inflammation.

Conclusions: Low bone volume, as opposed to turnover, is a significant risk factor for aortic calcification, independent of traditional risk factors. Our data underscore the role of inflammation in the bone-vascular axis in CKD.

Funding: Pharmaceutical Company Support - Fresenius Medical Care, Germany

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

Underline represents presenting author/disclosure.

502A
Diabetics had significantly lower soluble Klotho levels. In multivariate analysis, PCS remained significantly correlated with soluble Klotho levels, independent of age and eGFR and explaining 13% of its variation.

Conclusions: Low eGFR, high age and high p-cresyl sulphate levels are independently associated with low soluble Klotho levels.

FR-PO604
Sclerostin: A New Player in the CKD Vascular Disease Solenne Pelletier,1 Cyrille B. Confavreux,2 Julie Haeasebaert,3 Fujim Guebre-egziabher,2 Justine Bacchetta,2 Marie-christine Carlier,4 Maurice Laville,5 Roland Chapurat,5 Marie-helene Lafage-proust,5 Gerard M. London,8 Denis Fouque.1

Background: Several proteins that inhibit mineralization of bone, such as DMP1 and E11, have been identified in CKD patients. Sclerostin is mainly produced by osteocytes and plays a key role in the inhibition of bone formation. Whether the expression of sclerostin is increased in CKD is unknown.

Conclusions: Serum sclerostin is increased in HD. We studied relationships between sclerostin and diabetes, hypertension, age, gender, BMI, eGFR, Alb-creatinine, sodium-potassium, sodium-creatinine, carbonate, phosphate, calcium-phosphate, 25OHD, 25OHD3, 1,25OHD, vitamin D, vitamin D3, vitamin D2, ANP, BNP, N-terminal pro-BNP, cTnI, TSH, PTH, FGF23, 17-OH-P, 17-ketosteroids, 11-deoxycortisol, 11-deoxycorticosterone, aldosterone, renin, HOMA, C-reactive protein, a2-macroglobulin, PAI-1, plasminogen activator inhibitor-1, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), carboxyterminal propeptide of type I procollagen (P1NP), procollagen type I C-terminal propeptide (PⅠCP), procollagen type II C-terminal propeptide (PⅡCP), procollagen type III N-terminal propeptide (PⅢNP), osteocalcin, serum fetuin A, intact parathyroid hormone (iPTH), and fibroblast growth factor 23 (FGF23) in HD patients. We evaluated relationships between sclerostin and classical cardiovascular risk factors, renal function, nutritional, and mineral markers.

Methods: 102 HD patients (mean age, 66.4 ± 8.9 years) and 30 healthy age-, sex-, and menopausal-status-matched individuals were examined between April and June 2011. The HD patients underwent treatment based on the treatments guideline for patients with CKD-mineral bone disorders.

Results: In the HD patients, the mean intact PTH and phosphate levels were 190 ± 185 pg/mL and 5.2 ± 1.4 mg/dL, respectively. The sclerostin levels of the HD patients were extremely high and varied widely compared with those of controls (1647 ± 778 vs. 12.6 ± 47.8 ng/mL, P < 0.0001). A multivariate logistic regression analysis of the data showed that the serum sclerostin levels were significantly associated with male gender (β = 0.679, P = 0.016, Odds Ratio [OR] = 3.89), phosphate levels (β = -0.484, P = 0.009, OR = 1.62), duration of HD (β = -0.078, P = 0.047, OR = 1.08), and use of cinacalcet hydrochloride (β = -0.035, P = 0.018, OR = 0.24). Serum sclerostin levels were negatively correlated with serum levels of bone-specific alkaline phosphatase (r = -0.254, P = 0.010) and tetratrate-resistant acid phosphatase isoform type 5b (r = -0.229, P = 0.021).

Conclusions: Serum phosphate levels may influence serum sclerostin levels in HD patients without severe hyperparathyroidism.

FR-PO606
Sequential Skeletal, PTH, FGF23 and Sclerostin Changes in Rats with Renal Failure and Secondary Hyperparathyroidism Cheryl P. Sanchez, Subburaman Mohan,1,2 Pediatrics, Loma Linda Univ, Loma Linda, CA; 2Medicine, Loma Linda Univ, Loma Linda, CA.

Background: Studies have shown low in cortical and trabecular bone in chronic kidney disease.

Methods: To determine the time course changes in PTH, FGF23, sclerostin and skeletal abnormalities, 39 male rats, underwent 5/6 nephrectomy (Nx=27) or sham Nx (Control, n=12). Nx rats were fed standard rodent diet (Nx-C, N=13), or high phosphate diet (Nx-Phos, N=14). Femur and lumbar bone mineral density (BMD) were obtained at baseline, 12 and 25 days post-Nx, and micro-CT was obtained 25 days post-Nx.

Results: There were no differences in femur length or gain in body length. Serum creatinine increased after Nx. After 12 days post-Nx, iPTH and FGF23 levels were higher in Nx-Phos, 1232±563 pg/mL and 0.35±0.33 ng/mL, compared to Nx-C, 771±155 pg/mL and 0.12±0.08 ng/mL, and Control, 464±126 pg/mL and 0.10±0.09 ng/mL, p<0.001. Serum sclerostin levels did not change. Lumbar BMD declined in Nx-Phos 12 days post-Nx, 0.40±0.07% compared to Nx-C and Control. 0.11±0.01% and 0.11±0.01 g/cm², p<0.05. The percent gain in lumbar BMD at 25 days post-Nx was lower in Nx-Phos, 79%, compared to Nx-C and Control, 99% and 112%, p<0.02. Femur BMD did not change between groups. Cortical (femur) BV/TV by micro-CT was lower in Nx-Phos, 0.64±0.05% compared to Nx-C and Control, 0.53±0.02% and 0.54±0.02%, p<0.033. Trabecular (lumbar) BV/TV declined by 20% in Nx-Phos compared to Nx-C and Control, p<0.01, likely due to lower trabecular number and increase in trabecular spacing, p<0.001. There was a 46% decrease in connectivity density and an increase in structural model index in Nx-Phos, 3.9±1.2, compared to Nx-C and Control, 2.0±1.0, p<0.0001, suggesting more rodlike trabecular bone appearance. iPTH and FGF23 negatively correlated with trabecular and cortical BV/TV, R = 0.5, p<0.01, iPTH increased with FGF23, R = 0.8, p<0.01 compared to micro-CT, BMD did not detect alterations in cortical bone.

Conclusions: The findings show that changes in trabecular bone occur early in kidney failure accompanied by an increase in iPTH and FGF23.

FR-PO607
The Role of DMP-1, E11 and Sclerostin on High Phosphorus Induced Vascular Calcification and Early Intervention by Sodium Thiosulfate in Remnant Kidney Rats Yi Yu, Dept of Blood Purification, Dongfang Hospital of Fujian province, Fuzhou, Fujian, China.

Background: To observe the expression of DMP-1, E11 and Sclerostin involved in vascular calcification in remnant kidney rats with hyperphosphatemia, and the early effect of sodium thiosulfate (STS) on the progression of vascular calcification.

Methods: Sprague Dawley rats (n=35) underwent 5/6 nephrectomy (n=21) or sham operation (n=14). They were fed with diet containing high phosphorus (HP) [phosphate(P):2.2%, calcium (Ca) 1.6%] or normal phosphorus (NP) [P:0.9%], Ca (1.2%)] for 16 weeks, then divided into 5 groups: (1) sham operation rats receiving NP diet (SNP, n=7), (2) sham operation rats receiving HP diet (SNP, n=7), (3) remnant kidney rats receiving HP diet (SNP, n=7), (4) remnant kidney rats receiving HP diet with STS (SNP+STS, n=7), (5) remnant kidney rats receiving HP diet with STS (THP, n=7). Rats in the THP group were intraperitoneally injected with STS 0.4 g/ml/kg three times a week for 16 weeks. Vascular calcification was confirmed by Von kossa staining. DMP1, E11 and Sclerostin mRNA were determined by RTPCR. E11 expression in aorta were determined by immunohistochemistry or Western blot.

Results: After 16 weeks, Scr, P, iPTH and uric protein were significantly higher in NHP than those in SNP group (P<0.05). With the treatment of STS, THP rats showed a marked decrease in those (P<0.05) compared with NHP group. Significant vascular calcification was found in NHP group while a little in SNP group and none in STS group. The aorta expression of DMP1, E11 and Sclerostin mRNA were higher in NHP than in SNP group (P<0.05), their expression decreased in THP compared with NHP group (P<0.01). The aorta expression of DMP1, E11 and Sclerostin mRNA were higher in NHP than in SNP group (P<0.05), their expression decreased in THP compared with NHP group (P<0.01).

Conclusions: The increase of expression of DMP1, E11 and Sclerostin in aorta showed that vascular calcification involves changes in VSMC transition into osteocyte-like phenotype. Sodium thiosulfate may delay the progression of vascular calcification by down-regulation of DMP1, E11 and Sclerostin.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO608
Effect of Core-Binding Factor α1 Gene Silenced by siRNA on the Calcification of Vascular Smooth Muscle Cells Induced by High Phosphate
Yi Yu. Dept of Blood Purification, Dongfang Hospital of Fujian Province, Fuzhou, Fujian, China.
Background: To investigate the effect of core-binding factor α1 (Cbfα1-1) gene silenced by siRNA on the osteogenic differentiation and calcification of vascular smooth muscle cells (VSMC) induced by high phosphate in vitro.
Methods: VSMC were cultured in vitro and passage 3 to 8 were used for the experiment. Four of the Cbfα1-1 siRNA were designed and synthesized. VSMC were transfected by using cationic lipid vectors (Lipofectamine 2000). We optimized transfection condition by the FAM fluorescent labeling-siRNA and screened effective siRNA sequence by RT-PCR. VSMC were transfected with effective siRNA sequence. VSMC were divided into four groups: (1) normal phosphate group (Pi 1.3 mmol/L); (2) high phosphate group (Pi 2.6 mmol/L); (3) siRNA transfection group: high phosphate (2.6 mmol/L) + Cbfα1-1 siRNA; (4) negative transfection control group: high phosphate (2.6 mmol/L) + negative control siRNA. Cbfα1-1 and osteopontin (OPN) mRNA and protein expression were detected by RT-PCR and Western Blot. Calcium deposition was visualized by Alizarin stain method.
Results: The transfection efficiency was about 55% at the condition of Cbfα1-1 siRNA with concentration of 100 nmol/L and 8 μg/well. Cbfα1-1 siRNA592 was chosen as effective sequence with suppression ratio up to 81.8%. 24h and 48h after transfection, the expression of Cbfα1-1 mRNA in siRNA transfection group was significantly lower than that in high phosphate group and negative transfection control group (P<0.01). 48h and 72h after transfection, the expression of Cbfα1-1 protein in siRNA transfection group was significantly lower than that in high phosphate group and negative transfection control group (P<0.01). While Cbfα1-1 gene was silenced by siRNA, in siRNA transfection group, the mRNA and protein expression of OPN were significantly declined (P<0.05), and the calcium deposition in cell layers was reduced.
Conclusions: Cbfα1-1 siRNA can effectively inhibit the expression of Cbfα1-1 mRNA and protein in VSMC, thus suppress transformation of VSMC into osteoblast-like cells and calcification induced by high phosphate. Cbfα1-1 may be a potential therapeutic target in vascular calcification of chronic kidney disease.
Funding: Government Support - Non-U.S.

FR-PO609
The Combined Therapy with Calcitriol and a Calcimimetic Agent, R568, Ameliorates Phosphorus-Induced Calcification with Altered Expression of SIRT1 and ALP in Human Vascular Smooth Muscle Cells
Masanori Tokunaga1, Shunsuke Yamada1, Tomoe Fujino1, Kazuhiko Tsuruya1, Takanari Kitazono2, Hiroaki Ooboshi1. 1Dept of Internal Medicine, Fukushima Dental College, Fukushima, Japan; 2Department of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan.
Background: Vascular calcification is life-threatening pathophysiological abnormality, especially in chronic kidney disease (CKD)-mineral bone disorder (MBD). The main contribution factor for vascular calcification is phosphate (P), but it is difficult to control P retention completely in CKD. Therefore, we examined direct effects of calcitriol and/or a calcimimetic agent, R568, both of which are effective for treatment of secondary P retention completely in CKD. Therefore, we examined direct effects of calcitriol and/or a calcimimetic agent, R568.
Methods: Human VSMCs were cultured in medium containing 2.9 mM P and treated with 10−9~10−6 M calcitriol and/or 10−9~10−5 M R568 in various combinations for two weeks. Precipitated calcium contents and expression of various factors which is involved in calcification were evaluated.
Results: Only 10−9 and 10−8 M calcitriol and 10−8 M R568 in monotherapy significantly inhibited calcification by 10−20% (P<0.01), but the treatment of calcitriol combined with 10−8 M R568 suppressed calcification to about 50% of monotherapy at all concentration. Calcitriol increased the mRNA expression of mammalian sirtuin 1 (SIRT1) which prevents vascular calcification, as well as alkaline phosphatase (ALP) which promote vascular calcification dose-dependently. Both increases became significant at 10−9 and 10−8 M (P<0.01). R568 significantly inhibited ALP mRNA expression at all concentration (P<0.01). The combination therapy with calcitriol and 10−8 M R568 decreased ALP mRNA expression with similar increase of the mRNA expression of SIRT1 to calcitriol monotherapy.
Conclusions: In conclusion, the combination therapy with calcitriol and a calcimimetic agent, R568, can directly ameliorate P-induced vascular calcification more effectively than monotherapy with calcitriol or R568, by reducing ALP expression and increasing SIRT1 expression, respectively.
Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO610
Circulating Soluble Receptor for Advanced Glycation End Product (sRAGE) Levels but Not s100A12 (EN-RAGE) Are Associated with Vascular Calcification in Patients on Hemodialysis
Ji Yong Jung1, Han Ro1, Chungsik Lee3, Sun Moon Kim3, Ae Jin Kim1, Hyung Soo Kim1, Jae Hyung Chang1, Hyun Hee Lee1, Wooyoung Chung1. 1Div of Nephrology, Dept of Internal Medicine, Gachon Univ of Gil Medical Center, Incheon, Korea; 2Div of Nephrology, Dept of Internal Medicine, Chosun University College of Medicine, Jeonju; 3Div of Nephrology, Dept of Internal Medicine, Changbuk National Univ Hospital, Cheonju, Korea.
Background: The receptor for advanced glycation end products (RAGE) has emerged as a central modulator of vascular inflammation and athero-sclerosis. Soluble RAGE (sRAGE) and extracellular RAGE-binding protein S100A12 (EN-RAGE) are anti-inflammatory and pro-inflammatory ligands of RAGE, respectively, in the development of vascular complications. We determined the levels of sRAGE and EN-RAGE in hemodialysis (HD) patients and evaluated their relationship with vascular calcification.
Methods: We performed a cross-sectional study with 199 hemodialysis patients. Plain X-ray images of the lateral lumbar spine from all subjects were studied to calculate semiquantitative vascular calcification scores (VCSs), as described by Kauppila. Commercially available ELISA kits were used to quantify the serum concentration of sRAGE and EN-RAGE.
Results: The patients were 57.1 ± 13.7 years of age; 54.3% were male, and 49.2% were diabetic, and 36.2% had a history of cardiovascular disease. Kauppila scores revealed 40 patients (20.1%) with a high VCS (>7). In a univariate analysis, serum sRAGE was negatively associated with high VCS (log sRAGE, P = 0.035), whereas EN-RAGE showed a positive tendency (log EN-RAGE, P = 0.431). Even after adjustments for confounding risk factors, sRAGE was independently associated with a high VCS (log sRAGE, OR = 0.491, 95% CI: 0.262 – 0.918, P = 0.026).
Conclusions: This study demonstrated that the circulating sRAGE level was inversely associated with VCS in HD patients independent of the EN-RAGE level and the severity of systemic inflammation. Longitudinal observations and intervention studies are warranted to establish whether this link is causal.
Funding: Private Foundation Support

FR-PO611
Inorganic Pyrophosphate and Aortic Valve Calcification
Swathra Rathn1, Ajit Priyadarvajan Yoganathan2, Warin Charles O'Neill1. 1School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA; 2The Wallace H. Coulter Dept of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA; 3Renal Div, Emory Univ School of Medicine, Atlanta, GA.
Background: Aortic valve (AV) calcification is common in chronic kidney disease but the underlying molecular mechanisms are not well understood. An ex vivo model of AV calcification was developed and the role of orthophosphate and inorganic pyrophosphate (PPI), factors well known to influence vascular calcification, was investigated.
Methods: Freshly obtained porcine AV leaflets were cultured for up to 8 days in DMEM medium containing varying concentrations of phosphate up to 3.8mM with and without inorganic pyrophosphate (IP, an enzyme that specifically hydrolyzes PPI).
Results: Cell viability and apoptosis were preserved as shown by MTT and Verhoff-Vangieson elastin stains. Calcification, measured as the incorporation of 45Ca in the valves and confirmed with alizarin red staining, occurred only in the presence of IP and added phosphate and was prevented by etidronate, a non-hydrolyzable analog of PPI. Calcification was also inhibited both with the fibrovascular and ventricularis sides of the leaflets. There was no further calcification when alkaline phosphate, a non-selective phosphatease, was added, indicating that other phosphorylated compounds were not inhibiting calcification. Leaflets released PPI into the medium, which was enhanced by MLS39949, a specific inhibitor of tissue non-specific alkaline phosphatase (TNAP). Leaflets synthesized 3PP from extracellular [32P] ATP, which was significantly decreased in the presence of β-methylene-ATP, inhibitor of ectonucleotide pyrophosphorylase phosphodiesterase, (ENPP1).
Conclusions: An ex vivo model of aortic valve calcification was successfully developed. ENPP1 inhibitors is a key endogenous inhibitor of calcification in this model and its levels appear to be controlled through synthesis by ENPP1 and hydrolysis by TNAP. This suggests that preventive therapy could be based on non-hydrolyzable PPI analogs such as bisphosphonates or on agents that enhance ENPP1 activity or inhibit TNAP action.
Funding: Private Foundation Support

FR-PO612
L-lysine Ameliorates Vascular Calcification in Adenine-Induced Uremic Rats
Akhiro Shimomura1, Isao Matsui1, Takayuki Hamano2, Kazunori Inoue1, Yassuo Kusunoki1, Chikako Nakano1, Yoshiharu Obi1, Yoshihara Tsukahara2, Hiromi Rakugi1, Yoshitaka Isaka1, Chikako Takahashi1, Hiroshi Hatakeyama1, Hiroyuki Oka3, Yoshinori Furuichi1, Atsushi Tsukiyama1, Hiromi Sato1. 1Dept of Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Osaka, Osaka, Japan; 2Dept of Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Osaka, Osaka, Japan.
Background: Vascular calcification (VC) is one of the major problems in CKD. Although several studies in both animals and humans have tried to reduce the extent of VC, satisfactory therapies have not been established. Therefore, it is important to develop novel strategies. In 2006, Price et al. reported that low protein (LP) diet exacerbates VC in

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

504A
were not measured.

Results: At age 18 weeks, groups LP had no VC, whereas groups Ade and Gly had comparable levels of severe VC. L-Lys supplementation almost completely ameliorated VC. Physical parameters and renal functions were not different among groups Ade, Gly, and Lys. Dietary L-Lys strongly suppressed plasma level of iPTH in adenine-induced uremic rats, and thereby protected the femora from osteoporotic changes. Using LC/ESI/MS/MS, we found that dietary L-Lys elevated plasma alanine (Ala), proline (Pro), arginine (Arg), and homocitrulline (Homo). Analyses in vitro revealed that L-Pro inhibited apoptosis of cultured human VSMCs, whereas L-Lys, L-Arg, and L-Homo-Arg dose-dependently attenuated spontaneous precipitation of minerals in a solution of supersaturated calcium/phosphate.

Conclusions: Dietary L-Lys ameliorated VC in adenine-induced uremic rats. Our findings provide a novel therapeutic approach for VC.

FR-PO613
Association of Serum Phosphorus Variability with Coronary Artery Calcification among Hemodialysis Patients

Haining Li, Mengjing Wang, Li You, Jing Chen. Nephrology, Fudan Univ., Shanghai, China.

Background: Coronary artery calcification (CAC) is associated with increased mortality in maintenance hemodialysis (MHD) patients, but the pathogenesis of this condition isn’t well understood. We evaluated the relationship of CAC score (CACS) and variability of serum phosphorus in MHD patients.

Methods: Cross-sectional observational study. Setting & participants: 77 adults on MHD at Huashan Hospital (Shanghai). The mean dialysis vintage was 5.9 ± 4.4 years. Blood chemistry was recorded every 3 months from January 2008 to July 2010. Predictor factor: Phosphorus variation was defined by the standard deviation (SD) and coefficient of variation (CV). Outcomes: Three categories of CACs (< 10, 10-400, and > 400). Measurements: Phosphorus variation was calculated from patient records, CAC was measured by computed tomography, and CACs were calculated by the Agatston method. Results: The mean patient age was 61.7 ± 11.3 years and 51% of them were men. The mean CACs was 609.6 (± 1062.9), the median CACs was 168.6, and 78% of patients had CACs more than 0. Multivariate analysis indicated that female gender (OR = 0.20, 95% CI = 0.11-0.38), SD-phosphorus calculated from the most recent 6 measurements (OR = 1.90, 95% CI = 1.16-3.11) were significantly associated with CACs. However, the variability of serum phosphorus in MHD patients was independently associated with CACs.

Table 1. Multiple logistic regression analysis of factors associated with CAC score tertile in MHD patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Female</td>
<td>0.27 (0.09-0.79)</td>
<td>0.20 (0.10-0.38)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>2.12 (1.23-3.63)</td>
<td>2.04 (1.18-3.55)</td>
</tr>
<tr>
<td>Lab values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALB (g/dL)</td>
<td>0.955</td>
<td>0.915</td>
</tr>
<tr>
<td>CHF (1/g/dL)</td>
<td>2.50</td>
<td>0.04</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>1.251</td>
<td>0.014</td>
</tr>
<tr>
<td>P (mmol/L)</td>
<td>1.459</td>
<td>0.177</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>0.654</td>
<td>0.014</td>
</tr>
<tr>
<td>Mean and sd of CACs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CACS</td>
<td>505.5</td>
<td>1.26</td>
</tr>
<tr>
<td>Mean CACS</td>
<td>168.5</td>
<td>1.22</td>
</tr>
<tr>
<td>SD (HA)</td>
<td>2.06</td>
<td>0.11</td>
</tr>
</tbody>
</table>

FR-PO614
Reversibility of Uremic Vascular Calcification
Koba A. Lomashvili, Courtney A. Washington, W. Charles O'Neill. Renal Div, Emory Univ, Atlanta, GA.

Background: Research on vascular calcification has focused on formation rather than reversal. Since hydroxypatite is insoluble under physiologic conditions, reversal requires a biologic process. Whether vascular calcification is reversible and by what mechanism are unknown and have important therapeutic implications.

Methods: Mice were fed 0.45% adenine for 2 months to produce uremia and a 2% phosphorus diet (1000 mg/kg thrice weekly) to induce vascular calcification. After 2 months, calcified abdominal aortas were transplanted orthotopically into normal littermates and harvested after 6 and 12 weeks. The allografts were examined histologically by hematoxylin and eosin (H&E) or tartrate-resistant acid phosphatase (TRAP) staining for osteoclasts, and calcium content (measured after acid extraction by the cresolphthalein method) was compared to that in the untransplanted donor aorta.

Results: Calcification at transplantation was variable (17 to 2360 mmoles/mg; median: 686; normal: <7) and exclusively medial. Survival after transplantation was greater than 90% and there were no signs of rejection. The reduction in remnant calciﬁcation was 47 +/- 12% (n=8) and 51 +/- 13 % (n=5) respectively. This reduction was 37 +/- 10% in heavily calcified (<600 mmol/mg) allografts compared with 66 +/- 15% in less calcified allografts. The allografts were histologically similar to untransplanted calcified aorta with calcium deposits readily apparent in heavily calcified allografts and no evidence of cellular inﬁltration or cell-mediated resorption. TRAP staining was negative. There was no calcification of normal aortas transplanted into normal mice.

Conclusions: Approximately half the calcification in uremic aortas is reversible by 12 weeks without histologic evidence of cell-mediated resorption. Almost all of the reversal occurs by 6 weeks and is in less heavily calcified aortas. The results suggest that vascular calcification consists of a readily reversible component that presumably represents non-apatitic calcium and a non-reversible component that likely represents apatitic calcium. The inability to resorb this latter component is likely due to the failure to recruit osteoclasts.

Funding: NIDDK Support

FR-PO615
The Role of Nrf2 in Human Aortic Smooth Muscle Cells Calcification and Mechanism Research

Li Wang. Renal Dept, Sichuan Provincial People’s Hospital, Chengdu, China.

Background: To discuss the role and mechanism of Nrf2 in calcification of HASMCs. Methods: HASMCs were cultured in vitro and incubated with beta-glycerophosphate to induce a diffuse mineralization and oxidative stress. Additionally, sulforaphane treatment and short interfering RNA were used to regulate the expression of Nrf2 gene. Calcium deposition was detected by the O-CPC colorimetry method and normalized with regard to protein content. Intracellular ROS levels were measured using DCFH-DA. The expression of Nrf2, HO-1, Runx2, and SM22a were assessed by Western Blot.

Results: After 12 days of treatment, calcium deposition was significantly increased in calcification medium group than normal medium group. Within 12 hours of treatment, beta-glycerophosphate increased ROS production, this production being further enhanced after 72h. The beta-glycerophosphate-induced oxidative stress was associated with an early expression of Nrf2 and HO-1 followed by Runx2 and OPN expression at 72h. The beta-glycerophosphate could induce a diffuse mineralization in HASMCs. Nrf2 protect HASMCs from oxidative stress and calcification by participating in resistance to oxidative stress.

Funding: NIDDK Support

FR-PO616
A Novel Method to Quantify Relationships between Vascular Calcifications and Bone in Chronic Kidney Disease Patients

Janina M. Fasch, Thomas L. Nickolas. Radiology, Medical Univ of Vienna, Vienna, Austria; Medicine, Columbia Univ, NY, NY.

Background: In chronic kidney disease (CKD) vascular calcifications (VC) are highly prevalent. They are associated with increased cardiovascular risk and fracture. However, research in osteo-vascular interactions is impeded by the high radiation dose delivered by methods used to quantify VC severity and their skeletal relationships. High-resolution peripheral QCT (HRPQCT), Scanco Medical, measures bone mass and microarchitecture at the distal radius and tibia, detects VCs and delivers low radiation dosage. We determined whether HRPQCT simultaneously quantifies relationships between VCs and bone mass and microarchitecture.

Methods: We enrolled patients with CKD stages 2+3 (n=18), 4+5 (n=14), hemodialysis (HD, n=16), and an age, sex, race matched reference group with normal kidney function (n=21). Tibia HRPQCT scans were reviewed for lower leg arterial calcifications (LLAC) with a semi-automated, image-processing algorithm. LLAC mass was expressed in mgHA and there were no signs of rejection. The reduction in remnant calciﬁcation was 47 +/- 12% (n=8) and 51 +/- 13 % (n=5) respectively. This reduction was 37 +/- 10% in heavily calcified (<600 mmol/mg) allografts compared with 66 +/- 15% in less calcified allografts. The allografts were histologically similar to untransplanted calcified aorta with calcium deposits readily apparent in heavily calcified allografts and no evidence of cellular infiltration or cell-mediated resorption. TRAP staining was negative. There was no calcification of normal aortas transplanted into normal mice.

Conclusions: Approximately half the calcification in uremic aortas is reversible by 12 weeks without histologic evidence of cell-mediated resorption. Almost all of the reversal occurs by 6 weeks and is in less heavily calcified aortas. The results suggest that vascular calcification consists of a readily reversible component that presumably represents non-apatitic calcium and a non-reversible component that likely represents apatitic calcium. The inability to resorb this latter component is likely due to the failure to recruit osteoclasts.

Funding: NIDDK Support
radius total density (r = -0.30, p < 0.05) and Tb thickness (r = -0.30, p < 0.03), and tibia total (r = -0.30, p < 0.05) and Ct density (r = -0.30, p < 0.05) and Ct thickness (r = -0.20, p < 0.05).

Conclusions: In summary, HrPQCT simultaneously quantifies LLAC and assesses relationships between LLAC and bone mass and microarchitecture. LLAC was more severe in patients with advanced CKD and relationships between VCs and bone mass, microarchitecture and formation suggested pathogenic associations between vascular and bone biology that require further study. We conclude that HrPQCT will facilitate the elucidation of osteo-vascular biology.

Funding: NIDDK Support

FR-P0617
The Role of Adipocytes in Calciphylaxis Nader Kassis Akl, Neal X. Chen, Kalishia O'Neill, Keith March, Dmitry O. Traktuev, Sharon M. Moe. Indiana Univ, Indianapolis, IN.

Background: Calciphylaxis is a fatal disease in dialysis patients and hyperphosphatemia and obesity are risk factors. The close proximity of the calcified arterioles to adipocytes, and the fact that osteoblasts, adipocytes, and vascular smooth muscle cells (VSMC) have a common mesenchymal origin led us to test the hypothesis that adipocytes can calcify in the presence of elevated phosphate and/or that adipocytes exposed to phosphate can induce VSMC calcification.

Methods: 3T3-L1 preadipocytes and human adipose stromal cells (ASC) were induced into mature adipocytes and then treated with media with high phosphorus. Calcification was assessed by biochemical assay after HCl extraction. Total RNA was isolated and real-time PCR performed to determine the expression of genes for osteoblast and adipocyte differentiation. Adipocytes were also co-cultured with VSMC cultured in low or high phosphate conditions.

Results: The results demonstrated that both adipocytes and human ASC calcify in high phosphorus media (3.5 and 2.2 fold greater than cells without phosphate, respectively, both p < 0.01). In addition, compared to normal phosphorus, adipocytes treated with high phosphorus had increased expression of RUNX2 at 24 hrs (1.02±0.40 vs. 0.68±0.03, p < 0.01) and decreased expression of PPARγ (0.97±0.27 vs. 0.65±0.18, p < 0.004) at day 3 and CEBPα (1.56±0.57 vs. 1.11±0.23, p < 0.02) at day 7, indicating a switch to more osteoblast like phenotype. Furthermore, VSMC calcification was increased when co-cultured with adipocytes compared to VSMC alone (2.13±0.19 vs 0.04±0.20, p = 0.007 ) at day 3. In contrast, there was no difference in adipocyte calcification when co-cultured with or without VSMC.

Conclusions: Adipocytes are capable of calcifying in media that contains high phosphorus, in part by up-regulation of osteoblast genes and down-regulation of adipocyte genes. Furthermore, adipocytes exposed to elevated phosphorus can induce calcification of VSMC in a paracrine manner. The results suggest that adipocyte exposure to elevated phosphorus may be an initiating step in calciphylaxis.

Funding: NIDDK Support, Veterans Affairs Support

FR-P0618
High Phosphate Diet Induces Aortic Calcification in a Mouse Adenine CKD Model Wei Ling Lau,1 Sogol Pahlevan,2 Kamyar Kalantar-Zadeh,1 Cecilia M. Giachelli,3 Nosratola D. Vaziri.1 1Nephrology, Univ of California, Irvine, School of Medicine, Orange, CA; 2Bioengineering, Univ of Washington, Seattle, WA.

Background: Hyperphosphatemia is a non-traditional risk factor for vascular calcification (VC) leading to unfavorable cardiovascular outcomes, the pathophysiology of which can be examined in rodent models of chronic kidney disease (CKD). Here we characterize biochemical and VC outcomes when calcification-prone DBA/2J mice are subjected to adenine diet to induce uremia, followed by normal vs. high phosphate (NP vs. HP) feeding.

Methods: Kidney failure was induced in DBA/2J mice via 0.2% adenine in food x18 days, followed by NP (0.5% phosphate) or HP (1.2% phosphate) diet x18 months. The study groups were: healthy controls on NP diet (CTL), CKD on NP diet (CKD-NP), and CKD on HP diet (CKD+HP) (r=4 per group). A subset of mice was fed adenine diet x21 days to document blood urea nitrogen (BUN) trends.

Results: Serum BUN was significantly elevated after 18 days on adenine diet and was 107.8±7.2 mg/dL at day 21 (Figure 1A). Kidney histology showed patchy interstitial nephritis and glomerulosclerosis. At termination of the main study (after 3 months of NP vs. HP diet), serum creatinine remained significantly elevated in CKD groups (0.34±0.04 vs. 0.18±0.03 mg/dL in CTL). The CKD+HP group had increased serum phosphorus, serum FGF23 (Figure 1B) and aortic calcium content (Figure 1C). These parameters were equivalent between the CTL and CKD-NP groups.

Conclusions: In mice with CKD stage 2, we demonstrated increased production of Dkk-1 in remnant kidneys and increased circulating Dkk-1, sclerostin and c-klotho. There was an osteopontin low turnover osteodystrophy and stimulation of VC. Neutralization of Dkk-1 by a monoclonal antibody (mab) stimulated bone formation rates, prevented the osteodystrophy and CKD stimulated VC. The Dkk-1 mab preserved the expression of membrane c-klotho in the aorta and kidney. In addition, the aortic expression of the osteoblastic transcription factor, RUNX2 was inhibited, and vascular smooth muscle contractile protein expression was increased. Increased plasma c-klotho and FGF23 levels were not affected by the Dkk-1 mab, but FGF23 levels were reduced to normal by a Pi binder. In a treatment (not a prevention) protocol Pi binder therapy had no effect on VC or the osteodystrophy, but when combined with the Dkk-1 mab, the CKD-MBD as characterized in the CKD-2 mice was completely reversed.

Funding: Clinical Revenue Support

FR-P0620
Pathogenesis, Prevention and Treatment of the Chronic Kidney Disease-Mineral Bone Disorder Yifu Fang,1 Charlie Ginsberg,1 Michael E. Seifert,2 Toshifumi Suganuma,1 Hartmut H. Malluache,1 Keith A. Hruska,1 Pediatrics, Wash. Univ, St. Louis, MO; 2Pediatrics, St. Ill.Sch. of Medicine, Springfield, IL; 3Medicine, Univ of Kentucky, Lexington, KY.

Background: The CKD-MBD is recognized as a major contributor to cardiovascular risk during kidney disease, but the cause of the syndrome is unknown, and there is no current therapy. At its inception, the CKD-MBD is characterized by an osteodystrophy, vascular calcification (VC) and stimulation of osteocytic protein levels in the circulation. We tested the hypothesis that the CKD-MBD is caused by increased renal production of circulating Wnt inhibitors.

Methods: In the background of atherosclerosis and high-fat feeding with CKD during kidney disease, but the cause of the syndrome is unknown, and there is no current therapy. At its inception, the CKD-MBD is characterized by an osteodystrophy, vascular calcification (VC) and stimulation of osteocytic protein levels in the circulation. We tested the hypothesis that the CKD-MBD is caused by increased renal production of circulating Wnt inhibitors.

Funding: Clinical Revenue Support

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

Underline represents presenting author/disclosure.

506A
FR-PO621
Abnormal DXA Scans in Hemodialysis Patients Predict Risk of Hip Fractures
Scott A. Rason,1 Richard M. Dell.1 1Nephrology, Kaiser Permanente, Los Angeles, CA; 2Orthopedic Surgery, Kaiser Permanente, Downey, CA.

Background: In 2011 and 2012 kidney week we presented data from Kaiser Permanente DXA scan data base. There was a strong correlation between normal DXA scans in hemodialysis (HD) patients and low hip fracture (FX) risk. Last year we had 1954 HD patients with DXA scans. KDGIDO makes the following recommendations for DXA scans in HD patients. 2.2.2 In patients with CKD stages 3-5D with evidence of CKD-MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B). This is based on 13 studies with the most subjects in any of the studies was 242. 5 studies showed no correlation with FX rates and 8 showed some correlation with low BMD and increased FX rate. We now have 2387 active HD patients in our data base who have had DXA scans with scores.

Methods: We reviewed the HD data base of 4912 HD patients at Kaiser Permanente So. CA. of which 2387 had DXA scans with T-scores. The DXA scans were done between 1/1/07 to 12/30/11. We wanted to see if there was any correlation between DXA scan results and hip FX in this population.

Results: We found the following results 485 patients had a normal DXA with 5 hip FX with a 1.03 % FX rate. 1898 patients had an abnormal DXA (T-score <-1) with a FX rate of 4.6%. With osteoporosis (T-score <-2.5) had a FX rate of 9.33%.

Conclusions: The KDGIDO guidelines our data show that normal DXA scan results are not predictive of hip fracture risk in HD patients over time. Our data has been substantiated in other studies.

Funding: Clinical Revenue Support

FR-PO622
Pathogenesis of Cortical Deficits and Decreased Bone Stiffness after Kidney Transplantation
Kyle K. Nishiyama, Elizabeth Shane, Thomas L. Nickolas. Medicine, Columbia Univ, NY, NY.

Background: Fractures are more than 4-fold higher after kidney transplantation (KTx) than in the general population. We reported that hyperparathyroidism is associated with lower Ct density, thickness and area, and stiffness and failure load. The purpose of this study was to evaluate the presence of iron deposits on bone biopsy of hemodialysis patients.

Methods: We studied the distal radius and tibia by high-resolution peripheral QCT (HRPQCT, Scanco Medical) in 31 patients (22 men, 9 women; age 52±13years) within 2 weeks of and 1 year after KTx. Ct porosity (Cp) was quantified. Whole bone stiffness and failure load were estimated using finite element analysis. PTH and markers of bone formation (BSAP, Osteocalcin, PINP) and resorption (CTX and Trap5b) were measured at 3, 6 and 12 months after KTx and were time-averaged. Mixed linear models were used to determine longitudinal changes.

Results: At 1 year, 74% of patients had HPT (PTH 65 pg/mL). At the radius, Ct density decreased by 2.2±1.8%, thickness by 2.2±0.8% and area by 2.5±10.8% (all p<0.05); Cp0 increased by 78±9% (p=0.001) and trabecular area by 4.6±1.8% (p=0.006). Stiffness and failure decreased by 3.3% and 3.4±1.4% (both p<0.05) respectively. At the tibia, Ct density decreased by 1.9±0.6% and thickness by 1.1±0.5% (both p<0.05); Cp0 increased by 30.5% (p=0.05). Changes in stiffness and failure load were not significant. At 1 year greater Cp0 was significantly associated with lower Ct density, thickness and area, and stiffness and failure load (all p<0.05). Increases in Cp0 were strongly associated with higher levels of PTH (r=-0.45, p=0.05) and BTMs (Osteocalcin and Stiffness r=-0.70). Osteocalcin and Failure Load were also significantly associated with iron deposits (r=0.64, p=0.001).

Conclusions: In conclusion, persistent HPT and elevated bone turnover after KTx drive Ct deterioration and decreased bone stiffness. Further studies are needed to determine whether mitigating the adverse effects of HPT on Ct bone protects against fracture.

Funding: Clinical Revenue Support

FR-PO623
Altered Material Properties Are Responsible for Bone Fracture in Rats with Chronic Kidney Disease
Yoshiko Iwasaki,1 Junichiro J. Kazama,2 Masafumi Fukagawa.1 1Health Sciences, Oita Univ of Nursing and Health Sciences, Oita, Japan; 2Niigata Univ Medical and Dental Hospital, Niigata, Japan; 3Tokai Univ School of Medicine, Isehara, Japan.

Background: Patients with chronic kidney disease (CKD) have considerably higher risk of fracture. Abnormalities in parathyroid function and/or bone mineral density cannot fully account for their increased bone fragility, while the role of uremia on it remains obscure. In this study, KOX rats with hyperparathyroidism (HPO-KOX) were underwent partial nephrectomy (Nx). Those without hyperparathyroidism (Non-HPO-KOX) were made by Nx and thyroparathyroidectomy (TPTx) followed by a continuous exogenous physiological dose of PTH supplementation. Control rats (HPO-Cont or Non-HPO-Cont) were prepared for each group. Both renal bone elasticity was invaso-novally assessed by a direct mechanical assessment method. Bone chemical compositions were analyzed by a ramann spectroscopy and a micro X-ray diffraction.

Results: Serum creatinine levels were significantly elevated in the CKD groups. Serum calcium, Uric acid, and creatinine levels were increased. Serum ALP was rather decreased in the Non-CKD groups. Multiple regression analysis revealed that apatite orientation and mineral matrix ratio, but not BMD, were independently associated with bone elasticity.

Conclusions: Regardless of parathyroid function or bone turnover, altered bone material properties induced by uremia were responsible for bone fragility in CKD animals.

Funding: Government Support - Non-U.S.

FR-PO624
High Frequency of Iron Bone Deposits in a Brazilian Hemodialysis Population with Renal Osteodystrophy
Camila Barbosa L. Oliveira,1 Alline S. A. Oliveira,1 Carla Queiroz Neves,2 Clarissa Jacob Barros Carvalho,3 Vanda Jorgjetti,1 Jose Edevanilson Guieros,1 Ana Paula Guieros.1 1Nephrology, UFPE, Recife, Pernambuco, Brazil; 2Nephrology, UFPE, Recife, Pernambuco, Brazil; 3Nephrology, USP, Sao Paulo, Brazil.

Background: Little is known about iron bone deposits in dialysis patients. Previous studies have demonstrated the association between iron and the development of low bone turnover. The purpose of this study was to evaluate the prevalence of iron deposits on bone biopsy of hemodialysis patients.

Methods: We performed a retrospective analysis of 158 patients underwent bone biopsy in the period from March 2003 to March 2013. Clinical data were evaluated: age, sex, time on dialysis and occurrence of fractures. Laboratory tests: total calcium, phosphorus, intact parathyroid hormone (PTH pg/mL), alkaline phosphatase (ALP, U/L), iron (µg/dL) and ferritin (ng/mL). Bone biopsy was performed after double tetracycline labeling and specimens were classified as osteitis fibrosa (OF), mixed disease (MD), adynamic bone disease (ABD), osteosclerosis (OS) or osteomalacia (OM). To evaluate iron bone deposits, sections were stained with Perl's blue and for assessment of iron (µg of iron/g bone dry weight). Aluminum intoxication was used. Aluminum intoxication (Al) or iron intoxication (IBD) were defined when more than 20% of the trabecular bone surface were covered by metal. Patients were divided into 2 groups: IBD group (patients with IBD) and NIBD group (patients free of IBD). We performed a comparative analysis between the groups to factors associated with IBD.

Results: The prevalence of IBD was 32.3%, There were no differences between the groups regarding clinical parameters. ALP (median 138 vs 297; p<0.001) and iPTH (median 645 vs 1514; p<0.001) levels were lower in IBD group. Ferritin levels were higher in IBD group (median 528 vs 313; p=0.019). ABD (p=0.029) and aluminum intoxication (p=0.001) were closely associated with IBD.

Conclusions: We found high prevalence of siderosis on the bone of a Brazilian hemodialysis population. IBD was associated with low bone turnover and with aluminum intoxication. More studies are needed to assess the clinical importance of IBD.

Funding: Government Support - Non-U.S.

FR-PO625
Renal Osteodystrophy: 10-Year Experience of a Brazilian Center
Alline S. A. Oliveira,1 Carla Queiroz Neves,1 Clarissa Jacob Barros Carvalho,1 Camila Barbosa L. Oliveira,1 Vanda Jorgjetti,1 Jose Edevanilson Guieros,1 Ana Paula Guieros.1 1Nephrology, UFPE, Recife, Pernambuco, Brazil; 2Nephrology, USP, Sao Paulo, Brazil.

Background: Chronic kidney disease mineral bone disorder (CKD-MBD) is highly prevalent among patients with end stage renal disease. The aim of the presente study was to evaluate the clinical and laboratory profile of patients who underwent bone biopsy. Methods: We performed a retrospective analysis of 158 hemodialysis patients underwent bone biopsy from March 2003 to March 2013. Clinical data were evaluated: age, sex, time on hemodialysis. Laboratory tests consisted of total calcium (Cat, mg/dL), phosphorus (Pmg/dL), intact parathyroid hormone (iPTH, pg/mL) and alkaline phosphatase (ALP, U/L). Bone biopsy was performed after double tetracycline labeling. The specimens were classified histologically as osteitis fibrosa (OF), mixed disease (MD),
FR-PO626

The Skeleton as a Reservoir of Calcium in Dialysis Patients: The Less You Have, the More You Lose


Nephrology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil.

Background: Calcium (Ca) balance during dialysis session is an important, but unrecognized tool for the management of CKD patients. Current mathematical models estimate dialysis Ca balance employing Ca gradient between serum and dialysate, as well as ultrafiltration (UF). The skeleton, despite being the most important reservoir of Ca, is not included in these models.

Methods: The aim of this study was to verify the influence of bone on Ca mass transfer during dialysis in CKD patients with severe hyperparathyroidism (SHPT) who were submitted to bone biopsy. Fourteen patients (11 males), aged 45 ± 12 yrs, on hemodialysis for a median of 75 (48-138) months were dialysed using two different (Ca)Cl2, 1.25 and 1.75mol/L.

Results: When a (Ca)Cl2 of 1.25mol/L was used, all 2 patients that had a negative Ca mass transfer (median=-283 mg (<782, +439)), total serum Ca and PTH remained relatively stable (Δ (-0.17 mg/dl and 109 pg/ml, ns). In a d[Ca] of 1.75mol/L, all 3 patients had positive Ca balance (median +103 mg (291, 676)), total serum Ca increased and PTH drifted and reagents stability. The kit manufacturers should be keen to improve reagents variability.

Conclusions: Ca balance during dialysis is influenced by bone Ca balance. This is an underestimated variable and should be included in the future calculation of the Ca balance.

Funding: Government Support - Non-U.S.

FR-PO627

Inter-Method Variability for the Measurement of Bone Alkaline Phosphatase: Implication for the Monitoring of CKD-MBD

Etienne Cavalier,1 Pierre Delaney.2 1Clinical Chemistry, Univ of Liege, CHU Sart-Tilman, Liege, Belgium; 2Nephrology, Dialysis Transplantation, Univ of Liege, CHU Sart-Tilman, Liege, Belgium.

Background: KDIGO suggested measuring PTH or bone-specific alkaline phosphatase (b-ALP) to evaluate bone disease. Little information is however available regarding the variability among the b-ALP methods; we aimed to compare the values obtained by 3 different automated b-ALP in a population of hemodialyzed (HD) patients.

Methods: Serum from 81 HD, prior a hemodialysis session was obtained and stored at -80°C until analysis. b-ALP was determined with the Beckman, DiaSorin Liaison and IDS-iSYS in a single batch on the same day. Intact PTH (iSYS) and 3rd generation PTH (Liaison) were also determined.

Results: b-ALP median (95%CI) for Access, iSYS and Liaison were: 16.4(14.9-19.6), 20.9(18.8-25.6) and 14.7(13.4-16.9)μg/L, respectively. Passing-Bablok (PB) regressions were Access/Liaison = 2.64x+189 μg/L, Access/iSYS = 2.83x+190 μg/L and Liaison/iSYS = 1.53x-141 μg/L. Correlation (r=0.77) between Liaison and PB was 0.72 but not with iSYS (r=0.58). Osteoid accumulation (OS/BS) and osteoclast surface (p=0.03) was higher in patients with osteomalacia than in those with adynamic bone, while bone mineral density as assessed by μCT was lower.

In dialysis patients, bone volume measurements by both methods were highly correlated (BV/TV: r=0.70, p<0.001; Tb.Th: r=0.47, p<0.001; Tb.Sp: r=0.53, p<0.0001).

Methods: Canopies and PTHR1 immunoreactivity did not differ between groups. PTH levels correlated with canopies (r=0.31, p<0.01 and r=0.30, p<0.01), osteoid accumulation (OS/BS: r=0.58, p<0.01 and r=0.43, p<0.01) and osteosclerotic surface (r=0.67, p<0.001 and r=0.32, p<0.01).

Conclusions: Measurements of bone volume can be accurately assessed with CT. Skeletal mineralization may also be assessed as bone mineral density is lower in patients with excessive osteoid accumulation and similar amounts of bone volume and higher in patients with adynamic bone. The potential value of an extensive assessment of bone by pQCT, CT and bone histomorphometric variables remains to be determined.

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

FR-PO628

Relationship Between Bone Parameters on Histomorphometry and microCT

R.C. Pereira,1 David S. Bischoff,2 Dean T. Yamaguchi,3 Barbara Gales,4 Isidro B. Salusky,5 Katherine Wesseling-Perry.1 1Pediatrics, UCLA, Los Angeles, CA; 2Medicine, VA Healthcare System, Los Angeles, CA.

Background: Biochemical markers are imperfect markers of bone histology in renal osteodystrophy (ROD); thus, bone histomorphometry remains the gold standard for the assessment of bone turnover, mineralization, and volume in CKD. While newer imaging techniques, including QCT and pQCT, have promise in predicting overall bone structure and volume, the ability of CT to assess other histomorphometric parameters remains unknown.

Methods: We compared to bone histomorphometry variables to microCT (μCT) analysis of 68 bone biopsy cores from dialysis patients with normal to high bone turnover, adynamic bone and pure osteomalacia and 14 controls.

Results: As expected, osteoid accumulation as assessed by bone histomorphometry was higher in patients with osteomalacia than in those with adynamic bone, while bone mineral density as assessed by μCT was lower.

In dialysis patients, bone volume measurements by both methods were highly correlated (BV/TV: r=0.70, p<0.001; Tb.Th: r=0.47, p<0.001; Tb.Sp: r=0.53, p<0.0001).

Conclusions: Measurements of bone volume can be accurately assessed with CT. Skeletal mineralization may also be assessed as bone mineral density is lower in patients with excessive osteoid accumulation and similar amounts of bone volume and higher in patients with adynamic bone. The potential value of an extensive assessment of bone by pQCT, CT and bone histomorphometric variables remains to be determined.

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

FR-PO629

Canopy Cells in Renal Osteodystrophy (ROD): Potential Role in Dysregulated Coupling of Bone Formation and Resorption

Thomas Levin Andersen,1 Peter A. Friedman,2 Barbara Gales,3 Isidro B. Salusky,4 Katherine Wesseling-Perry.1 1Pediatrics, UCLA, Los Angeles, CA; 2Pharmacology and Chemical Biology, Univ of Pittsburgh, Pittsburg, PA; 3Yeje - Lillebaelt Hospital, Univ of Southern Denmark, Vejle, Denmark.

Background: Disruption of canopy—flat cells which are lifted from the bone surface to form an enclosed compartment over the remodeling surface—impairs bone formation (BF) due to osteosclerosis in pts with multiple myeloma. Their role in ROD is unknown.

Methods: Canopies were assessed in 106 bone biopsies of pediatric pts with CKD stages 2-5 and quantified on a scale of 0 to 4 (0: no surfaces with canopy lift; 0.5: 1-2 surfaces; 1: 3-4 surfaces; 2: 5-6 surfaces; 3: 7-9 surfaces; 4: >10 surfaces). PTH1R immunoreactivity were assessed (rabbit anti-human PTH1R (Graunsch Labs, Schwabhausen, Germany)) and quantified on the same scale.

Results: PTH1R immunoreactivity was observed in canopies and in flat cells attached to the bone surface, although not in osteoblasts, osteostetes, or osteocytes. Circulating PTH values were 24 lower and fewer canopies were seen in CKD than in dialysis pts. Bone PTH1R immunoreactivity did not differ between groups. PTH levels correlated with canopies (r=0.34, p<0.01) but not with bone PTH1R. Canopies and PTH1R immunoreactivity correlated with BFR (r=0.31, p<0.01 and r=0.30, p<0.01), osteoid accumulation (OS/BS: r=0.58, p<0.01 and r=0.43, p<0.01) and osteosclerotic surface (r=0.67, p<0.001 and r=0.32, p<0.01).

Conclusions: Canopy cells may be involved in the coupling of bone formation and resorption through their role as mineralization accelerators.

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

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

Underline represents presenting author/disclosure.

508A
FR-PO630
The Relationship between Micropetrosis and Osteocyte Number in Hemodialysis Patients with Hypoparathyroidism
Aji Aiyama,1 Masaaki Inaba,1 Yoshihiro Tominaga,1 Kosaku Nitta,1 Shigeru Satoh.1 1Akita Univ School of Medicine; 2Osaka City Univ Graduate School of Medicine; 3Nagoya 2nd Red Cross Hospital, 4Tokyo Women’s Medical Univ.

Background: Bone microcracks are frequently found in patients with low bone turnover in micropetrositis in these patients. We hypothesized that the cause or duration of low turnover may alter these findings.

Methods: Fifteen HD patients with low bone turnover with or without total parathyroidectomy (PTX) or cinacalcet were assessed by bone histomorphometry of iliac crest bone biopsy. Group I: taken before and at 1 year (yr) after PTX (n=10) and before and after cinacalcet after 1 yr of treatment (n=4). Group II: HD patients with long-term (over 3 yrs due to unknown causes) low iPTH (< 60 pg/mL; n=3) after PTX (n=3) and before and after cinacalcet after 1 yr of treatment (n=4). Group II; histomorphometry of iliac crest bone biopsy. Group I; taken before and at 1 year (yr) after PTX (n=10) and before and after cinacalcet after 1 yr of treatment (n=4).

Results: In group I, serum iPTH decreased from 1 yr (216.6 ± 103.1(SD) to 145.8 ± 90.0 N/mm2, p=0.016), but N.Ot/(BV-Mp.V) and Mp.V/BV did not change. For group II, iPTH was 15.9 pg/mL at the time of PTX. Bone loss initiate just after administration of glucocorticoid, and the degree of osteoporosis in patients with low bone turnover with or without total parathyroidectomy (PTX) or cinacalcet may be due to decreased osteocytes survival, perhaps caused by cinacalcet or PTX at 1 yr may be different than that observed in patients without a known cause of low turnover for a long term. The latter may be due to decreased osteocytes survival, perhaps caused by the micropetrositis.

Funding: Pharmaceutical Company Support - Kirin, Chugai, Bayer

FR-PO631
Synergistic Effect of Etidronate Combined with Menatetrenone for Glucocorticoid-Induced Osteoporosis in Patients with Chronic Glomerulonephritis
Yuka Makita,1 Hitomi Suzuki,1 Masao Ikeda,1 Hiromitsu Fukuda,1 Satoshi Mano,1 Takashi Kobayashi,1 Yasuhiiko Kanaguchi,1 Tatsuya Aoki,1 Teruo Hidaka,1 Katsuhiko Asanuma,1 Yasuhiko Tomino.1 1Nephrology, Juntendo Univ Faculty of Medicine, Tokyo, Japan; 2Tokyo Women’s Medical Univ.

Background: Glucocorticoid therapy is useful for treatment of chronic glomerulonephritis (CGN), however, glucocorticoid may induce secondary osteoporosis. Bone loss initiate just after administration of glucocorticoid, and the degree of osteoporosis depends on the cumulative dose of glucocorticoid. Although bisphosphonate treatment is well known to improve the bone quality and reduce the risk of bone fractures, recent studies have shown that vitamin K2 also maintain stable bone mineral density (BMD). Furthermore, vitamin K2 is essential for bone formation cooperation with osteoclast. Thus, we examined the clinical efficacy of bisphosphonate alone or bisphosphonate combined with vitamin K2 for preventing glucocorticoid-induced bone loss in in patients using serum levels of N-terminal telopeptide of type I collagen (NTx) and ucOC as biomarker.

Methods: We conducted a 6-month prospective randomized study at Juntendo university hospital. Overall 43 patients (mean age 39.4 ± 17.0) with CGN commencing with prednisone were recruited from 2011 to 2013. These patients were randomized to Etidronate (17.5 mg/week) alone (Etidronate group, n=19) or Etidronate (17.5 mg/week) with Menatetrenone (45 mg/day) (Combined group, n=24) treatment groups. Serum levels of NTx and ucOC as well as BMD were measured before and after 3 and 6 months of commencing with prednisone.

Results: In the Etidronate group, the percentage changes of serum levels of NTx after 3 and 6 months were -6.1 % and -9.8 %, whereas those were -28.3 % and -27.0 % in the Combined group. The percentage changes of serum levels of ucOC after 3 and 6 months were -14.5 % and -10.6 % in the Etidronate group and 51.3 % and -50.0 % in the Combined group, respectively. There were no significant differences in BMD between these groups during the study.

Conclusions: Our data suggested that combination therapy of Etidronate with Menatetrenone may have synergistic effect to prevent glucocorticoid-induced osteoporosis in patients with CGN.

FR-PO632
Blood Tests Predictive of Bone Loss in CKD-5D Patients
Harmut H. Malluche,1 Daniel Davenport,2 Marie-Claude M. Faugere.1 1Div of Nephrology, Univ of Kentucky; 2Dept of Surgery, Univ of Kentucky.

Background: Low bone mass is frequently seen in patients with chronic kidney disease on dialysis (CKD-5D) and abnormalities in bone volume are an integral part of renal osteodystrophy. Patients with CKD-5D have 4.4 times the risk of hip fracture compared to the general population. This prospective study was conducted to determine whether serum biochemical parameters can help to predict bone loss in CKD-5D patients.

Methods: In CKD-5D patients, bone mass was measured by QCT and DXA of the hip and spine at baseline and after 1 year. At time of these bone mass measurements, blood tests were done including: PTH; FGF-23; sclerostin; procollagen type 1 N-terminal propeptide (PINP), and tartrate-resistant acid phosphatase-5b (TRAP-5b). Demographic and clinical characteristics were recorded.

Results: 69 patients completed the study (Table). Bone loss was observed by QCT in the hip in 52% of the patients and in the spine in 36%; by DXA in the hip in 35% and in the spine in 36%. Bone loss in the hip was lower in black patients and in patients exercising regularly (both p<.05). Bone loss was not greater in diabetics and did not correlate with either BMI or dialysis vintage. TRAP-5b, sclerostin and FGF-23 were significantly higher in losers than non-losers (p<.05). Bone loss by QCT of the hip correlated with baseline PINP, TRAP-5b and sclerostin (rho=.24, .25, .25, 371 esp, all p<.05). Bone loss by DXA of the spine correlated with FGF-23 (rho=.393, p<.003). Sclerostin and TRAP-5b were independent predictors of bone loss by QCT of the hip after adjustment for age, race and exercise (β=−8.4, p=.008 and β=1.4, p=.011 resp). Log FGF-23 predicted bone loss by DXA of the spine (β=.64, p=.003).

Conclusions: The available blood tests, TRAP-5b, sclerostin, and FGF-23 can be used to assess risk for bone loss in CKD-5D. These findings are relevant for a major clinically challenging problem.

Funding: Other NIH Support - R01DK080770, Private Foundation Support

FR-PO633
A Retrospective Review of Bone Density Scans in Different Stages of Chronic Kidney Disease
Bhanu Prasad Tikkisetty,1 Jennifer St.orge.2 1Nephrology, Regina Qu’Appelle Health Region, Regina, Canada; 2Research and Health Information Service, Regina Qu’Appelle Health Region, Regina, Canada.

Background: Our renal program undertook a retrospective chart review of all patients who underwent a baseline dual-energy X-ray absorptiometry (DXA) scan in our nephrology program between Jan 2001 and Jan 2013. The purpose of the study was to determine if there was a preferential site of bone loss in CKD patients across different disease stages.

Methods: A total of 410 patients were included in the dataset. Measures included glomerular filtration rate (GFR) in ml/min as per the Modification of Diet in Renal Disease formula, bone density measurements including T-scores and Z-scores for the lumbar spine, both hips, and the one-third distal radius, as well as the number of fractures. We compared these measures across patients in CKD Stages 2 through 5.

Results: We found a significant decline in median bone density across Stages 2 through 5 for total hip (X’=3.167, p=0.001) and femoral neck (X’=3.127, p=0.005) sites, but not lumbar spine or one-third distal radius. Increasing serum phosphorus was significantly associated with reduced bone mineral density in the total hip (β=−.15, p<.05, Spearman’s ρ) and trended towards significance for femoral neck (β=−.10, p=.056, Spearman’s ρ). The percentage of patients suffering from a fracture, however, did not significantly change with CKD stage using a between-groups analysis (X’=3.62, p=.09, Cramer’s V = 1.3, p<.05).

Conclusions: There is a demonstrable decline in total hip and femoral neck bone density with progression of CKD staging. In contrast, lumbar spine and distal radius bone mineral density were not affected by CKD stage. DXA scans provide information on BMD, they do not comment on trabecular and cortical microarchitectute and the resolution is too
FR-PO634
Prescribing Practices and Response to Cinacalcet Treatment in Secondary Hyperparathyroidism – A Single Centre Experience - Nadeeka Kumamari Rathnamalala, Graham Warwick, John Walls Renal Unit, Univ Hospitals of Leicester, Leicester, United Kingdom.

Background: Managing bone disease in advanced chronic kidney disease (CKD) can be challenging. With the introduction of cinacalcet in the United Kingdom, guidelines from the National Institute for Health and Care Excellence (NICE) have been issued to guide its use. The aim of this audit was to determine if cinacalcet was used in line with NICE and Kidney Disease Improving Global Outcomes (KDIGO) guidelines.

Methods: This was a retrospective observational study of patients under the care of a large tertiary nephrology centre in the UK. Data was extracted from the electronic medical records and included prevalent dialysis nephrology and transplant clinic follow ups from 01.08.2012 to 31.10.2012.

Results: 65 subjects were identified (M:F 38:27). Mean age was 62 (+/- 17) yrs and 89.2% were Caucasians. Majority (84.6%) were receiving renal replacement therapy (RRT) while 7.7% were transplanted and 7.7% were pre-dialysis CKD on RRT. 94.5% on RRT were on unit based haemodialysis for mean of 6.1 yrs. 50.8% had contraindications for parathyroidectomy while 49.2% declined surgery.

76.9% of patients were already on a phosphate binder and this did not change over one year on cinacalcet. Only 62.5% of patients were on vitamin D analogues but at the end of one year this had increased to 71.1%. 82.6% of patients were started on 30mg cinacalcet and 59% and 62.2% remained on 30 mg at 6 and 12 months respectively.

84.4% of the study population had iPTH levels above the KDIGO targets while only 76.9% of patients were already on a phosphate binder and this did not change over one year on cinacalcet. Only 62.5% of patients were on vitamin D analogues but at the end of one year this had increased to 71.1%. 82.6% of patients were started on 30mg cinacalcet and 59% and 62.2% remained on 30 mg at 6 and 12 months respectively.

Conclusions: All subjects were started on cinacalcet treatment due to contraindications to parathyroidectomy or preference to have medical treatment. Cinacalcet did not significantly reduce the need for a phosphate binder but there increased requirement for vitamin D analogues. In a significant number of patients the treatment was not reduced to the target dose but escalation was often not performed according to guidelines.

FR-PO635
Lanthanum Carbonate or Dietary P Restriction Ameliorates Endothelial Dysfunction in Adenine-Induced Chronic Kidney Disease Rats - Haruka Ueda, Yutaka Taketani, Hisami Okumura, Hironori Yamamoto, Eiji Takeda. Dept of Clinical Nutrition, Univ of Tokushima, Tokushima, Japan.

Background: Cardiovascular disease (CVD) is the most important cause of mortality in chronic kidney disease (CKD) patients. Hyperphosphatemia has been identified as an independent risk factor for CVD in CKD patients, as elevation of serum phosphorus (Pi) levels can be involved in endothelial dysfunction as well as vascular calcification. Dietary Pi restriction and Pi binders are useful for correction of hyperphosphatemia, however, it has been unknown whether these treatments have similar beneficial effect on endothelial function or not. Here, we investigated the effect of lanthanum carbonate or dietary Pi restriction on endothelial function in adenine-induced chronic kidney disease rats.

Methods: Adenine-induced CKD model rats were prepared by feeding 0.5% adenine-containing diet for 35 days on male 7-wk-old Sprague-Dawley rats. The adenine-induced CKD rats were divided 5 groups and treated with either control diet (CP; 1%P), low P diet (LP; 0.2%;P), 1.5% lanthanum carbonate (La1.5; 1.5%LaCO3), 3% lanthanum carbonate (La3; 3%LaCO3), or 6% lanthanum carbonate (La6; 6%LaCO3) for 14 days. Plasma were collected at sacrifice day and measured P, intact-PTH, FGF23, and creatinine. Aortic rings were also prepared and measured acetylcholine-dependent vasodilation by isometric transducers.

Results: Plasma P, intact-PTH, and FGF23 levels were significantly decreased by similar level and plasma calcium levels were increased in LP and La6 groups compared with CP group. Acetylcholine-dependent vasodilation was impaired in adenine-induced CKD rats. This impairment was significantly and similarly improved in LP and La6 groups compared with CP group. However, correction of hyperphosphatemia was not enough in La1.5 and La3 groups that so impaired vasodilation was not significantly ameliorated.

Conclusions: In conclusion, both dietary Pi restriction and lanthanum carbonate can ameliorate endothelial dysfunction observed in adenine-induced CKD rats, but the improvement would be depended on the correction rate of serum P level.

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

FR-PO636
β-Glycerophosphoric Acid Promotes Vascular Smooth Muscle Cells Transdifferentiation and Calcification via miR-125b Downregulation and Ets1 Induction - Bing Wen, Junwei Yang. 2nd Affiliated Hospital, Nanjing Medical Univ, Nanjing, China.

Background: Vascular calcification is highly prevalent in patients with chronic kidney disease (CKD) and is associated with increased risk of cardiovascular disease and mortality. Accumulated evidences suggested that vascular smooth muscle cells (VSMCs) to osteoblast-like cells transdifferentiation (VOT) plays a crucial role in promoting vascular calcification. MicroRNAs (miRNAs) are a novel class of small RNAs that negatively regulate gene expression via repression of the target mRNAs. In the present work, we sought to determine the role of miRNAs in VSMCs phenotypic transition and calcification induced by β-glycerophosphoric acid (β-GP).

Methods: Primary cultured rat aortic VSMCs were treated with β-GP for different time. The protein levels of SM-22α, cbfα1, osteocalcin, and osteopontin in VSMCs were tested by Western Blotting assay. miR-125b expression was detected by real-time RTP. Calcium deposition was determined by Alizarin Red S staining.

Results: 1) In VSMCs, after β-GP treatment, the expressions of cbfα1, osteocalcin and osteopontin were significantly increased and SM-22α expression was decreased. ALP activity was induced by β-GP in a time and dose dependent manner. Calcium deposition was detected in VSMCs incubated with calcification media; 2) miR-125b expression was significantly decreased in VSMCs after incubated with β-GP. miR-125b mimic could inhibit β-GP-induced osteogenic markers expression and calcification of VSMCs whereas miR-125b inhibitor promoted the phenotypic transition of VSMCs and calcification; 3) miR-125b targeted Ets1 and regulated its protein expression in VSMCs. Downregulating Ets1 expression by its siRNA inhibited β-GP-induced the VSMCs phenotypic transition and calcification.

Conclusions: Our study suggests that β-glycerophosphoric acid, a donor of phosphorus, can stimulate VSMC transdifferentiation and calcification, which is probably through miR-125b downregulation and Ets1 induction.

Funding: Government Support - Non-U.S.

FR-PO637
Phosphate Overload Induces Local and Systemic Inflammation and Malnutrition in Uremic Rats - Shunsuke Yamada, Masanori Tokumoto, Masatoshi Taniguchi, Kazuhiko Tsuruya, Takanari Kitazono. 1 Div of Nephrology, Fukuoka Dental College, Fukuoka, Japan; 2Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 3Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Phosphate (Pi) overload plays a pivotal role in the development of cardiovascular disease (CVD) in chronic kidney disease (CKD) patients. Inflammation and malnutrition also contribute to the high prevalence of CVD in patients with CKD. However, the impact of Pi overload on inflammation and malnutrition remains to be elucidated.

Methods: The present in vivo study determined the effects of Pi overload on inflammation, malnutrition and CVD (cardiac weight and aortic calcium content) in CKD rats fed a diet containing 0.3% adenine, 19% protein and different concentrations of Pi (ranging from 0.3% to 1.2%) for eight weeks. The effects of lanthanum carbonate on Pi-related changes were also investigated. Furthermore, we examined the direct effects of Pi overload on cultured human vascular smooth muscle cells (VSMCs) in an in vitro study.

Results: Pi loading dose-dependently induced malnutrition (decreased body weight and serum albumin) and CVD (increased cardiac weight and aortic calcium content) without aggravating the kidney function in the CKD rats. The CKD rats exhibited dietary Pi loading-dependent increases in the serum tumor necrosis factor (TNF-α) levels, the mRNA expression of TNF-α in the aorta, heart and kidneys and the levels of an oxidative stress marker (8-hydroxy-2'-deoxyguanosine) in the urine and aorta. Treatment with 6% lanthanum carbonate blunted almost all of the changes induced by Pi loading. A linear regression analysis showed that the serum Pi level was closely correlated with the extent of inflammation, malnutrition and CVD. In the cultured VSMCs, high Pi medium increased the mRNA of TNF-α and Pit-1, and decreased that of Klotho.

Conclusions: Dietary Pi overload induces a sequence of events, including inflammation, malnutrition and CVD in CKD rats. Pi binders have the potential to counteract the changes induced by Pi overload.

FR-PO638
Therapeutic Effects of ONO-1301 on Vascular Calcification in a Rat Model of Adenine-Induced Chronic Kidney Disease - Yohei Maeshima, Hiroyuki Watatani, Norikazu Hinamoto, Katsuyuki Tanabe, Kana Masuda, Haruyo Ujike, Hitoshi Sugiyama, Sakai Yoshiki, Hirofumi Makino. 1 CKD and CVD, Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; 2Medicine and Clinical Science, Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; 3ONO Pharmaceutical Co., Osaka, Japan.

Background: Cardiovascular disease is a leading cause of mortality in patients with CKD, and vascular calcification is a key modifier of disease progression. ONO-1301 (ON3) is a novel prostacyclin analog possessing thromboxane synthase inhibitory activity. We recently reported the renoprotective effects of ONO in experimental models of diabetic retinopathy in diabetic retinopathy, the ONO-1301 prevented the progression of diabetic retinopathy in diabetic rats. In the present study, we examined the therapeutic effects of ON3 on the vascular calcification in adenine-induced chronic kidney disease rats.
nephropathy and obstructive uropathy. Here, we aimed to investigate the therapeutic efficacies of ONO on progressive CKD and vascular calcification in a rat model of adenine-induced CKD.

**Methods:** Male Sprague-Dawley rats at 13 weeks of age were fed with the diet containing either 0.75% (CKD) or 0% (control) adenine along with 2.5% protein. After 3 weeks, animals were divided into one of two treatment groups with equivalent kidney dysfunction. For the following 5 weeks, animals were fed with standard rat chow, and ONO (6mg/kg/day) or vehicle buffer was orally administered. Urine, serum, kidneys and thoracic aorta were obtained and subjected to evaluation.

**Results:** Treatment with ONO did not significantly improve adenine-induced renal insufficiency and renal histological alterations. However, vascular calcification (von Kossa staining), the Ca and Pi content of the thoracic aorta and serum osteocalcin levels were significantly decreased by treatment with ONO compared with the control CKDanimals. In addition, treatment with ONO significantly recovered the levels of matrix GlA Protein and Fetuin-A suppressed by adenine-induced CKD, and suppressed the overexpression of RUNX2 in the VSMC of the thoracic aorta (immunohistochemistry).

**Conclusions:** Taken together, these results suggest the protective role of ONO on vascular calcification via regulating the levels of RUNX-2 and locally acting inhibitors of vascular calcification in the experimental CKD model.

**Funding:** Pharmaceutical Company Support - ONO pharmaceuticals

**FR-PO639**

**Usefulness of Tubular Reabsorption of Phosphate as a Probable Surrogate Marker for Phosphate Regulation in Chronic Kidney Disease**

**Yu Ah Hong,1 Myung Hyun Lee,1 Ji Hee Lim,1 Min Young Kim,1 Ji Hyun Yu,1 Seun Deuk Hwang,1 Bum-Soon Choi,1 Chul Woo Yang,1 Yong-Soo Kim,1 Cheol Whee Park.1**

**1Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary’s Hospital, College of Medicine, The Catholic Univ of Korea; 2Div of Nephrology, Dept of Internal Medicine, Korean Univ.**

**Background:** Fibroblast growth factor 23 (FGF23) and soluble α-Klotho, which are emerging potential biomarkers of phosphorus and vitamin D metabolism, change progressively beginning in early chronic kidney disease (CKD) to maintain normal phosphorus. However, its use for an early surrogate marker of CKD-mineral and bone disorder (MBD) is limited in clinical practice. The tubular reabsorption of phosphate (TRP) has been commonly used to assess the renal tubular phosphate transport. The aim of this study was to investigate the earliest biomarker for CKD-MBD related to the estimated GFR (eGFR) in CKD patients.

**Methods:** We performed a cross-sectional study in 93 stable patients with predialysis CKD stage 1-5. TRP, eGFR, calcium, phosphate, intact PTH (iPTH), 25-hydroxyvitamin D3, serum FGF23 and urine soluble α-Klotho levels were measured.

**Results:** As renal function declined, TRP significantly decreased (P <0.001; r =0.763) and both iPTH and serum FGF23 increased (P <0.001; r =0.598, P <0.001; r = -0.453, respectively) for the augmentation of phosphaturia. Decreased eGFR and increased iPTH were found to be independently associated with decreased TRP, but did not associate with urine soluble α-Klotho and serum FGF23 in the multiple linear regression analysis. Increased serum FGF23 was only independently associated with decreased eGFR. The areas under the curve (AUC) for serum FGF23 and TRP are 0.598 and 0.739, respectively (P < 0.05).

**Conclusions:** TRP is a simple, useful and cost-saving method compared with serum FGF23 and urine soluble α-Klotho for the assessment of the altered mineral metabolism of CKD patients.

**FR-PO640**

**Phosphate Binder Use and Mortality in Chronic Kidney Disease: A Propensity-Based Analysis**

**Sankar D. Navaneethan,1 Susana Arrigain,2 John W. Sharp,3 Joseph V. Nally,1**

**1Nephrology; 2Quantitative Health Sciences, Cleveland Clinic.**

**Background:** Higher serum phosphorus is associated with an increased mortality in chronic kidney disease (CKD). The practice patterns of phosphate binder use and their associations with mortality in non-dialysis dependent CKD were examined.

**Methods:** The factors associated with the use of calcium and non-calcium phosphate binders in those with stage 3 and 4 CKD were studied using logistic regression models. The associations between phosphate binder use and mortality were examined using propensity matching and Cox models.

**Results:** Out of 13,325 patients with serum phosphorus levels measured, 945 patients were on phosphate binders. 939 patients who had phosphate binder during follow up were matched using caliper width of 0.1. After matching, all of the baseline variables had standardized differences <0.10% between those who were and were not on binders.

238 (25%) of them were prescribed non-calcium based binders and the rest were on calcium based binders. Each 5 kg/m2 higher BMI (OR 1.12, 95% CI 1.01, 1.25), 1 mg/dl higher serum phosphorus (OR 1.35, 95% CI 1.13, 1.61) and 1 mg/dl higher serum calcium (OR 1.35, 95% CI 1.06, 1.72) were associated with higher odds of being prescribed a non-calcium based binder. In the matched cohort, phosphate binder use was not significantly associated with mortality who were treated for at least 6 months. However, those who were treated for one year with a binder had a non-significant lower mortality risk (Hazard ratio: 0.85, 95% CI 0.66, 1.10). There were no differences in the risk for death between calcium and non-calcium based binders.

**Conclusions:** Short-term use of phosphate binder was not associated with lower risk for mortality in stage 3 and 4 CKD. Our results also suggest the need for studying the potential benefits of long-term phosphate binder use in this population.

**Funding:** Pharmaceutical Company Support - Genzyme

**FR-PO641**

**Accelerated Progression of Vascular Calcification in Children with CKD Is Associated with Baseline Fetuin-A and Vessel Characteristics**

**Rukshana C. Shroff,2,3 Lesley Rees,3 Melanie Hiorns,3 John E. Deanfield,2 Cathy Shanahan.3**

**1 Renal Unit, Great Ormond Street Hospital for Children, United Kingdom; 2Vascular Physiology Unit, Institute of Child Health, United Kingdom; 3Radiology Unit, Great Ormond Street Hospital, United Kingdom; 4Cardiovascular Div, King’s College London, United Kingdom.**

**Background:** Vascular calcification is thought to begin early in CKD and progress rapidly on dialysis. We examined vascular changes as seen on vessel imaging with a quantitative and histological assessment of the vascular Ca load on arterial biopsy samples to study progression of vascular changes through pre-dialysis CKD, dialysis and after transplantation.

**Methods:** 48 children (16 pre-dialysis CKD 4.5 and 32 on dialysis) had vascular imaging (carotid intima-media thickness [cIMT], pulse wave velocity [PWV] and coronary artery calcification [CAC] on CT scan), biomarker analyses and an arterial biopsy (at the time of renal transplantation or PD catheter insertion). The Ca load in the vessel wall was quantitated and detailed histology performed to study hydroxypatite deposition, vascular smooth muscle cell apoptosis and osteogenic differentiation. 43 children (22 dialysis and 21 transplants) had a second set of imaging after 14.2 ± 3.9 months.

**Results:** The baseline vessel Ca load strongly correlated with cIMT in dialysis patients (p=0.005) whereas 11 of 16 pre-dialysis patients had normal cIMT. Dialysis patients had a significant annualised increase in cIMT and PWV (p<0.005 and p=0.03). CAC increased in 5 children with baseline CAC and was found in 3 other.

cIMT progression showed a close correlation with the vessel Ca load (r=0.67). Patients with cIMT progression had the highest apoptotic index implying vascular smooth muscle cell loss and greater osteogenic differentiation. The baseline cIMT (r=0.31) and Fetuin-A levels (r=0.41), but not FGF-23, 25-hydroxyvitamin D or osteopontin associated with cIMT progression. Changes in PWV and CAC did not correlate with vessel Ca load.

**Conclusions:** Calcification is rapidly progressive on dialysis and strongly correlates with baseline vessel wall characteristics and Fetuin-A levels. Fetuin-A may be a useful biomarker to predict rapid progression of vascular calcification in CKD.
FR-PO642

International Trends in Markers of Mineral and Bone Disorder (MBD) among Hemodialysis Patients

Francesca Tentori,1,2 Douglas S. Fuller,1 Bruce M. Robinson,1,3 Vittorio E. Andreucci,1 Takashi Akiba,1 Brian Bieber,1 Yun Li,1,3 Raymond C. Vanholder,4 Ronald L. Pisoni,1 1Arb Res Collab Hlth, Ann Arbor; 2Vanderbilt Univ, Nashville; 3Uni of MI, Ann Arbor; 4Univ Hosp, Gent; 5Univ Federico II, Naples; 6TWMC, Tokyo.

Background: Recent MBD guidelines (KDIGO ‘09) and changes in reimbursement systems (e.g., Jan ’11 US bundled payment) may have led to changes in clinical practice and impacted levels of serum phosphorus (P), calcium (Ca), and PTH. We tested this hypothesis within each region of the international DOPPS cohort.

Methods: Survey-weighted linear spline regressions adjusted for seasonality, age, black race (in US), sex, vintage, and catheter use to estimate temporal trends in frequency of PTH measurement; mean serum parathyroid hormone (PTH), P, Ca, and corrected Ca (Ca alb); and reported target levels between Aug ’10 and Dec ’12.

Results: The % of patients with a PTH measurement in a 3-mo period declined in the US (96% to 84%) and Europe (EUR; 84% to 75%); but not in Japan (JP; 79% to 75%). There were no trends in the frequency of Ca and P measurement. Mean P fell 0.15 mg/dl (to 5.09 mg/dl) in the US and 0.08 mg/dl (to 4.84 mg/dl) in EUR; no trend was observed in JP (5.33 mg/dl). No clear trend in mean Ca or Ca alb levels were observed for US (mean Ca 9.10 mg/dl and EUR (mean 9.25 mg/dl)); Ca alb fell 0.17 mg/dl in JP (9.02 mg/dl in Dec ’12). US mean PTH level rose 27% to 432 pg/ml between Aug ’10 to Apr ’11, stabilizing thereafter. No changes were seen in EUR (mean 333 pg/ml) or JP (mean 149 pg/ml). Reported upper limit of PTH target levels increased in the US but not EUR or JP; no changes in Ca or P upper limits were observed.

Conclusions: Trends towards lower P (US and EUR) and higher PTH (US) levels are strong and may reflect practice changes in response to KDIGO guidelines and US bundled payment. The potential impact of these changes on clinical outcomes remains to be determined.

Funding: Pharmaceutical Company Support - DOPPS is supported by research grants from Amgen, Kyowa Hakko Kirin, AbbVie, Sanoﬁ Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, with additional country-speciﬁc support provided in Canada by Amgen-Canada, Janssen, BHC Medical, Takeda and Kidney Foundation of Canada, and in Germany by Hexal and WiNe Institute. Support from the DOPPS sponsors is provided without restrictions on publications.

FR-PO643

The PARADIGM Trial: Cinacalcet versus Vitamin D as Monotherapies for Treatment of Secondary Hyperparathyroidism in Patients on Dialysis

James B. Wetmore,1 Konstantin Gurevich,2 Stuart M. Sprague,3 Gerald A. Da Roza,3 John E. Buerkert,4 Maureen T. Reiner,5 William G. Goodman,6 Kerry Cooper,1 Hennepin County Medical Center; 2Fresenius Medical Care Russia; 3NorthShore U Health System; 4U British Columbia; 5Columbia Nephrology Associates; 6Amgen Inc.

Background: Cinacalcet (Cin) and vitamin D (vitD), often used in combination, have not been compared directly as monotherapy for the treatment of secondary hyperparathyroidism (SHPT) in patients on dialysis.

Methods: This study compared the efficacy of Cin to vitD as monotherapies in reducing parathyroid hormone (PTH) levels over 1 yr of treatment. The primary endpoint was mean % PTH reduction between wks 40-52. After SHPT treatment washout, patients (N=312) with PTH > 450 pg/ml were randomized to vitD (n=157) or Cin (n=155).

Results: Relatively severe SHPT was present at baseline, with mean (SD) PTH 846 (431) pg/ml in the Cin arm and 816 (426) pg/ml in the vitD arm. PTH reduction was modest and did not differ between study arms (12% Cin vs 7% vitD, P = 0.346). Mean (SD) dose of Cin = 83.1 (5.0) mg/day and vitD = 20.0 (12.4) mcg/wk (paricalcitol equivalents). Secondary efﬁcacy measures also did not differ between arms. Hypercalcemia and hyperphosphatemia were more common in the vitD arm, while hypocalcemia was more common in the Cin arm. Post hoc analyses revealed that the use of dialysate calcium < 2.5 mEq/L or non-use of calcium-based binders negatively impacted PTH reduction during Cin monotherapy (reported separately).

Conclusions: Patients with relatively severe SHPT demonstrated modest reductions in PTH when using Cin or vitD as monotherapies. Combined treatment, using agents with unique mechanisms of actions and divergent effects on Ca and P levels, may be required among those with more advanced disease.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
FR-PO645

Metabolic Acidosis Stimulation of Bone Fibroblast Growth Factor 23 Requires Intracellular Calcium Signaling and Prostaglandin Synthesis

Nancy S. Krieger, Christopher D. Culbertson, Kelly Kyker-Snowman, David A. Bushinsky. Medicine, Univ of Rochester, Rochester, NY.

Background: Serum fibroblast growth factor 23 (FGF23) increases in chronic kidney disease (CKD) and decreases renal phosphate (Pi) reabsorption and serum 1,25(OH)2D3. Patients with CKD have decreased acid excretion leading to metabolic acidosis (MET). MET is buffered by bone with release of calcium (Ca) and Pi. FGF23 is synthesized in osteoblasts and osteocytes and we have shown that MET stimulates FGF23 in mouse bone and primary osteoblasts. We hypothesize that MET increases FGF23 through intracellular Ca(2+) signaling and prostaglandin release.

Methods: Neonatal mouse calvariae or primary osteoblasts were incubated in neutral (NTL, pH=7.44, Pco2=38 mmHg, [HCO3-]=13 mM) medium ± 2-APB (50 µM), an inhibitor of Ca2+, or ± NS398 (1 µM), an inhibitor of prostaglandin synthesis. Medium FGF23 was measured by ELISA; calvarial or cell RNA was analyzed by realtime PCR with expression normalized to RPL13A.

Results: Both 2-APB and NS398 significantly inhibited MET-induced medium FGF23 protein and calvarial FGF23 RNA as well as bone resorption at 48h (not shown).

Conclusions: In primary cells where there is no mineral Pi present, 2-APB significantly inhibited the MET-induced increase in FGF23 RNA expression at 6h (NTL=0.9±0.2, MET=1.6±0.3, NTL+2-APB=1.0±0.3, MET+2-APB=1.1±0.2). NS398 also significantly inhibited the MET-induced increase in FGF23 RNA expression in primary osteoblasts at 6h (NTL=1.5±0.4, MET=3.2±0.6, NTL+NS398=1.8±0.3, MET+NS398=0.9±0.2).

Funding: NIDDK Support, Private Foundation Support

FR-PO646

Comparative Effects of FGF23 Antagonism with Calcimimetic versus FGF23 Neutralizing Antibody in Uremic Rats


Background: Fibroblast growth factor 23 (FGF23), a 32kD protein secreted by bone, is a phosphaturic hormone important in phosphate and vitamin D (VitD) regulation. As renal function declines serum FGF23 increases and is associated with progressive renal failure, left ventricular hypertrophy and increased mortality.

Methods: To determine effects of FGF23 antagonism in preclinical uremic (CKD) rats, we compared effects of decreasing serum FGF23 with calcimimetic, R-568, versus FGF23 antibody neutralization in male, S-D rats (5/6Nx) or sham-operated) on a high P diet. End points: serum PTH, Ca²⁺, P, bone, survivability, vascular calcification.

Results: Calcimimetic R-568 in 5/6Nx rats increased serum P, decreased Ca²⁺, PTH, FGF23, and FGF23 mRNA and protein in bone without significant static or dynamic histomorphometric changes. A separate group of CKD rats treated with 10ng VD3 had increased serum FGF23; concomitant treatment with R-568 decreased FGF23 and PTH in VitD-treated rats. Suppression of FGF23 in serum/bone by R-568 is likely through activation of the parathyroid calcium-sensing receptor and resulting decrease in PTH, a regulator of FGF23. FGF23-Ab significantly increased serum P, Ca²⁺, VitD, renal 24-h P excretion and improved high turnover bone disease/mineralization in CKD rats. However, FGF23-Ab promoted aortic calcification and death in CKD rats.

FR-PO647

Neutrophil Gelatinase-Associated Lipocalin (NGAL) Stimulates In Vitro Production of Fibroblast Growth Factor-23 (FGF23) in MLO-Y-4 Osteocyte Cultures

Shweta Bansal, ¹,² Khaled Khazim,¹ Basant Bhandari,¹ Sherry L. Werner,¹ Hanna E. Abboud,¹ Paolo Panti.¹ ¹Dept of Medicine/Div of Nephrology, Univ of Texas Health Sciences Center at San Antonio, Texas; ²Renal Section, ALMAVA Hospital, San Antonio, TX.

Background: Regulation of FGF23 in chronic kidney disease (CKD) remains only partially defined. Besides established actions of phosphorus and 1,25(OH)2D3 on FGF23 in CKD, positive correlation has been described between FGF23 and interleukin-6 and tumor necrosis factor-α (TNFα) in this patient population suggesting a possible stimulatory action of inflammation on FGF23 expression. We recently found strong positive correlation between FGF23 and the acute phase reactant NGAL (r=0.72, p=0.001) in CKD patients. This association was independent of renal function, serum phosphorus and C-reactive protein, suggesting direct functional interaction between NGAL and FGF23. Since osteocytes are the only cell type producing FGF23 and they express the endocytic receptor megalin which binds NGAL with high affinity, we hypothesized that close association between NGAL and FGF23 in CKD patients is explained by direct stimulatory action of NGAL on the osteocytic synthesis and secretion of FGF23.

Methods: MLO-Y-4 osteocytic cells were conditioned overnight with serum-free medium, incubated with 0.5-5 nM NGAL, 10 nm 1,25(OH)2D3, 10 ng/ml TNFα or vehicle for 24 hours and finally tested for FGF23 mRNA expression by quantitative RTPCR.

Results: FGF23 mRNA expression was increased 1.6 ± 0.5 fold by 2.5 mN NGAL (n=3), 3.2 ± 0.3 fold by 1.25(OH)2D3 (n=2), and was not affected by exposure to TNFα.

Conclusions: NGAL directly stimulates FGF23 production in vitro although with lower strength than 1,25(OH)2D3. Since circulating NGAL is very high and 1,25(OH)2D3 is low in CKD patients, we propose NGAL may contribute to the increased production of FGF23 in CKD.

Funding: Veterans Affairs Support

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

513A
Serum 1,25 D levels increased in only the early CKD group (early CKD, 36.0 [33.0-39.0] to 47.0 [33.0-78.0], p < 0.05; advanced CKD, 14.5 [13.0-19.0] to 14.5 [9.3-17.0], p = 0.12). Serum intact PTH levels decreased in only the advanced CKD group (early CKD, 23 [19-27] to 25 [21-30], p = 0.08; advanced CKD, 124 [73-145] to 85 [61-168], p < 0.05).

Conclusions: Our findings suggested that standard low-protein diet decreases serum FGF23 levels with various benefits on CKD-MBD control from early to advanced CKD stages.

Funding: Private Foundation Support

FR-PO649
Serum Mineral Parameters Are Associated with Blood Cell Morphology in Non-Diabetic Chronic Hemodialysis Patients Basri Budak,1 Mehnur Kanbay,1 Ali Akcay,1 Ali Riza Odabas,2 Serkan Kubilay Koc.1

Methods: Seventy non-diabetic chronic HD patients (male/female: 41/29) were enrolled in the study. Exclusion criteria were as follows; presence of diabetes mellitus, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, presence of any kind of hematological disorder including iron deficiency anemia. Serum PTH, calcium and phosphorus levels were determined together with hemoglobin, red blood cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), white blood cell count, platelet count, mean platelet volume (MPV) and platelet distribution width (PDW).

Results: Mean age was 58 ± 14 years and mean dialysis vintage was 98 ± 58 months. Serum mean PTH level was 398 ± 339 ng/ml; calcium, 8.53 ± 0.89 mg/dl and phosphorus, 4.43 ± 1.38 mg/dl. Serum PTH was significantly inversely associated with RDW (r = 0.24, p = 0.03). Serum phosphorus levels were significantly associated with MCV (r = 0.24, p = 0.004), WBC (r = 0.30, p = 0.001), platelet count (r = 0.38, p = 0.001) and MPV (r = -0.32, p = 0.008).

Conclusions: Serum PTH was not related to parameters of blood cell morphology except for RDW. Increased serum phosphorus levels were associated with increased total leukocyte and platelet counts which may represent increased inflammation. Also high serum phosphorus levels significantly associated with low red blood cell and platelet volumes.

FR-PO650
Low FGF-23 Levels Suggest Malnutrition in Maintenance Hemodialysis Patients Sonoo Muzzin,1 Yoshiko Nishizawa,1 Kazuomi Yamashita,1 Kyoko Ono,1 Maya Oda,1 Tsuru Nakazono,1 Kohji Usui,1 Kenichiro Shimogoto.1

Methods: Non-conditional logistic regression analysis showed that age, duration of dialysis, diabetes, FGF23 and Klotho protein, hsCRP, lipids and other biochemical parameters were analyzed and compared between the two groups, while non-conditional logistic regression were used for multivariate analysis to determine the risk factors for CIMT thickening.

Results: Among the 88 MHD patients, increased CIMT was found in 53 patients (60.2%), while the remaining 35 patients (39.8%) had normal CIMT. The median of the two sets of Klotho was 1.5mm and 1.0mm respectively. Univariate analysis indicated that the average age of patients with CIMT thickened group (66±10.61 years) was 10.6 years higher than that of the group with normal CIMT was 58±6.11 years (p=3.32, P<0.001). Diabetes prevalence of the CIMT thickened group was 37.7%. Diabetes prevalence of the group with normal CIMT was 17.1% (x²=4.294, P=0.038). The median of the two sets of FGF23 were 127.82 ng/L and 86.74 ng/L respectively, the difference was statistically significant (Z=3.713, P<0.000). The median of the two sets of hsCRP were 5.43 ng/L and 2.19 ng/L respectively, the difference was statistically significant (Z=3.547, P<0.000).

Conclusions: Serum hsCRP, FGF23 and age are independent risk factors for CIMT thickening in MHD patients.

Funding: Private Foundation Support

FR-PO651
The Fasting Fractional Excretion of Phosphate Is Correlated with FGF23 Levels, Mortality and Morbidity in CKD Patients Not on Dialysis Patricia Quadros Branco,1 Teresa Adragao,1 Ricardo Vizinho,1 Maria Augusta Cabrita Silva Gaspar,1 Andre L. Weigert,1 Joao Faro-Viana,2 Jose Diogo Barata,1

Methods: We studied 120 CKD pts (73% male, 27% diabetic, mean age 65 ± 13.7 years) divided into 3 groups: 1) early CKD (95.7% respectively in CKD stages 3, 4 and 5) during 23.9 ± 7.9 months.

Results: FGF23 (C-Terminal, ELISA Immutopics). FEP(%) was calculated with the formula (UPO4 x PCr):(PPO4 x UCr) x 100. Blood and urine samples were taken simultaneously in a fasting steady state, after discarding overnight urine (Payne RB).

Results: (4.1-5.9] and FGF-23 (pg/ml) [1120 (272-4080) vs. 1570 (357-5860)] levels in patients with carotid artery atherosclerosis, analyze the relationship between carotid intima-media thickness(CIMT) and serum high sensitive c-reactive protein(HsCRP), fibroblast growth factor 23(FGF23), Klotho protein levels.

Study on Correlation between Carotid Intima-Media Thickness with Serum HsCRP, FGF23 and Klotho Protein in MHD Patients Ying Sun, AiQun Chen, Hua Wu. Nephrology. Beijing Hospital of the Ministry of Health, Beijing, China.

Background: To understand the clinical feature of the maintenance hemodialysis(MHD) patients with carotid artery atherosclerosis, analyze the relationship between carotid intima-media thickness(CIMT) and serum high sensitive c-reactive protein(HsCRP), fibroblast growth factor 23(FGF23), Klotho protein levels.
However, it is unclear whether FGF23 is associated with carotid artery plaque (CAP) which is an indicator of atherosclerosis in predialysis patients. The aim of the present study was to clarify the relationship between FGF23 and CAP in patients with CKD not on dialysis.

**Methods:** Two-hundred seventy-seven predialysis CKD patients were enrolled in this cross-sectional study. CAP was assessed by B-mode Doppler ultrasound. Intact FGF23 was measured using a two-site monoclonal antibody ELISA in each patient. The risk factors for CAP were evaluated using a logistic regression model.

**Results:** We found CAP in 66.8% of the patients. The prevalence of CAP increased across CKD stages: 23.3% in CKD stages 1-2, 67.6% in stage 3, 76.2% in stage 4, and 79.8% in stage 5 (p<0.001). In a multivariable analysis, age, smoking, diabetes mellitus and log FGF23 (odds ratio [OR], 2.51; 95% confidence interval [CI], 1.26 to 5.36) were each identified as a risk factor for CAP. The study population was divided in quartiles of FGF23 levels. The prevalence of CAP was higher with increasing quartiles of FGF23 levels (first quartile 38.2%; second quartile 70.0%; third quartile 80.0%; fourth quartile 78.3%). Compared with the lowest FGF23 quartile, each subsequent quartile had a progressively higher OR for CAP, adjusted for confounders (OR for second quartile, 4.70 [95% CI, 1.74 to 13.42]; for third quartile, 5.83 [95% CI, 1.89 to 19.30]; and for fourth quartile, 7.72 [95% CI, 2.08 to 31.25], respectively).

**Conclusions:** The prevalence of CAP is increased with the decline in the kidney function. FGF23 was also identified as an independent factor for CAP in patients with CKD not on dialysis.

**Funding:** Private Foundation Support

**FR-PO654**

**Increases in FGF23 May Not Be the Initial Trigger of Secondary Hyperparathyroidism in Early CKD**

**Isabel Martínez,**1 Ramón M. Saracho,2 Yolanda Almaden Peña,3 Adriana S. Dusso,3 Mariano Rodriguez.4 **1Nephrology, Hospital Güell, Barcelona, Spain; 2Nephrology, HUSA, Spain; 3IMIBIC, Cordoba, Spain; 4IRBLleida, Spain.**

**Background:** Secondary Hyperparathyroidism (SH) starts at early stages of CKD and elevations in FGF23 were shown to precede the changes in serum calcium, phosphate and calciotriol predisposing to increases in PTH. This study examined the contribution of early increases in FGF23 to the onset of SH in CKD stage 1.

**Methods:** Thirty three patients, CKD1 (creatinine clearance >90ml/ml) of different etiologies, were included. At baseline and at 6 months, FGF23, PTH, calcium, phosphorus, and calciotriol were measured.

**Results:** Median age was 56 years, 75% males. At baseline, mean values of FGF23, PTH, calcium, phosphorus and calciotriol were 160.8±121.5 pg/ml, 141.2±86.9 pg/ml, 2.48±0.59 mg/dl, 3.88±1.82 mg/dl and 30.6±22.3 pg/ml, respectively. After 6 months, FGF23 and PTH significantly increased (p<0.05), while calcium, phosphorus and calciotriol significantly decreased (p<0.05). The increase in PTH was significantly higher in patients with higher FGF23 at baseline (p<0.05).

**Conclusions:** FGF23 increases in early stages of CKD could not be identified as an initial trigger for SH.

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

**FR-PO655**

**The Modification of the Effect of FGF23 on the Coronary Artery Calcium Score by Fractional Excretion of Phosphate in Patient with Pre-Dialysis CKD**

**Shin-young Ahn,**1 Seungmi Lee,2 Kook-Hwan Oh,3 Curie Ahn,2 Dong Wan Chae.1 **1Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam-si, Republic of Korea; 2Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.**

**Background:** A recent study demonstrated that cardiovascular (CV) mortality was highest in the population having low FEP below high FGF23 level. Hence, we investigated the effect of FGF23 on the intermediate variables known to be related to CV mortality such as CACS, pulse wave velocity (PWV) and LVH according to the FEP level in an on-going observational cohort of CKD in Korea.

**Methods:** KNOW-CKD is an on-going, prospective, university hospital based observational cohort study under the sponsorship of Korean Center for Disease Control and Prevention. Cross-sectional analysis was performed in 702 patients. Severe CAC was defined as Ca score of ≥200 Agatston units (AU) and we regarded mean of the brachial-ankle PWV (MAPWV) ≥ 1600 cm/s as a significant arterial stiffness.

**Results:** We developed four categories defined by FGF23 and FEPQo above or below their medians as follows: low FGF23/low FEPQo, high FGF23/low FEPQo, low FGF23/high FEPQo, high FGF23/high FEPQo. The participants with high FGF23/high FEPQo had more frequently diabetes, hypertension, and advanced CKD compared with the other three groups. They also had lower Hb, albumin, and 1.25 vitamin D and had higher serum P, alkaline phosphatase, and intact PTH. The mean values of CACS and MAPWV were significantly higher in this group and the incidence of LVH was also highest in this group. After multivariable regression analysis, neither of these groups nor FGF23 level could be an independent risk factor for severe CAC, significant arterial stiffness, or LVH. But, in subgroup analysis, high FGF23 was an independent risk factor for severe CAC in the patients with low FEPQo (OR=2.309, 95% CI=1.036-5.145, p=0.041).

**Conclusions:** The participants with high FGF23/high FEPQo demonstrated the most severe features in CAC, PWV and LVH largely due to the more frequent presence of comorbidities such as diabetes, hypertension, and advanced CKD. Only in the participants with low FEPQo, high FGF23 was an independent risk factor for severe CAC.

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

**FR-PO656**

**Fibroblast Growth Factor 23 Predicts Progression of Chronic Kidney Disease in Children**

**Anthony A. Portale,**1 Alison G. Abraham,2 Myles S. Wolf,3 Isidro B. Salusky,4 Harald Jüppner,5 Bradley A. Warady,6 Susan L. Furth.7 **1Univ of CA San Francisco; 2University of Washington, Honolulu, HI; 3Children's Hospital of Philadelphia; 4University of Miami Miller School of Medicine; 5Univ of CA Los Angeles; 6Harvard Medical School; 7Univ of Missouri-Kansas City; Univ of Pennsylvania.**

**Background:** Plasma FGF23 concentrations increase early in the course of chronic kidney disease (CKD) in children and predict disease progression in adults. Whether FGF23 associates with risk of CKD progression in children is unknown.

**Methods:** We measured plasma C-terminal FGF23 and determined GFR annually by plasma iothalamate clearance or the CKiD estimating equation in 418 children with CKD stages 2-4 enrolled in the Chronic Kidney Disease in Children (CKiD) study. We analyzed the association of baseline plasma FGF23 on time to 50% decline in GFR or start of renal replacement therapy using parametric regression stratified by glomerular or non-glomerular disease, adjusting for age, gender, race, GFR, proteinuria, blood pressure, serum phosphate, and PTH.

**Results:** At baseline, median age was 12 [IQR: 8, 15] years, GFR was 46 [34, 58] ml/min/1.73 m², and plasma FGF23 was 140 [97, 216] RLU/ml 2.5-fold higher than in healthy children. During a median follow-up of 62 [40, 73] months, 31% of subjects reached the CKD progression endpoint, 35 of 80 (44%) with glomerular and 94 of 338 (28%) with non-glomerular disease. Time to the endpoint was shorter in children with glomerular compared to non-glomerular disease (17 [4, 35] vs. 29 [19, 47] months) (P<0.001). Compared to non-progressors, progressors had lower GFR, higher levels of FGF23 and proteinuria, and lower 1,25(OH)2D (P<0.005). In univariate analyses, doubling of FGF23 was associated with modest reductions in time to the endpoint, 18% [95% CI = -33, 49] shorter time with glomerular, and 12% [95% CI = -6, 27] shorter time with non-glomerular disease, reductions of borderline significance.

**Conclusions:** Increased plasma FGF23 is a novel risk factor for CKD progression in children.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Abbott, Genzyme

**FR-PO657**

**Evaluation of Serum FGF23 Concentration in a Small Subset of Patient-Samples from the EVOLVE Randomized Trial by Two Independent iFGF23 Assays**

Marina Stolina, Denise C. Dwyer, Chun-ya Han, Bastian Dehmel, William G. Richards. **Amgen Inc.**

**Background:** Fibroblast growth factor 23 (FGF23, a phosphaturic hormone) is a regulator of calcium-phosphate metabolism. Increased FGF23 in serum from patients on dialysis is associated with increased mortality, treatment-resistant secondary
hyperparathyroidism and left ventricular hypertrophy. Growing interest in plasma/serum FGF23 as a clinical test highlights a need for a comparison of available assays in order to facilitate more meaningful interpretation of data.

**Methods:** In this study we compared the performance of 2 commercially available human intact FGF23 (iFGF23) assays: ELISA from Kainos Laboratories (Tokyo, Japan) and Luminex-based microbead assay (Millipore, Billerica, MA, USA) in a cohort of healthy adults (control, n=8) and baseline samples from patients on dialysis participating in the EVOLVE clinical trial (n=20).

**Results:** Both Millipore microbead iFGF23 and Kainos ELISA iFGF23 demonstrated 75-95% recovery of purified FGF23 standards in an inter-assay setting and acceptable (65-95%) recovery of the range of hRFGF23 concentrations spiked in to control serum. For the healthy adult group, median (25th-75th percentile) serum FGF23 was 30 (24-40) pg/ml (Kainos ELISA), and 12 (8-42) pg/ml (Millipore microbead); for the dialysis group corresponding serum FGF23 were 9780 (1955-18590) and 12090 (2195-17420) pg/ml. Kainos ELISA and Millipore microbead iFGF23 assays demonstrated close method agreement accessed by inter-assay correlation analysis of individual results (R²=0.9265, p<0.0001). Based on the range of FGF23 in serum from patients with chronic kidney disease, the broad functional concentration range of Millipore microbead assay (14-10,000 pg/ml) allowed for the use of a single 1:10 dilution for serum with FGF23 > 10,000 pg/ml. Due to the narrow functional dynamic range (10-800 pg/ml) of Kainos ELISA, substantial serial dilutions and repeat testing will likely be required.

**Conclusions:** Overall, the Kainos ELISA and Millipore microbead iFGF23 assays demonstrated desirable interchangeable analytical performance and may support clinical utility.

**Funding:** Pharmaceutical Company Support - Amgen Inc.

**FR-PO658**

**Fibroblast Growth Factor 23 and All-Cause Mortality in Hemodialysis Patients**

**Patients** David A. Drew, Hocine Tighiouart, Tammy Scott, Kristina Lou, Saeed Kamran Shaffi, Li Fan, Daniel E. Weiner, Mark J. Sarnak. Tufts Medical Center, Boston, MA.

**Background:** Fibroblast growth factor 23 (FGF-23) levels are elevated in hemodialysis patients. Few longitudinal studies have evaluated whether high FGF-23 levels independently contribute to mortality in this population.

**Methods:** We measured FGF-23 levels at baseline in 263 maintenance hemodialysis patients who had enrolled in the Cognition and Dialysis longitudinal cohort. The cross-sectional association between baseline patient characteristics and FGF-23 level was assessed using multivariable linear regression. Multivariable Cox regression with adjustment for demographics, cardiovascular risk factors, and measures of mineral metabolism was used to explore the association between FGF-23 levels with all-cause mortality.

**Results:** Mean (SD) age was 63 (17) years, 54% were women and 22% were African American. The median FGF-23 level was 3100 RU/ml (25th-75th percentile, 1100 - 8000 RU/ml). Younger age, lower prevalence of diabetes, longer dialysis vintage and higher levels of calcium and phosphorus were independently associated with higher FGF-23 levels (p < 0.05). Based on the range of FGF23 in serum from patients with chronic kidney disease, the wide functional concentration range of Millipore microbead assay (14-10,000 pg/ml) allowed for the use of a single 1:10 dilution for serum with FGF23 > 10,000 pg/ml. Due to the narrow functional dynamic range (10-800 pg/ml) of Kainos ELISA, substantial serial dilutions and repeat testing will likely be required.

**Conclusions:** Overall, the Kainos ELISA and Millipore microbead iFGF23 assays demonstrated desirable interchangeable analytical performance and may support clinical utility.

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

**FR-PO660**

**Pretransplant FGF23 Levels Are a Good Marker of Post-Transplant Calcium and Phosphorus Metabolism**

**Patients** Makoto Tsujita, Daijo Inaguma. Kidney Disease Center, Nagoya Daini Red Cross Hospital, Japan.

**Background:** Hypercalcemia and hypophosphatemia often occur after kidney transplantation. Recently, preemptive kidney transplantation (PET) has increased in Japan; however, it is not well-known whether PET is beneficial in calcium (Ca) and phosphorus (Pi) metabolism.

**Methods:** Thirty-two consecutive patients were enrolled in this study at Nagoya Daini Red Cross Hospital in 2011. Fifteen patients were in the PET group and 17 patients were in the non PET group. Parameters of Ca and Pi metabolism including full-length fibroblast growth factor 23 (FGF23) and intact parathyroid hormone (iPTH) were measured before transplantation and 1, 3, and 24 weeks after transplantation.

**Results:** FGF23 decreased dramatically in both groups after transplantation; however, FGF23 before transplantation and at 1 and 3 weeks after transplantation was significantly lower in the PET group than in the non PET group (p < 0.05). In contrast, although iPTH levels were higher in the PET group than in the non PET group before transplantation, the levels were lower at 24 weeks (p < 0.05). Corrected Ca (cCa) was lower at 24 weeks in the PET group (p < 0.05), whereas Pi was lower in the non PET group at 1 and 3 weeks (p < 0.05), but not significantly different at 24 weeks.

**Conclusions:** FGF-23 was independently associated with worse performance on a composite memory score, even after adjustment for potential confounders, including measures of mineral metabolism. High FGF-23 levels in HD patients may contribute to cognitive impairment.

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

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

**Underline represents presenting author/disclosure.**
Multivariate linear regression analysis revealed that FGF23 before transplantation was a better predictor of Ca and Pi disorders in early post-transplant recipients.

**Conclusions:** This study suggests that PET has beneficial effects on Ca and Pi metabolism and that pretransplant FGF23 levels are a good marker of post-transplant Ca and Pi metabolism.

---

**FR-PO661**

**Kidney Injury Increases FGF23 Independent of Reduced Glomerular Filtration Rate**


*Univ of Miami.*

**Background:** The mechanism of FGF23 elevation in CKD remains poorly understood. Decreased GFR is a primary determinant of high FGF23 in advanced CKD, but levels can be elevated in certain CKD patients despite near-normal GFR.

**Methods:** We tested the hypothesis that kidney injury itself increases FGF23. We measured serum phosphate, calcium, FGF23, PTH, 25D, and iohexol GFR in 3 groups: 1) CKD (N=19), 2) stable, long-term kidney transplant recipients (KT; N=8), and 3) kidney transplant donors and individuals with age-related GFR loss but no other evidence of CKD (N=11). We measured the same biochemical profile but used eGFR in healthy volunteers (N=20).

**Results:** Median FGF23 was comparable in kidney donors, individuals with age-related GFR loss and healthy volunteers. In contrast, median FGF23 was significantly higher in CKD group and median PTH was significantly higher in KT group, compared to healthy volunteers. Median FGF23 was significantly higher in CKD than KT patients (117 vs. 78 RU/mL, P=0.03) despite comparable mean iohexol GFR (53 vs. 57 mL/min/1.73 m²; P=0.47). Dietary phosphorus and calcium, serum calcium, PTH, 25D and 1,25D did not significantly vary between CKD and KT groups, suggesting that differences in FGF23 were not driven by these variables. However, serum phosphate was significantly higher in CKD group than KT group (3.6 versus 3.0 mg/dL, P=0.004).

**Conclusions:** Despite similar iohexol GFR, FGF23 is significantly higher in CKD patients compared to KT recipients. Differences in serum phosphate between the two groups may mediate these relationships. Our findings suggest that in CKD, the presence of kidney disease itself, independent of GFR reduction, could contribute to FGF23 excess.

*Funding:* NIDDK Support, Private Foundation Support

---

**FR-PO663**

**High Dose Intravenous Iron and Intact FGF23 in Uremic Rats**

Eva Gravesen,1 Jacob Hofman-Bang,1 Ewa Lewin,2,1 Klaus Olgaard,1 1Nephrological Dept P, Rigshospitalet, Univ of Copenhagen, Copenhagen, Denmark; 2Nephrological Dept B, Herlev Hospital, Univ of Copenhagen, Copenhagen, Denmark.

**Background:** Intravenous iron has been proposed to induce elevation of fibroblast growth factor 23 (FGF23), hypophosphatemia and osteomalacia. High FGF23 are associated with increased mortality in the CKD population. CKD patients often develop iron deficiency, anemia and need for i.v. iron. As such it is important to study the possible effects of iron on FGF23. In the present study the effect of of two different iron preparations, iron (III) isosmolate 1000 (Mono) and ferric carboxymaltose (Ferri) are examined on plasma FGF23 levels in this rat model.

**Methods:** A single high dose of 60 mg/kg b w of iron (III) isosmolate 1000 (A), or ferric carboxymaltose (B), or vehicle, was given i.v. and the effects on plasma FGF23, phosphate, Ca, PTH, transferrin, ferritin and iron was examined. NR rats were kept on a high phosphorus diet (0.9% calcium and 1.2% phosphorus), n=8 in each group. In study 1 samples for determination of FGF23 were obtained at time 0, 30, 60, 120, 180 min, and after 48 hours, and in study 2 at baseline and after one week. FGF23 was measured by the intact FGF23 assay from Kainos lab. Japan.

**Results:** The rats had significant uremia and hyperparathyroidism.Study 1: In the vehicle group FGF23 levels at baseline were 1354±167 pg/mL and 1551±329 at 30 minutes, and 990±155 at 48 hours. In group (A) FGF23 levels at baseline were 1191±184 and 1219±279 at 30 minutes and 890±257 pg/mL at 48 hours. In group (B) FGF23 levels at baseline were 1506±231 and 2027±267 at 30 minutes, and 1143±202 pg/mL at 48 hours. In study 2, FGF23 levels were 2986±780 pg/mL and 2279±475 after one week in the vehicle group, baseline FGF23 was 171±179 in the iron (III) isosmolate 1000 group and 1841±243 after one week. In the ferric carboxymaltose group baseline was 1560±347 and 1647±327 after one week. No significant differences in FGF23 levels were observed at any time point between the groups.

**Conclusions:** A single high dose of either iron (III) isosmolate 1000 or ferric carboxymaltose had no effect on intact FGF23 levels for up to one week after an intravenous injection in uremic rats.

*Funding:* Pharmaceutical Company Support - Amgen Inc.
Results: cIMT (mm) levels were higher in diabetic (0.84 ± 0.16) and non-diabetic CKD patients (0.70 ± 0.09) than controls (0.56 ± 0.36), p = 0.001. The mean CAC score (Agatston score: higher in diabetic (44±399) and non-diabetic CKD patients (98 ± 244) than controls (1.13 ± 0.74), p < 0.001. FGF-23 levels (pg/ml) were higher in diabetic CKD patients (237 ± 108) and non-diabetic CKD patients (199 ± 81) than controls (93 ± 2), p = 0.001. There was a positive correlation between cAC and cIMT levels. Log-FGF-23 levels were found to be positively correlated with cIMT and cAC. FGF-23 levels were also positively correlated with systolic blood pressure, duration of diabetes, phosphorus, Ca × P product and PTH. Multiple regression analysis showed that blood glucose and systolic blood pressure were independent factors associated with CAC, and that log-FGF-23, blood glucose, systolic blood pressure and albumin were independent factors associated with cIMT.

Conclusions: Diabetes and FGF-23 is associated with cAC and cIMT in CKD and the effect of FGF-23 seems to be independent of its regulatory function on phosphorus metabolism.

Funding: Government Support - Non-U.S.

FR-P0655

Acute and Six Months Mineral Metabolism Adaptation in Living Kidney Donors: A Prospective Study

Sophie M. De Seineux, Belen Ponce, Thomas Ermandez, Karine Hadaya, Andrea Trombetti, Pierre-Yves F. Martin.
Nephrology, Unit Hospital of Geneva, Geneva, Switzerland.

Results: After nephrectomy, donors presented transient hypocalcemia and secondary hyperparathyroidism. Both circulating FGF23 and α-Klotho decreased during the first post-operative days and FGF23 decline was positively correlated to hypocalcemia. At 6 months after donation, donors had lower eGFR and 1.25(OH)2D compared to predonation levels. Whereas 25(OH)D was unchanged. PTH levels increased at 6 months, resulting in decreased serum phosphate levels and renal tubular reabsorption of phosphate. In comparison to pre-donation, FGF23 levels were unchanged whereas circulating α-Klotho levels were lower than pre-donation. In unphosphonated rats, tissue Klotho expression levels did not change in the remnant kidney.

Conclusions: We show that acutely after nephrectomy, FGF23 is regulated by calcium levels. Six months after kidney donation, donors developed secondary hyperparathyroidism and lower phosphate levels probably related to 1.25(OH)2D deficiency. FGF23 levels did not rise in this specific population, whereas α-Klotho levels were only slightly decreased compared to predonation levels. Mineral metabolism adaptation to loss of kidney function in donors includes decrease in 1.25(OH)2D and increase in PTH and fractional excretion of phosphate resulting in decreased secrete phosphate level, independently of FGF23. These results challenge the primary role of FGF23 in phosphaturia and decreased vitamin D hydroxylation in renal mass reduction.

Funding: Government Support - Non-U.S.

FR-P0666

Solute Klotho Predicts Renal Phosphate Excretion in Moderate to Severe Chronic Kidney Disease

Kraiwiporn Kiattisunthorn, Chanchira Janwijit, Siriraj Medical School, Mahidol Univ, Thailand.

Results: Plasma, serum and urine were collected from 28 stage 3-5 CKD patients after fasting overnight. Maximal tubular reabsorption normalized by GFR (TmP/GFR) was used to determine renal threshold to filtered phosphate independent of dietary phosphorus, tissue release of phosphorus, and GFR. Serum creatinine was measured by enzymatic creatinine assay, whereas 24-hour phosphate was estimated using formula by CKD-EPI. Concomitant plasma Klotho was measured using human klotho ELISA kit (CUSABIO Biotech, Newk, DE) [infra- and inter-assay CV 4.9-8.1% and 8.3-13%, respectively]. Plasma c-terminal FGF23 was measured using human FGF23 (c-term) ELISA kit (Immunotops, Inc., CA, USA) [infra- and inter-assay CV 1.4-3.3% and 2.4-5.1%, respectively].

Results: Patient characteristics were shown in Table 1.

Funding: Private Foundation Support

PKP-0668

Klotho Expression Profile in a Wide Range of Human Tissues

Kathryn S. Lilley, Thomas F. Hiemstra, Li-Li Hsiao, Daniel Zehnder, Brigham and Women's Hospital, 2Warwick Medical School, United Kingdom; 3Univ of Cambridge, United Kingdom.

Results: Klotho is a 130kDa protein that imparts anti-aging properties and functions as a co-factor for the phosphatonin, FGF-23. Previous studies have shown that it is produced in the kidney, parathyroid gland, vascular tissue and chordee pleus of the brain. However, no study has explored its expression profile across different tissue types in humans at-to-date.

Methods: Ethics (IRB) approval was first obtained for this study. A wide range of formalin fixed normal human tissues removed during routine therapeutic or diagnostic procedures and part of the clinical tissue bank was analyzed by immunohistochemistry. For each tissue, at least 5 different cases were analyzed. A full length Klotho protein detecting antibody (Abcam, Cat. No. ab69208) was utilized at a concentration of 1:100 to 1:150.

Results: As previously described, significant renal Klotho protein expression was observed in the proximal and distal part of the tubular epithelium. On extensive analysis of tissues, differential Klotho expression was found in skin, intestine, endocrine androgenic and adrenocortical tissues, and also throughout the peripheral nervous system. The epithelial layer of the skin, small bowel, colon, mammary tissue, endodermite, prostate and salivary in tissues showed strong Klotho expression. The same observation was made for endocrine cells of the thyroid, islet cells of the pancreas and adrenal medulla. In neural tissue, Klotho expression was found primarily in neuronal cells, intermediate cells, cells of the reticular and cerebellum and neurons of the spinal cord, but also the myenteric plexus of the intestine. Smooth muscle cell (SMC) Klotho expression was confirmed in arteries of all tissues analyzed, but also observed in SMC of the intestine and myometrium. Hepatocytes did not stain for Klotho protein.

Conclusions: This study is the first to report the expression profile of Klotho in human tissues. Expression of Klotho may indicate a diverse function for Klotho in different tissues and cell types and render these cells a target for FGF-23 function.

Funding: Private Foundation Support
FR-PO669
Serum Soluble Klotho Level Is Associated with Aortic Aortic Calcification in Patients on Maintenance Hemodialysis
Hong Cai, Yucheng Yan, Renhua Lu, Minfang Zhang, Mingli Zhu, Weiming Zhang, Zhaohui Ni, Jia Qi Qian. Renal Dept, JiaoTong Univ RenJi Hospital, Shanghai, China.

Background: To determine the relationship between soluble Klotho and abdominal aortic calcification in maintenance hemodialysis(MHD) patients.

Methods: 129 cases of MHD patients were collected prospectively. Serum soluble Klotho levels were detected by ELISA. Abdominal lateral plain were used as a criteria to determine the abdominal aortic calcification. The abdominal aorta calcification score(AAC) was calculated. The level of soluble Klotho were observed in patients with different degree of calcification. Logistic regression analysis was used to determine the risk factors for abdominal aortic calcification in MHD patients. The standard statistics were used along with ROC analysis to evaluate the diagnostic value of soluble Klotho in abdominal aortic calcification.

Results: 87 in 129 patients had abdominal aortic calcification. The median AAC was 4.0(0.00, 11.00). The median Klotho concentration was 0.69(237.78, 1.82).63 ng/ml and the soluble Klotho concentration was negatively correlated with AAC. Risk of moderate to severe abdominal aortic calcification in patients with lowest quartile of the soluble Klotho concentration was significantly higher than those in highest quartile[OR=4.004, 95%CI(1.350-11.826), P=0.012], even by adjustment for demographic data, lifestyle factors and biochemical markers [OR=4.542, 95%CI(1.368-15.081), P=0.012], even by adjustment for demographic data, lifestyle factors and biochemical markers. Multivariate Logistic regression analysis showed that serum soluble Klotho levels and smoking were independent risk factors for severe calcification of the abdominal aorta. ROC-AUC of serum soluble Klotho to moderate to severe abdominal aortic calcification was 0.746(cutofE265.39mg/ml, accuracy 88.5% specificity 56.2%, P=0.001).

Conclusions: The lower serum soluble Klotho was independent associated with severe abdominal aorta calcification. Serum soluble klotho may have diagnostic value of MHD patients with severe abdominal aortic calcification. But still need to be further confirmed.

Funding: Government Support - Non-U.S.

FR-PO670
Soluble Klotho (sKl) and Fibroblast Growth Factor 23 (FGF23) Alterations in Pediatric (Ped) Renal Transplant (Tx) Patients (Pts) with Good Function Rachana Srivastava, Eileen D. Brewer, Poyyapakkam Srivaths.

Aim: To determine whether high-dose ergocalciferol and high-dose alfacalcidol could be the optimal choice for the treatment of secondary hyperparathyroidism in chronic hemodialysis patients.

Methods: We retrospectively reviewed 47 chronic hemodialysis patients to whom calcitriol could not be the optimal choice for the treatment of secondary hyperparathyroidism in chronic hemodialysis patients. We then compared the different components of mineral metabolism with paired Student’s t-tests pre and post conversion.

Results: Before the switch, the mean dose of alfacalcidol was 3.50 mcg per week. After being transferred to calcitriol, the mean dose was decreased by 20% to 2.86 mcg (p<0.0001). We observed a significant decrease in PTH of 11.87 pmol/L (p < 0.02), with a mean PTH of 94.47 and 82.60 pmol/L pre and post switch respectively. The mean corrected calcium level increased by 0.08 mmol/L (p = 0.001). No significant hypercalcemia was observed during this study. There was no significant change in phosphorus levels. Also, we observed a mean decrease of PTH of 9.45 pmol/L (p = 0.07) as well as an increase of the mean corrected calcium of 0.05 pmol/L (p = 0.05) in a subgroup of patients (n=22) for whom the medication was administered during the hemodialysis session, ensuring 100% compliance.

Conclusions: According to our study, calcitriol seems more effective than alfacalcidol in lowering serum PTH level in chronic hemodialysis patients. This suggests that calcitriol could be the optimal choice for the treatment of secondary hyperparathyroidism in chronic hemodialysis patients.

Funding: Private Foundation Support

FR-PO671
Association with Fetuin-A and Ecotopic Calcification in α-Klotho Mutant Mice
Nozomi Yokoyama,1 Hironori Yamamoto,2 Yuta Takakita,2 Masayuki Iwano,3 Eiji Takeda,4 "Clinical Nutrition, Health Bioeconomics, Univ of Tokushima, Tokushima, Japan; 2Health and Nutrition, Human Life, Sun-at Univ, Ehime, Japan; 3Nephrology, General Medicine, Faculty of Medical Sciences, Univ of Fukui, Fukui, Japan.

Background: α-klotho mutant (kl/kl) mice exhibit hyperphosphatemia, hypercalcification and hypervitaminosis D. These abnormalities are associated with growth retardation and ectopic calcification. Fetuin-A is a hepatic secretory protein acting as a systemic calcification inhibitor. However, it is still unknown about the role of fetuin-A in kl/kl mice.

Methods: Wild-type (WT) mice and kl/kl mice at 3- or 6-wk-old were used and given free access to regular chow and water. For histology using paraffin sections of kidney, aorta and heart with hematoxylin-eosin staining and immunohistochemistry (IHC), respectively. Gene expression analysis were performed using western blots (WB) and Real-time RT-PCR methods.

Results: Analysis of serial kidney, aorta and heart sections by IHC and von Kossa staining showed a high regional expression of fetuin-A protein in 6-wk-old kl/kl mice and its localization merged with calcifying sites. We also confirmed its co-localization with the calcified lesions in aorta and heart of chronic kidney disease rats. Interestingly, the high regional expression of fetuin-A in kidney was also observed at 3-wk-old kl/kl mice which had none of the renal calcification. Although WB analysis observed markedly high expression of fetuin-A in kidney of kl/kl mice, its renal mRNA levels were no significant differences between WT and kl/kl mice. In contrast, fetuin-A mRNA levels in liver of kl/kl mice were significantly increased than WT mice from 3-wk-old. Moreover, we found that plasma fetuin-A mRNA levels in kl/kl mice were significantly higher than WT mice.

Conclusions: These results suggest that the up-regulation of hepatic fetuin-A mRNA expression in kl/kl mice contributes to increase plasma fetuin-A levels and co-localize with calcified lesions as a inhibitor of hyperphosphatemia-induced ectopic calcification.

Funding: Government Support - Non-U.S.

FR-PO672
Transfer of Oral Alfacalcidol to Oral Calcitriol in the Treatment of Secondary Hyperparathyroidism in Chronic Hemodialysis Patients
Sandra Baszczyk, Jean-Philippe Lafrence, Vincent Pichette, Robert Zoë Bell, Martine Leblanc, Sarah Bezzaoucha, Michel Vallée. Nephrology Dept, Maisonneuve-Rosemont Hospital, Univ of Montreal, Montreal, Canada.

Background: There is no clear evidence in the literature regarding the optimal vitamin D therapy for the treatment of secondary hyperparathyroidism in chronic hemodialysis patients. Recent studies suggest that 1α-hydroxyvitamin D3 (1,25(OH)2D3) is the treatment of choice for patients with secondary hyperparathyroidism. We aimed to determine whether high-dose alfacalcidol could be more effective than alfacalcidol.

Methods: We compared 15 chronic hemodialysis patients treated with alfacalcidol therapy for the treatment of secondary hyperparathyroidism in chronic hemodialysis patients. Patients were randomised into two groups: 1) 1α-hydroxyvitamin D3 (1,25(OH)2D3) 0.5 µg/kg i.m. once a month and 2) high-dose alfacalcidol 30 µg/kg/day. Mean vitamin D levels at baseline were 28±12 ng/mL in group 1 and 25±9 ng/mL in group 2. In group 1, we observed a significant increase in iPTH of 19.4±6.0 pmol/L (p = 0.009). In group 2, there was no significant change in iPTH levels (p = 0.92) as well as an increase of the mean corrected calcium of 0.05 pmol/L (p = 0.05) in a subgroup of patients (n=22) for whom the medication was administered during the hemodialysis session, ensuring 100% compliance.

Conclusions: According to our study, calcitriol seems more effective than alfacalcidol in lowering serum PTH level in chronic hemodialysis patients. This suggests that calcitriol could be the optimal choice for the treatment of secondary hyperparathyroidism in chronic hemodialysis patients.

Funding: Private Foundation Support
Vitamin D Status in the Chronic Renal Insufficiency Cohort: Impact of Vitamin D-Binding Protein (DBP) Concentrations and Polymorphisms

Michelle Denburg,1 Thomas Jemielita,1 Jayanta Gupta,2 Martin Hewison,2 Myles S. Wolf,3 Mary B. Leonard,1 1Univ of Pennsylvania; 2UCLA Orthopaedic Hospital; 3Univ of Miami.

Background: Serum DBP concentrations influence bioavailability of 25-hydroxyvitamin D (25D). The 3 major DBP polymorphisms differ in affinity for 25D and racial distribution. Methods: Serum 25D, DBP, and PTH were measured in 1280 CRIC participants (pts). Free and bioavailable (bio) 25D were calculated using total 25D, albumin (Alb) and DBP levels, and with mathematical modeling based on DBP polymorphisms (geno-free and geno-bio). Linear regression was used to determine correlates of total, free, and bio 25D. Results: Median DBP was lower in black pts (10.6 vs 24.3 mg/dl, p<0.001) and 92 and 32% of black and non-black pts had <50 and <20 ng/ml 25D, respectively. Winter, obesity, diabetes, hypocalcemia, albuminuria, and lower eGFR were independently associated with lower levels of all forms of 25D, while older age, dietary vitamin D, and calcifedirol therapy were positively associated with all forms. Black race was associated with lower total, free and bio 25D using genotype-specific affinities, but higher free/bio if genotype was not considered.

Conclusions: Marked differences in racial distribution of serum DBP and DBP polymorphisms must be considered when assessing vitamin D status, particularly in the estimation of free/bio 25D.

Funding: NIDDK Support, Private Foundation Support
A Novel Vitamin D Receptor Modulator, VS-105, Reduces Blood Pressure and Improves Cardiac Function in 5/6 Nephrectomized Uremic Rats


Background: Vitamin D receptor modulators (VDRMs) are commonly used to manage hyperparathyroidism secondary to chronic kidney disease (CKD). A majority of CKD patients die from cardiovascular complications. Clinical observations demonstrate that VDRM therapy may provide cardiovascular and survival benefit for CKD patients. However, current on-market VDRMs exhibit a narrow therapeutic index (TI) of 1-4-fold (hypercalcemic side effects vs. PTH suppressing efficacy). VDRM-induced hypercalcemia remains a serious concern, which leads to the need for frequent drug dose titration and serum calcium monitoring. Significant clinical benefit may be derived from a VDRM with expanded TI and cardiovascular protective effects.

Methods: 5/6 nephrectomized (NX) male Sprague Dawley rat with established uremia exhibits elevated PTH, hypertension and abnormal cardiac function. Previously we have shown that after 2-weeks of i.p. or oral dosing in 5/6 NX rats, VS-105 in a non-hypercalcemic dose range suppressed PTH and reduced cardiac fibrosis (TI at ~50-fold). In this study, treatment of 5/6 NX rats by VS-105 (0.5 μg/kg, oral gavage, once daily, for 8 weeks) in the presence or absence of enalapril (30 mg/kg, p.o., via drinking water) suppressed serum PTH effectively without raising serum calcium.

Results: VS-105 alone reduced systolic blood pressure (from 174 ± 6 to 145 ± 9 mmHg, p<0.05) as effectively as enalapril (from 174 ± 6 to 164 ± 7 mmHlg, p<0.05). Echocardiographic evaluation showed that VS-105 also improved cardiac function such as E/A ratio, ejection fraction, and fractional shortening. Enalapril or VS-105 alone reduced left ventricular hypertrophy (LVH) significantly and VS-105 plus enalapril did not exhibit further reduction in LVH. The lack of hypercalcemic toxicity of VS-105 is due to its lack of effects on stimulating intestinal calcium transport and inducing the expression of intestinal calcium transporter genes such as Calb3 and TRPV6.

Conclusions: These studies demonstrate that VS-105 is a novel VDRM with an overall therapeutic profile that supports clinical development for its expanded use in pre-dialysis and dialysis CKD patients to achieve cardiovascular benefits of VDR activation.

Funding: NIDDK Support

FR-PO697

African-American and South Asian Patients with Chronic Kidney Disease and Vitamin D Deficiency Have a Blunted Response to Therapy with Standard High Dose Ergocalciferol Therapy

Gavin Dreyer, Magdi Yaqoob. Nephrology, Barts Health NHS Trust, United Kingdom.

Background: Patients from ethnic minority (EM) groups with CKD have a higher risk of cardiovascular morbidity and mortality and a higher prevalence of vitamin D deficiency. To date, no studies have investigated the response to ergocalciferol of patients from ethnic minorities with CKD and vitamin D deficiency in the UK.

Methods: We prospectively analysed 93 patients with non-dialysis dependent CKD who were prescribed high dose ergocalciferol for vitamin D deficiency between 1/8/2008 and 1/8/2010. Baseline 25 hydroxy vitamin D levels were measured at or more than 30 days beyond the last planned dose of ergocalciferol. Ethnicity was self reported and White ethnicity compared to a combined group containing African-American and South Asian patients. A 25 hydroxy vitamin D level of > 30 ng/ml after therapy was the main outcome measure.

Results: White patients (n=33) were older compared to EM patients (n=60), mean age (years) W = 64.4, EM 55.6, p<0.003. Ethnic minority patients had a higher proportion of diabetes (W = 18.2%, EM 35.0%, p<0.001). There was no difference in stage of CKD at baseline. Baseline 25 hydroxy vitamin D levels were lower in EM compared to W patients (W = 15.8 ng/ml, EM = 11 ng/ml, p<0.001). The mean duration of ergocalciferol therapy was 7.1 months, the mean total dose of ergocalciferol prescribed was 360.65 μg and neither differed significantly between groups. In a logistic regression analysis adjusted for age, sex, baseline 25 hydroxy vitamin D level, stage of CKD and cause of kidney disease, EM status was associated with a higher odds of failing to attain the primary outcome (OR 3.57, p=0.044, 95% CI 1.04 – 13.54).

Conclusions: EM patients may require intensified therapy with ergocalciferol including higher doses and longer duration of treatment to achieve recommended levels of 25 hydroxy vitamin D. Given this group has a higher burden of diabetes and cardiovascular risk, particular attention is required when prescribing and monitoring ergocalciferol in ethnic minority patients in order to achieve current recommended targets of serum 25 hydroxy vitamin D.

FR-PO680

Effects of 25-OH Vitamin D Levels on Homoglobin in the Chronic Kidney Disease Population

Jack Ellis, David Owshalimpur. Dept of Medicine, Madigan Army Medical Center, Tacoma, WA.

Background: As chronic kidney disease (CKD) progresses, so do the complications of bone mineral disease and anemia, contributing to the morbidity, mortality and overall health care expenditures in this population. 1.25-OH vitamin D has been shown to decrease serum parathyroid hormone (PTH) levels and improve anemia. 25-OH vitamin D has been shown to decrease PTH levels. One prior study found decreased erythropoietin (EPO) use in hemodialysis patients with increased 25-OH vitamin D levels after repletion with ergocalciferol. We examined the association between 25-OH vitamin D levels and anemia in the CKD 3-5 population, expecting that higher 25-OH vitamin D levels would correlate with increased hemoglobin levels.

Methods: A retrospective review of adult (18 years or older) patients with CKD 3-5 from January 2005 to January 2011 using the electronic health record in one Pacific Northwest center to determine the association between 25-OH vitamin D levels and hemoglobin. Secondary endpoints include reviewing data for any correlation between multiple variables to include PTH, ferritin, transferrin saturation, hemoglobin, and hematocrit.

Results: Three hundred and five CKD 3-5 patients were reviewed and 289 records had 25(OH) vitamin D levels. There was a significant correlation between 25-OH vitamin D level and hemoglobin. There was a statistically significant correlation between PTH and ferritin and a statistically significant inverse correlation between 25-OH vitamin D level and ferritin by Pearson correlation coefficients.

Conclusions: Although one prior study did show ergocalciferol use in hemodialysis patients resulted in decreased erythropoietin use, our study did not find a statistically significant correlation between hemoglobin and 25-OH vitamin D in CKD 3-5. Interestingly, an unadjusted analysis found both a direct correlation between ferritin and PTH and an inverse correlation between ferritin and 25-OH vitamin D levels. This is the first time in the literature which an inverse correlation between 25-OH vitamin D and ferritin and a direct correlation between PTH and ferritin has been reported in the CKD population.

Funding: Other U.S. Government Support

FR-PO681

Serum 25-Hydroxy Vitamin D Status Is Predictive of Hospitalization-Free Survival in Pre-dialysis and Dialysis Patients with Chronic Kidney Disease

Dong Ho Yang, So-young Lee, Seongeun Suh, Hun Jeong. Internal Medicine, Bundang CHA Medical Center, CHA Univ, Seongnam, Republic of Korea; Internal Medicine, Seoul Bukbu Hospital, Seoul, Republic of Korea.

Background: Vitamin D has pleiotropic effects important for the proper functioning of multiple systems. We investigated whether serum 25-hydroxy vitamin D (25(OH)D) levels influence hospitalization-free survival in patients with chronic kidney disease.

Methods: In this prospective study, serum levels of 25(OH)D were obtained from 210 patients with chronic kidney disease in the winter of 2009. Data regarding hospitalizations were collected over the subsequent 5 years.

Results: Vitamin D deficiency, as defined by a serum 25(OH)D level below 15 ng/ml, was observed in 76.7% of the patients. The mean 25(OH)D serum level was 13.6 ± 7.8 ng/ml in predialysis patients (n=62) and 11.3 ± 6.7 ng/ml in dialysis patients (n=148). During the 3-year follow-up period, 167 patients (28 predialysis and 79 dialysis) were hospitalized because of infections (27.4%), cardiovascular (23.6%), and cerebrovascular disease (7.5%). The predialysis and dialysis groups were divided into two subgroups based on the mean 25(OH)D serum levels: above and below average Kaplan-Meier analysis revealed that the risk of hospitalization was significantly lower in both predialysis and dialysis patients with above average serum 25(OH)D levels (log rank test: P = 0.04 and 0.02, respectively). Multivariate Cox proportional hazards models also demonstrated that the risk of hospitalization was significantly lower for patients with above-average serum 25(OH)D levels (hazard ratio [HR] 0.26, 95% confidence interval [CI] 0.12-0.57) and dialysis groups (HR 0.35, 95% CI 0.20 - 0.62).

Conclusions: Serum 25(OH)D status is predictive of hospitalization-free survival in patients with chronic kidney disease. The risk of hospitalization over the next 3 years is significantly reduced in predialysis patients with an initial 25(OH)D level above 13.6 ng/ml and 11.3 ng/ml, respectively.

FR-PO682

Continuously Vitamin D Receptor Activation and Dose Adjustment According to PTH Level Directly Influence Pulse Wave Velocity Among Maintenance Hemodialysis Patients

Siren Sezer,1 Zeynep Bal,1 Orhan Gülyüey,1 Ugur Bal,2 Mehtap Erkmen Uyar,1 Emre Tutal,1 Nurhan Özdemir Acar.1 1Dept of Nephrology, Baskent Univ Medical School, Ankara, Turkey; 2Dept of Cardiology, Baskent Univ Medical School, Ankara, Turkey.

Background: Vascular calcification (VC) represents an important contributor to the high rate of cardiovascular mortality associated to maintenance hemodialysis (MHD) patients. VC in large arteries of MHD was associated with increased pulse wave velocity (PWV). Recent studies suggest that systemic activation of VDRs may have direct effects on the cardiovascular system to decrease mortality in CKD. The aim of this study is to evaluate the effect of VDR activation on VC among MHD patients.

Methods: 156 patients with SHPT on chronic hemodialysis three times a week for at least 3 months were enrolled into the study. Patients were grouped according to type of VDRA: Group P (n:34) patients who receive paricalcitol; Group C (n:71) patients who receive calcitriol; Group PC (n:27) patients who receive paricalcitol plus calcitriol and Group CC (n:24) who receive calcitriol plus calcitriol. PWV were assessed at the beginning and end of the study.

Results: Mean PTH, P, Ca and ALP values were significantly higher in group PC compared to group P and C compared to group PC. In paricalcitol based treatment groups (Group P and Group PC), there was no change in PWV measurement. However, significantly decreased compared to baseline values (p<0.001). When the whole patient group was concerned, mean administered VDRA dose / PTH ratio and mean administered VDRA dose / PWV ratio were negatively correlated with PWV at the end of study (p=0.02 and p=0.01, respectively).

Conclusions: With this study, we demonstrated the benefit of continuously vitamin D receptor activation and dose adjustment according to PTH level on PWV and VC reduction in MHD patients.
correlated change of PWV during follow-up period (r = -0.312; p < 0.001 and r = -0.314; p < 0.001).

According to logistic regression analysis being in calcitriol based treatment group and using lower doses of VDRA for PTH supression were independent risks for the PWV increment. According to logistic regression analysis being in calcitriol based treatment group and using lower doses of VDRA for PTH supression were independent risks for the PWV increment. According to logistic regression analysis being in calcitriol based treatment group and using lower doses of VDRA for PTH supression were independent risks for the PWV increment. According to logistic regression analysis being in calcitriol based treatment group and using lower doses of VDRA for PTH supression were independent risks for the PWV increment.

Conclusions: This observational study showed that the importance of vitamin D supplementation with VDRA intensity and maintainability in the management of cardiovascular disease in end-stage renal disease patients. Additionally higher doses of adjusted VDRA for PTH could be protective on vascular calcification.

FR-PO683
The PARADIGM Trial: Impact of Dialysate Calcium and Calcium Based Binders
James B. Wettert, Konstantin Gurevich, Stuart M. Sprague, John E. Buerkert, Maureen T. Reiner, William G. Goodman, Kerry Cooper, Hennepin County Medical Center; Fresenius Medical Care Russia; North Shore U HealthSystem; U British Columbia; Columbia Nephrology Associates; Amgen Inc.

Background: The PARADIGM trial compared parathyroid hormone (PTH) levels during monotherapy with cinacalcet (Cin) or vitamin D (vitD) in patients on hemodialysis with secondary hyperparathyroidism (SHPT). PTH reduction did not differ between study arms (12% Cin vs. 7% vitD, P = 0.346).

Methods: Multivariate analysis revealed a large treatment by region interaction (US vs non-US, p < 0.001). Practice patterns differed in regard to use of low (<2.5 mEq/L) dialysate calcium concentrations (DCC) and calcium containing phosphate binders (CB). Low DCC was used in only US patients, while non-US patients were more likely to be on CB. Overall 15% of all study patients were on low DCC and 45% were on CB. In this post-hoc analysis, PTH reductions were stratified by DCC (>2.5 vs <2.5 mEq/L) and by CB use.

Results: Patients treated with DCC ≥2.5 mEq/L had nominally greater PTH reduction while on Cin compared to vitD (P = 0.042). Conversely, with DCC <2.5 mEq/L, there was no difference in PTH reduction. Cin dose did not vary according to DCC, while vitD dose was higher in patients on DCC<2.5 mEq/L; although, this did not result in greater PTH reduction. Cin treated patients also had greater PTH reduction than patients on vitD when on CB, but there was no difference in PTH reduction between arms when not on CB.

Conclusions: When used as monotherapy, the efficacy of Cin in reducing PTH levels compared to vitD may depend, in part, on the DCC and the choice of binder type.

FR-PO684
Whole Exome Resequencing and Homozygosity Mapping Identifying Mutation of ARHGAP4 as a Novel Single-Gene Cause of Nephrotic Syndrome
Carolin E. Sadowski, Shazia Ashraf, Svjetlana Lovric, Humphrey Fang, Virginia Vega-Warner, Stefanie Weber, Neven Soliman, Heon Yung Gee, Friedhelm Hildebrandt, D. Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA; Dept of Pediatrics, Univ of Michigan, Ann Arbor, MI; Howard Hughes Medical Institute, Chevy Chase, MD; Dept of Pediatrics, Univ of Essen, Essen, Germany; Dept of Pediatrics, Kazir Ani School of Medicine; Center of Pediatric Nephrology and Transplantation, Cairo Univ; Egyptian Group for Orphan Renal Diseases, Cairo, Egypt.

Background: Idiopathic nephrotic syndrome (NS) represents a heterogeneous group of glomerular disorders occurring mainly in children. 20% percent of the cases show primary steroid resistance with a 30% risk of relapse in a kidney transplant. Identification of single-gene causes of SRNS has furthered the understanding of its pathogenesis. However, additional genes and disease mechanisms remain obscure.

Methods: To identify a new causative gene for SRNS, we performed array based multiplex PCR (Fluidigm Access Array™) and next generation resequencing (NGS) to detect additional mutations in these genes.

Conclusions: We identified mutations of GLCCI1 and DDX53 as novel genes mutated in Steroid Resistant Nephrotic Syndrome.

Background: Idiopathic nephrotic syndrome (NS) is a malformation of the kidney glomerular filter that leads to proteinuria, hypoalbuminemia, edema, and renal failure. Identification of single-gene causes of SRNS has furthered the understanding of its pathogenesis. However, additional genes and disease mechanisms remain obscure.

Methods: To identify a new causative gene for SRNS, we performed array based multiplex PCR (Fluidigm Access Array™) and next generation resequencing (NGS) to detect additional mutations in these genes.

Conclusions: We identified mutations of GLCCI1 and DDX53 as novel genes causes of SRNS. The identification of novel genes for SRNS provides new steps toward our understanding of the pathomechanisms of SRNS.

FR-PO686
Next Generation Sequencing of 37 Genes Associated with Steroid Resistant Nephrotic Syndrome
Annequia Bierzynska, Hugh J. McCarthy, Gavin Iain Welsh, Moin Saleem, Harvard Medical School, Boston, MA; 2Dept of Pediatrics, Univ of Michigan, Ann Arbor, MI; 3Howard Hughes Medical Institute, Chevy Chase, MD, United Kingdom.

Background: Up to 40% of children presenting with Steroid Resistant Nephrotic Syndrome (SRNS) in early life will have a pathogenic single gene mutation in one of 37 genes currently associated with this disease. Little is known of the effect of polygenic variants. We followed up our previous findings that the increasing reliability of Next Generation Sequencing (NGS) provides the potential for revolutionising genetic investigation of this and similar patient groups.

Methods: We used exome sequencing to screen 100 paediatric SRNS patients for genes known to be associated with hereditary SRNS as well as to look for novel polymorphic variants in other genes, potentially involved in the disease. Patients were collected via a national UK Renal Registry with comprehensive detail of phenotype. Significant variants detected by NGS were confirmed by conventional Sanger sequencing.

Results: 9% of the patients had a previously described mutation and another 15% had a pathogenic variant. The majority of the remaining sequence variants were revealed known as well as novel disease associated variations in routinely tested genes such as NPHS1, NPHS2 and WT1 as well as in other, less common, genes such as SMARCAL1 or MYO1E. A phenotypically unexpected mutation was COL4A3 (homonymous missense) in a patient without hearing loss. Increased burden of R229Q (NPHS2), R313Q (ACTN) as well as other rare variants were noted in known SRNS genes in cases versus controls.

Conclusions: Our results demonstrate the obvious clinical need for sequencing multiple genes in SRNS where genetic identity is of two a defining feature. We identified mutations and potentially pathogenic variants in genes that would not routinely be sequenced under current testing practice. Our detailed phenotypic information enabled us as well to identify potential modifier variants from this cohort.

FR-PO687
Renal Cysts in Thin Basement Membrane Disease, a Marker of Progression?

Background: Thin basement membrane disease (TBMDD) is thought to be an entity with a good renal prognosis. However proteinuria is found in 50% of these patients and in some cases it is accompanied by renal function impairment. Some studies have reported simple renal cysts in proteinuric TBMDD.

Methods: Retrospective study comparing the characteristics and evolution of three group of patients (n=16 in all of them): 1) Biopsy-proven TBMDD and proteinuria >0.5g/24h (TBMDDP), 2) Biopsy-proven TBMDD and no proteinuria (TBMDDnoP) and 3) Biopsy-proven IgA nephropathy and proteinuria >0.5g/24h (IgAN).

Conclusions: We identified mutations of ARHGAP4 as a new cause of NS. We identify mutations of ARHGAP4 as a new cause of NS.
Results: Main results are shown in the table below.

<table>
<thead>
<tr>
<th></th>
<th>NPHS2</th>
<th>NPHS1</th>
<th>NPHS3</th>
<th>NPHS4</th>
<th>NPHS5</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCN</td>
<td>22/22 (100%)</td>
<td>22/22 (100%)</td>
<td>22/22 (100%)</td>
<td>22/22 (100%)</td>
<td>22/22 (100%)</td>
</tr>
<tr>
<td>GCN2</td>
<td>22/22 (100%)</td>
<td>22/22 (100%)</td>
<td>22/22 (100%)</td>
<td>22/22 (100%)</td>
<td>22/22 (100%)</td>
</tr>
</tbody>
</table>

Every patient with proteinuria >0.5g/24h was treated with RAAS blockers with good results. The most striking finding was the presence of simple renal cysts in 9 (56%) TBMDP patients, whereas only one IgAN patient and nobody in the TBMDnO group presented cysts. The cysts were multiples and bilateral in TBMDP.

Conclusions: The presence of bilateral simple renal cysts is common among biopsy-proven TBMD patients who develop proteinuria. This finding could help to orientate the diagnosis in patients with persistent hematuria and proteinuria. The pathogenesis of cyst formation in TBMD with proteinuria is presently unknown.

FR-PO688

NPHS2 V260E is a Frequent Mutation among Unrelated Black South African Children with Steroid Resistant Focal Segmental Glomerulosclerosis


Background: The incidence and histologic patterns of nephrotic syndrome (NS) vary with geographic location and ethnicity. We sought to determine the roles of APOL1 and NPHS2 variants in sporadic steroid resistant (SR) and steroid sensitive (SS) NS in children from Durban, South Africa.

Methods: We sequenced NPHS2 exons and genotyped APOL1 G1 and G2 in unrelated Indian and Black African children (median age 90 months, range 1-169) with sporadic SRNS (N=60) and SSNS (n=19), and in 116 Indian and Black controls. Kidney biopsies were available for all SRNS cases. FGSS was present in 30/38 (79%) Black and 16/22 (73%) Indian children with SRNS.

Results: Steroid resistance was more common in Blacks (94.4%) compared to Indians (55%) with NS (p<8.10). Heterozygosity in SRNS cases was noted for NPHS2 A61V, R292Q, and A242V. NPHS2 V260E was present in the homozygous state in 7 of 23 (30%) Black SR-FGSNS (FET=0.004) and in 1/2 SRNS cases with mesangial proliferative GN, and in no controls. V260E was observed in the heterozygous state in one Black African control (allele freq.=0.8%; 95% CI [0.02-4%]), but not in Indian cases or controls. APOL G1 and G2 frequencies were not significantly different between Black SRNS cases (18.5%) and controls (19.2%; p=0.05) nor was there significant association between 2 APOL1 risk alleles and SRNS (p=0.22). No significant associations with NPHS2 or APOL were found for SSNS in Black or Indian children.

Conclusions: NPHS2 V260E is a significant risk factor for SR-FGSNS in unrelated, Black African children; the variant may be polymorphic accounting for the high rate of SR-FGSNS among children in this Black African population. Further data will be necessary to determine population frequency distributions and history of this variant in Africa.

Funding: NIDDK Support, Other NIH Support - This research was supported in part by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research, Frederick National Laboratory for Cancer Research, National Institutes of Health (NIH; contract number HHSN261200800001E).

FR-PO689

Genetic and Acquired Abnormalities in the Alternative Complement Pathway in Patients with C3 Glomerulopathy


Background: Glomerular pathologies that are characterized by the isolated deposition of C3 are now called C3 glomerulopathies (C3G). These pathologies include DDD and C3 glomerulonephritis, but also immunoglobulin-negative MPGN I and III. It is thought that C3G can be caused by systemic dysregulation of the alternative and terminal complement pathway. Here we report a cohort of 29 C3G patients (all children at time of diagnosis) who have been screened for abnormalities in genes encoding (regulating) proteins of the alternative pathway.

Methods: In 29 biopsy proven C3G patients, mutational screening was performed of the alternative pathway genes CFH, CFI, MCP, CFHR5, C3 and CFB by means of PCR on genomic DNA and sequence analysis. For 22 of these patients, serum was available for screening for autoantibodies against CFH.

Results: In three patients (3/29; 10.3%) a potentially pathogenic genetic aberration was identified in CFH, one of these patients carried a variation in C3 as well. All sequence variations identified are located in domains important in heparin binding (SCR7 and SCR20); two of these have been previously described in aHUS patients. The sequence variation in C3 is involved in properdin binding and could lead to increased affinity of CFB for C3. In two other patients (2/29; 7%), autoantibodies against CFH, associated with dysregulation of the complement system as well, were identified.

Conclusions: In 5/29 (17.2%) of the patients with C3G, abnormalities in complement genes were found, either consisting of a genetic aberration in one of the screened genes or the presence of autoantibodies against CFH. These data indicate that dysregulation of the alternative complement pathway is involved in the pathogenesis of C3 glomerulopathy. More research is needed to understand the clinical observed complement activation in C3G.

FR-PO690

Atypical Hemolytic Uremic Syndrome and the Application of Whole Exome Sequencing

Dikee Westra, Elena Volokhina, Lambert Van den Heuvel, Nicole Van De Kat.

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, but severe disease that has a heterogeneous genetic background. Mutations in several genes encoding proteins of the alternative complement pathway have been associated with the disorder. Due to the heterogeneity seen in aHUS, making the genetic diagnosis via regular methods is labor intensive and time consuming. Therefore, whole exome sequencing (WES), in which the coding regions of the entire genome can be studied, might be an option for mutation detection in aHUS.

Methods: Exomes of ten patients diagnosed with familial aHUS were captured and sequenced using the 50MB AgileG's SureSelect human exome enrichment kit (Agilent, Santa Clara, CA, USA). One of these patients, with an identified CFH mutation, was taken along as a positive control.

Results: More than 47000 sequence variations were identified per patient. On average, ~25000 loci were false substitutions located in an exon or canonical splice site, all absent in the dbSNP database or present in less than 1% of our in-house database. Overall coverage of associated genes was 86%, but SCR19 and 20 in CFH were not covered. The CFH mutation in one patient was detected. Potential pathogenicity of other identified variations will be further displayed.

Conclusions: The hotspot for mutations in aHUS patients (SCR19-20 in CFH) was not covered with the used enrichment kit. Therefore, at this moment with this specific method, WES might not be the best option for genetic screening in patients with familial aHUS.

FR-PO691

A Disease-Causing Mutation of IN2F Impairs the Integrity of Podocyte Slit Diaphragm in Protagmine Induced Kidney Injury

Hua Sun, Victoria Charomnratana, Martin R. Pollak.

Background: Rho GTPases mediated actin dynamics determine the morphology of podocyte and the integrity of slit diaphragm. Our previous work established that INF2, a Rho GTPase, regulates cortical actin architecture responsible for the formation of lamellipodia and the trafficking of Rho/mDia mediated actin polymerization. By doing so, INF2 regulates the cortical actin dynamics and the integrity of slit diaphragm. Our previous work established that INF2 knock-in mice showed any sign of proteinuria or altered slit diaphragm.

Methods: An INF2 R218Q point-mutant "knock-in" mouse model was generated. Here we show that this INF2-R218Q mutation impairs the morphology and integrity of slit diaphragm in podocyte induced proteinuria in a transgenic mouse model.

Results: More than 47000 sequence variations were identified per patient. On average, ~25000 loci were false substitutions located in an exon or canonical splice site, all absent in the dbSNP database or present in less than 1% of our in-house database. Overall coverage of associated genes was 86%, but SCR19 and 20 in CFH were not covered. The CFH mutation in one patient was detected. Potential pathogenicity of other identified variations will be further displayed.

Conclusions: The hotspot for mutations in aHUS patients (SCR19-20 in CFH) was not covered with the used enrichment kit. Therefore, at this moment with this specific method, WES might not be the best option for genetic screening in patients with familial aHUS.

FR-PO691

A Disease-Causing Mutation of IN2F Impairs the Integrity of Podocyte Slit Diaphragm in Protagmine Induced Kidney Injury

Hua Sun, Victoria Charomnratana, Martin R. Pollak.

Background: Rho GTPases mediated actin dynamics determine the morphology of podocyte and the integrity of slit diaphragm. Our previous work established that INF2, a Rho GTPase, regulates cortical actin architecture responsible for the formation of lamellipodia and the trafficking of Rho/mDia mediated actin polymerization. By doing so, INF2 regulates the cortical actin dynamics and the integrity of slit diaphragm. Our previous work established that INF2 knock-in mice showed any sign of proteinuria or altered slit diaphragm.

Methods: An INF2 R218Q point-mutant "knock-in" mouse model was generated. Here we show that this INF2-R218Q mutation impairs the morphology and integrity of slit diaphragm in podocyte induced proteinuria in a transgenic mouse model.

Results: More than 47000 sequence variations were identified per patient. On average, ~25000 loci were false substitutions located in an exon or canonical splice site, all absent in the dbSNP database or present in less than 1% of our in-house database. Overall coverage of associated genes was 86%, but SCR19 and 20 in CFH were not covered. The CFH mutation in one patient was detected. Potential pathogenicity of other identified variations will be further displayed.

Conclusions: The hotspot for mutations in aHUS patients (SCR19-20 in CFH) was not covered with the used enrichment kit. Therefore, at this moment with this specific method, WES might not be the best option for genetic screening in patients with familial aHUS.

FR-PO691
The copy number variation of FCGR3A affects penetrance of lipoprotein glomerulopathy. Zhanguoxu Hu, 1 Maolu Tian, 1 Xiaoxia Liu, 1 Ye Tao, 1 Ping Fu, 2 Yuan Yang. 1 2 Dept of Nephrology; 2 Dept of Medical Genetics.

Background: Lipoprotein glomerulopathy (LPG) is a rare hereditary disorder mostly found in east Asia. Our previous work and related literatures have demonstrated that LPG is a dominant inherited disease with incomplete penetrance. However, the mechanism of incomplete penetrance is still unclear. Fcγ receptors play an important role on the pathogenesis of LPG based on evidences from animal studies. The copy number variation (CNV) of FcgR3 predisposes to glomerulonephritis in rats and humans. We supposed that the CNV affects penetrance of LPG.

Methods: LPG patients were diagnosed by renal biopsy, and the APOE mutation was detected by DNA sequencing. Asymptomatic carriers were defined as relatives carrying the identical APOE mutant, with urine protein less than 300 mg/d, eGFR over 60 min/m, and no active urine sediments. Between patients and carriers, the copy numbers of FCGR3A, FCGR3B and FCER1G were detected and analyzed by QRT-PCR, ABI copycaller Software v2.0 and SSPS.

Results: 28 LPG patients and 26 asymptomatic carriers with APOE Kyoto were enrolled. All come from the same county. The average age and genders distributions between two groups had no statistical difference. In the 54 APOE Kyoto individuals, the frequency of CNV of FCGR3A was 63%, higher than that of general population in China. The frequency of CNV of FCGR3A was higher in asymptomatic carriers than patients (76.9% vs. 50%, p=0.041). The frequency of high FCGR3A copy number (CN=3,4) was higher in carriers, compared with patients (73.1% vs. 42.9%, p=0.025). For FCGR3B, no CNV difference was observed between two groups (34.6% vs. 21.4%, p=0.171).

Conclusions: APOE Kyoto individuals with low or moderate FCGR3A copy numbers (CN=1,2) may be more susceptible to clinical onset of LPG. The high copy numbers may have reprotective effect in APOE Kyoto carriers. In our study, the frequency of CNV of FCGR3A are higher than that of other Chinese populations. Because these families all come from the same county, which is fairly isolated, the high frequency of CNV of FCGR3A may prevail in this county.

Exome Sequencing and In Vitro Studies Identify Podocalyxin as a Candidate FSGS Gene. Moumita Baru, 1 Eric Shieh, 2 Johannes S. Schledornfort, 2 Giulio Genovese, 1 Bernard S. Kaplan, 1 Martin R. Pollak. 1 Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; 2 Harvard Medical School, Harvard Univ, Boston, MA; 3 Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA; 4 Dept of Pediatrics, The Children’s Hospital of Philadelphia, Philadelphia, PA.

Background: The integral membrane protein podocalyxin (PODXL) has been shown to play a critical role for the function of podocytes in rodents, possibly by preserving slit diaphragm patency by its negative charge repulsion. However, whether disruption of podocalyxin function can lead to human disease has not been previously reported. Exome sequencing in a FSGS family revealed a suspicious PODXL variant and we explored its effect on biochemical function.

Methods: Exome sequencing was performed in 2 affected cousins of a family with dominant inherited FSGS. Sequencing in 175 probands of a familial FSGS cohort revealed a suspicious PODXL variant and we explored its effect on biochemical function.

Results: A cosegregating private variant, PODXL p.L442R, affecting the transmembrane region was identified in the index family. In comparison to wildtype, this mutation does not alter protein stability, extracellular domain glycosylation, trafficking to the cell surface, global subcellular localization, or interaction with ezrin. Comparison of these parameters between wildtype and other rare PODXL variants identified in the familial FSGS cohort revealed no differences.

Conclusions: A variant form of PODXL, p.L442R, is a candidate for causing disease in a FSGS family but its full effect on protein function remains unknown. Our work highlights the challenge faced in the clinical interpretation of exome data for small pedigrees with autonomaous dominant diseases.

Funding: Other NIH Support - DK54931 to M.R.P.; DK080947 to J.S.; NHLBI/ NHGRI Exome Project grant R01HL094963

Natural History and Protein Expression Pattern in Autosomal Recessive Alport Syndrome Based on the Comprehensive Strategy for Genetic Analysis. Hiroshi Kaito, 1 Kandai Nozu, 1 Masafumi Oka, 2 Naoya Morisada, 1 Takeshi Nishioji, 1 Koichi Nakashita, 1 Norishige Yoshikawa, 1 Kazunoto Iijima, 1 Kobe Univ Graduate School of Medicine, Japan; 2 Faculty of Medicine, Saga Univ, Japan; 1 Wakayama Medical Univ, Japan.

Background: Autosomal recessive Alport syndrome (ARAS) is a hereditary disorder caused by mutations in COL4A3 or COL4A4. The most serious problem in the diagnosis of ARAS has been the low mutation detection rate. Moreover, some ARAS cannot be successfully-diagnosed even if detailed pathological examination is completely performed. It is the urgent problem to establish the method of genetic diagnosis and to clarify the natural history of genetically-proven ARAS.

Methods: We retrospectively analyzed 29 patients in 23 pedigrees suspected of ARAS with family history and/or kidney biopsy findings. We utilized and followed the following 3 steps for mutation detection: (1) genomic DNA analysis; (2) mRNA analysis to detect a splicing abnormality; and (3) semi-quantitative PCR analysis to detect a heterozygous large deletion. Rat monoclonal antibodies that recognize type IV collagen α3, α4, and α5 were used for immunohistochemical staining.

Results: The mean age was 17.9±8.2 years old. Homozygous or compound heterozygous mutations could be detected in all cases. Four cases in 3 pedigrees had splicing abnormality with COL4A3. RNase protection assay for COL4A3 and COL4A4, no active urine sediments. Between patients and carriers, the copy numbers of FCGR3A, FCGR3B and FCER1G were detected and analyzed by QRT-PCR, ABI copycaller Software v2.0 and SSPS.

Conclusions: We could successfully detect disease-causing mutations in all cases, and this is the largest-scaled report on patients with genetically-proven ARAS. It is of is great help to use our strategy for genetic analyses of ARAS. We could also first elucidate the protein expression pattern of type IV collagen for ARAS, including α3 and α4. Moreover, prognosis for kidney function with ARAS may be severer than that of X-linked.

Funding: Government Support - Non-U.S.


Background: Alport syndrome (AS) is an inherited renal disease that leads to ESRD in all affected males. Studies of murine, canine and human AS showed that tubular injury and interstitial fibrosis are important contributors to renal disease progression in AS. Connective tissue growth factor (CTGF) has been implicated as a mediator of renal fibrosis and a marker of proximal tubular dysfunction in diabetic and non-diabetic kidney disease but has not been assessed in AS. We examined urinary CTGF in boys with early untreated AS.

Methods: 64 AM urine samples were collected over 3 years from 35 untreated boys (<18 yrs) with AS. Creatinine (Cr), albumin (Alb) and total protein (Pr) concentrations were measured in the UMMC Clinical Laboratory. Samples were classified as Normalbuminuric (N, Alb/Cr < 30 mg/g, N=35), Microalbuminuric (MA, Alb/Cr > 30, Pr/Cr < 0.2, N=15) or Proteinuric (Prot, Pr/Cr > 0.2, N=14). CTGF concentrations were determined by ELISA (Onkine Human CTGF ELISA Kit,Assay Biotech). CTGF (ng/mg) was calculated for each sample. The study protocol was approved by the U. of Minnesota IRB.

Results: CTGF/ Cr was higher in Prot samples (mean +/- SD 0.868 +/- 0.333) than in N (0.365 +/- 0.631) and MA (0.499 +/- 0.616) samples (ANOVA, p = 0.037; Prot vs N, p = 0.013 [t-test]). Linear regression showed positive correlations between Alb/Cr and CTGF/Cr (R = 0.254, p = 0.043) and between Prot/ Cr and CTGF/Cr (R = 0.294, p = 0.049). CTGF/Cr increased in 7/11 serially sampled subjects who advanced from N or MA to a higher stage (Prot or MA).

Conclusions: In untreated boys with AS, urinary CTGF excretion is higher in those with microalbuminuria or overt proteinuria than in those who are normalbuminuric. In normal subjects filtered CTGF is reabsorbed in the proximal tubule by megalin-mediated endocytosis. Increased urine CTGF levels in boys with AS may be secondary to altered megalin-mediated endocytosis. It is also possible that increased urine CTGF levels result from increased renal production. Further investigation of CTGF as a marker and potential mediator of renal disease progression and as a possible target of clinical intervention in AS is warranted.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO696
Breakdown of the GBM Ultrastructural Organization in Pierson and Alport Syndromes
Hani Salehman,1 Lei Zhang,2 Adish Dani,1 Jeffrey H. Miner,2 Andrey S. Shaw.1

Background: The glomerular filtration barrier is comprised of three layers: fenestrated endothelium, glomerular basement membrane (GBM), and podocyte foot processes. Numerous mutations, primarily in podocyte genes, cause a dysfunctional filtration barrier leading to proteinuria, with such mutations, in mice, the GBM and lead to proteinuria and end stage renal failure in Pierson and Alport syndrome, respectively.

Methods: We used sub-approximation resolution stochastic optical reconstruction microscopy (STORM) with a GBM molecular reference frame to identify nanoscale changes in localization associated with a defective GBM. Two mouse models were characterized for this study, Lamb2 and Col2a3 null, and they were compared with WT as well as with the Col2ap null.

Results: In stark contrast with WT and Col2ap KO mouse kidney, the GBM in both Lamb2 KO and Col2a3 KO mice manifested a breakdown of the highly organized molecular architecture. Two agrin layers observed by STORM in the healthy GBM were disrupted in both disease models. In the Lamb2 KO, collagen α2α3(IV) appeared increased in irregularly thick GBM areas. On the other hand, Col2a3 KO mice showed changes in laminin-521 positioning as well as in collagen α1α2(IV) localization when compared to WT. Using agrin as a reference, collagen α1α1α2(IV) shifted from its normal position near the endothelium to sites across the thickness of the GBM. Using STORM to analyze transgenic mice expressing laminin β1 in the Lamb2 KO background and collagen α3(IV) in the Col2a3 KO background, we observed restoration of the GBM’s molecular architecture to normal, which correlated with reduced proteinuria.

Conclusions: STORM can detect nanoscale changes in the molecular architecture of the GBM in disease models that correlated with disease progression. Further analyses of GBM architecture in Pierson, Alport, and other syndromes could reveal novel targets for therapies aimed at restoring the architecture of the GBM and the integrity of the filtration barrier.

FR-PO697
Identification of the Pathologic Role of miR-21 in Alport’s Kidney Disease
Joseph H. Boulanger,1 Wenping Song,1 Jie Zhang,1 Lisa M. Petostio,2 Xiaohong Cao,1 Rachel Yabkowitz,1 Steven R. Ledbetter,1 Susan C. Schiavi,1 Andrey S. Shaw.1

Background: Numerous mutations, primarily in podocyte genes, cause a dysfunctional filtration barrier associated with hearing loss, cornelia deformation, lenticonus, and perimacular or peripheral retinopathy. We describe here four women with X-linked or autosomal recessive Alport syndrome and retinal maculopathy.

Methods: All four individuals were examined by a renal physician for clinical features associated with hearing loss, cornelia dystrophy, lenticonus, and perimacular or peripheral retinopathy. Two molecular defect responsible.

Conclusions: STORM can detect nanoscale changes in the molecular architecture of the GBM in disease models that correlated with disease progression. Further analyses of GBM architecture in Pierson, Alport, and other syndromes could reveal novel targets for therapies aimed at restoring the architecture of the GBM and the integrity of the filtration barrier.

FR-PO700
Whole Exome Sequencing in Familial Kidney Disease
Daniel P. Gale,1 Thomas Michael Connor,1 Nadia Khan,1 Duriyee Deren Oguz,1 Fujin Fiona Lin,1 Guy H. Neild,1 Michael A. Simpson,4 Patrick H. Maxwell.2

Conclusion: The molecular diagnosis of AS is a crucial step in the management of patients with a clinical suspicion of AS in order to enable initiation of Pre-implantation Genetic Diagnosis (PGD), molecular diagnosis in family members prior to kidney donation and consideration of early ACE-inhibitor therapy. A nephrogenic diagnostic is a necessary step in order to make the information and molecular diagnosis accessible to patients and families.

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

525A
FR-P0701

Role of Potassium I Type I Receptor in TSC Renal Angiomyolipoma Pathogenesis Brian J. Sirisky,1 Hong Yin,2 Ryan J. Reichter,3 Anna R. Hellmann,3 Marlene Arjmand Bunni,4 Joshua C. Dillon,4 P. Darwin Bell,3 John J. Bissler.1 Nephrology and Hypertension, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Pathology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 3Medicine/Nephrology, Medical Univ of South Carolina, Charleston, SC.

Background: Tuberous Sclerosis Complex (TSC) is a hamartomatous disease that is generally linked to disruptions of TSC1 or TSC2. Nearly 80% of TSC patients develop renal tumors called angiomyolipomas. These lesions are highly vascularized, and associated with aberrant mammalian target of rapamycin (mTOR) signaling. About 2% of TSC patients have a severe polycystic kidney phenotype, associated with deletions in the adjacent TSC2 and PKD1 on chromosome 16p13.1, which commonly produces hypertension. Clinical observation suggested that tumor development was also decelerated when hypertension manifestations of TSC are managed with renin-angiotensin system (RAS) blockade.

Methods: We reviewed imaging from patients with the TSC2-PKD1 deletion syndrome for presence of renal angiomyolipomas, and noted whether or not they had been treated with angiomyolysis converting enzyme (ACE) inhibitors or angiomyolipin receptor blockers (ARBs). We evaluated angiotensin II type 1 receptor (AT1R) expression by immunohistochemistry in renal angiomyolipoma tissue from TSC patients. We also measured AT1R mRNA levels by qPCR in TSC-deficient human renal angiomyolipoma cells (TRI102), and in cells in which TSC2 has been re-expressed (TRI103) with and without mTOR inhibition by RAD001 (20nM, 48hrs).

Results: Of 56 patients studied, 43/7 treated with ACE inhibitors or ARBs had angiomyolipomas, while 9/19 untreated patients (47.3%) had these lesions (p=0.003 Fisher Exact Test). We observed robust AT1R expression in TSC-associated angiomyolipoma tissue. In TRI102 cells, AT1R levels were nearly 10-fold higher than in TRI103 cells, and were markedly reduced by RAD001 treatment.

Conclusions: These data suggest that AT1R may be upregulated in TSC-associated renal angiomyolipoma. In addition, these findings support a possible role of AT1R signaling in TSC pathogenesis, and suggest the potential of utilizing RAS blockade for tumor management in TSC.

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

FR-P0702

Long-Term Enzyme Replacement Therapy Is Associated with Reduced Proteinuria and Preserved Proximal Tubular Function in Women with Fabry Diseaseelin Masri,1 Henrik Birn,1 Rikke Nielsen,1 Erik J. Christensen,1 Mads Thaneas Prabakaran,1 Harrik Birn,1 Rikke Nielsen,1 Erik J. Christensen,1 Dept of Biomedicine, Aarhus Univ, Aarhus, Denmark; 2Dept of Nephrology, Aarhus Univ Hospital, Aarhus, Denmark.

Background: Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the GLA gene. Deficiency of α-galactosidase A (α-Gal A) causes intracellular accumulations of globotriaosylceramide (GL-3) and related glycosphingolipids in all organs, including the kidney, often leading to end-stage renal failure. In women with Fabry disease, accumulation of GL-3 in the podocytes and other renal cells induces progressive, proteinuric nephropathy, but not as severe as in men. Enzyme replacement therapy (ERT) with recombinant α-Gal A reduces cellular GL-3 deposits in podocytes and tubular epithelial cells. We have previously shown that α-Gal A is delivered to these cells by different pathways involving different receptors. This study investigated the long-term changes in albuminuria, eGFR and urinary markers of both glomerular and tubular dysfunction in women with Fabry disease treated with ERT.

Methods: A retrospective, single center, cohort study evaluating the long-term association between albuminuria and eGFR in women with Fabry disease with and without renal involvement. In particular, we analyzed changes in the profibrotic profile including the glomerular marker IgG, the tubular markers α-amylase and retinol-binding protein, and the shared tubular and glomerular markers albumin and transferrin.

Results: ERT was associated with a significant reduction in albuminuria and a relatively stable eGFR. The decrease in albuminuria was paralleled by a decrease in both glomerular and tubular protein markers.

Conclusions: The data indicate that long-term ERT is associated with stable renal function in women with Fabry disease and may advance both glomerular and tubular function.

Funding: Pharmaceutical Company Support - Genzyme Corporation - A Sanofi Company

FR-P0703

Fabry Disease (FD) Is Associated with Progressive Reduction in Glomerular Podocyte Mass in Young Patients Behzad Najarian,2 Michael Maurer,1 Einar Svardal.1 1Univ of Washington; 2Univ of Minnesota; 3Univ of Bergen.

Background: Chronic kidney disease is a major complication of Fabry nephropathy (FN). There is growing evidence that podocytes (PC) play an important role in progression of FN. We previously noted that PC GL-3 inclusion density [Vv(Inc/PC)] and foot process width (FPW) progressively increase with age. We aimed to examine if these findings are associated with a change in glomerular PC mass in young FD patients.

Methods: Renal biopsies from 12 (M=8/F=4) FD patients, aged 12 [4–19] year, median [range], urine protein creatinine (UPCR) 40 [0–223] mg/mmol, glomerular filtration rate (GFR) 106 [90–183] ml/min/1.73 m² were studied. Volume of glomeruli occupied by podocytes [Vv(Prox/glob)], capillaries [Vv(Cap/glob)] and mesangium [Vv(Mes/glob)], Vv(Inc/PC) and FPW were estimated by electron microscopy stereology. The results were correlated with age and renal function.

Results: Despite direct relationship between age and Vv(Inc/PC) (r=0.67, p<0.02), Vv(PC/glob) showed inverse relationship with age (r=-0.60, p<0.02), while, no relationship was found between age and Vv(Cap/glob) or Vv(Mes/glob), confirming a loss in glomerular podocyte mass. 40±5% of glomerular volume was composed of podocytes, 30±5% glomerular capillaries and 14±3% mesangium and about 10% urinary space between the capillaries. UPCR directly correlated with age (r=0.61, p=0.01), FPW (r=0.66, p=0.01) and Vv(Inc/PC), and inversely correlated with Vv(PC/glob). Vv(PC/ glob) was inversely correlated with FPW (r=-0.59, p=0.046).

Conclusions: Although we did not count PC in this study, since GL-3 accumulation leads to podocyte enlargement, our observation of reduced glomerular PC mass is strongly suggestive that FD is associated with progressive PC injury (FPW increase) and loss with age in young patients, both of which correlate with UPCR. These results are confirmatory to our other studies that show urinary podocyte loss increases with age in Fabry patients and correlates with UPCR.

Funding: NIDDK Support, Pharmaceutical Company Support - Genzyme, a Sanofi Company

FR-P0704

Endothelial Nitric Oxide Synthase Uncoupling and Microvascular Dysfunction in the Mesentery of Fabry Mice Liming Shu, Justin J. Kang, James A. Shayman. Univ of Michigan, Ann Arbor, MI.

Background: A defect in the gene for the lysosomal enzyme α-galactosidase A (GLA) results in the lysosomal storage disease Fabry disease (FD). This defect leads to premature death from cardiac and cerebrovascular events. However, gastrointestinal symptoms are often observed first during childhood and persist through life in these patients, and are not well understood.

Results: The progressive accumulation of Gb3 in mesenteric arteries (MA) was confirmed by TLC. No endothelium-dependent dilatation was seen in MA of Gla null mice at 8 months, and suppression in acetylcholine-mediated vasodilatation was seen at 2 months. Endothelium-independent dilatation with sodium nitroprusside was normal compared with age-matched WT mice. The microvascular defect in the MA of endothelium-dependent and -independent with a suppression of vasoactive mediator of eNOS. Phosphorylation of eNOS at the Ser1179 activation site was down-regulated while that of the inhibitory site Thr495 was significantly enhanced in aged Gla null MA. Increased levels of nitrated proteins (3-nitrotyrosine) were seen in parallel with changes in eNOS consistent with NO uncoupling in the MAs. The results: The enable microvascular endothelial dysfunction marked by early onset endothelial dysfunction and a total loss of acetylcholine-mediated dilatation with age in the MA of Gla deficient mice. The observed Gb3 accumulation and decrease in eNOS bioavailability in the MAs are consistent with the phenotype previously observed in macrovessels such as the carotid and aorta. In addition, the additional, density phosphorylation of Ser1179 and phosphorylation of Thr495 present in this vascular bed may contribute to the profound endothelial dysfunction consistent with Gb3 mediated eNOS uncoupling. This appears to be the first report of endothelial dysfunction in the mesenteric artery in a murine model of Fabry disease.

Funding: NIDDK Support

FR-P0705

Fabry Disease: Clinical Characterization of the Variant Phenotype R363H Mutation Eric L. Wallace, Leslie J. Jackson, David G. Warnock. Div of Nephrology, UAB.

Background: Fabry disease (FD) is a lysosomal storage disease caused by mutations in the α-galactosidase A (AGAL) gene and leads to globotriaosylceramide (Gb3) accumulation in lysosomes. Patients with classic FD phenotype, with no AGAL activity, present in childhood with acroparesthesias, hypohidrosis, angiokeratoma, and gastrointestinal symptoms. Ultimately, renal failure, cardiac involvement, and cerebrovascular disease develop. Variant phenotypes with later-onset presentation are recognized and caused by mutations, such as R118C and N215S, that spare some residual enzyme activity. AGAL mutations which cause no clinical manifestations of FD have also been identified.

Methods: We present a family with the variant phenotype R363H mutation and 5 years of clinical follow up characterizing this phenotypic variant of FD.

Results: The male, diagnosed at age 16, presented with acroparesthesias. He had no history of hypohidrosis,GI pain, or diarrhea. Angiokeratomas were notably absent. Laboratory studies revealed: creatinine, 0.8 mg/dL (eGFR by CKD-EPI 132 mL/min/1.73 m²); 24 hr urine protein, 78mg/24hr; plasma and leukocyte AGAL activity, 2 Units (Reference Range (RR) = 12.0 +/- 4.2 U/mL and 5.63 U/mg (RR = 34.6 +/- 14.6 U/mg), respectively, and undetectable urinary lyso-Gb3. Renal biopsy showed minimal multi-laminar inclusions in podocytes but none in the endothelium. Cardiac work up including echocardiogram and EKG showed no cardiac disease. Due to his lack of clinical manifestations, enzyme replacement therapy was not offered. After 5 years follow up, despite no symptoms, the patient is still free of symptoms including acroparesthesias. His eGFR by CKD-EPI is 96 mL/min/1.73 m², 24 hour urine protein is 162 mg/24hr while albuminuria was unchanged. The mother had no clinical manifestations of FD, her kidney biopsy showed no endothelial and only scant inclusions in podocytes.
Conclusions: The R363H mutation in the AGAL gene represents a mild phenotypic variant of FD. Current guidelines recommend treatment of all 16 yo males with FD. Evidence of AGAL mutation without clinical manifestations of the disease does not suffice to initiate therapy. Better characterization of the clinical course and informative biomarkers is needed to guide treatment decisions in non-classical Fabry variants.

FR-PO706

Systems Genetics Identifies PDGFRA as a Candidate Driver Gene for Lupus Nephritis Celine C. Berthier,1 Sharon Chung,2 Elizabeth E. Brown,2 Carl D. Langefeld,4 Matthias Kretzler.1 Univ of Michigan; 2Univ of California; 3Univ of Alabama; 4Wake Forest School of Medicine.

Background: Lupus nephritis (LN) is a serious manifestation of systemic lupus erythematosus (SLE) and shows familial aggregation and increased morbidity and mortality. Linking transcriptional profiles with gene candidates identified from genome wide association studies (GWAS - SLEGEN) using systems genetics strategies can facilitate identification of molecular mechanisms driving LN.

Methods: Affymetrix based expression profiles from 47 microdissected renal healthy biopsies (ERCb) were used in association with a meta-analysis of 3 LN GWAS studies. Results: The GWAS meta-analysis showed LN associated single nucleotide polymorphisms (SNPs) located near PDGFRA-GSX2 (P=2.7x10^-10), SLCA511 (P=3x10^-10). ID4 (P=4.3x10^-10), HSA2-SNTB1 (P=6.2x10^-10), COL4A1 (P=6.4x10^-10), HLADR2 and HLADR3 (2 well known SLE susceptibility loci) were also associated with LN (P=0.037 and 2.2x10^-10, respectively). Linked to disease phenotype, SNPs within as well as outside coding regions can impact the disease trait via associated transcript expression changes (expression quantitative trait locus or eQTL). Thus, renal gene expression profiles from LN biopsies (n=52) compared to living donor controls (n=15) were studied for the genomic regions identified in the LN GWAS. In both glomerular and tubulointerstitial compartments, PDGFRA (fold-change 2.57 and 2.40, respectively) and COL4A1 (fold-change 2.61 and 2.2x10^-10, respectively) were also associated with LN (P=0.037 and 2.2x10^-10, respectively). This work is the first large-scale genome wide investigation of LN and provides evidence of multiple biologically plausible LN susceptibility loci. Consistent with a functional role in LN, DQFRA and associated pathway members showed significant inductions in intra-renal mRNA levels in LN cases compared to controls.

Conclusion: This work provides evidence of multiple biologically plausible LN susceptibility loci. Consistent with a functional role in LN, PDGFRA and associated pathway members showed significant inductions in intra-renal mRNA levels in LN cases compared to controls. Funding: NIDDK Support

FR-PO707

Mutation Analysis in 288 Individuals with Isolated Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) in 20 Known Genes Daw-yang Hwang,1,2 Alina Hilger,1 Gabriel C. Dworschak,3 Stefan Kohl,1 Radovan Bogdanovic,2 Eljiah O. Kehinde,1 Heiko M. Reutter,1 Velibor Tasic,1 Friedhelm Hildebrant,1,2 1Dept of Nephrology, Boston Children’s Hospital, Boston, MA; 2Medical Faculty, Univ of Belgrade, Belgrade, Serbia; 3Dept of Surgery, Kuwait Univ, Safat, Kuwait; 4Institute of Human Genetics, Univ of Bonn, Bonn, Germany; 5Dept of Medicine, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 6Cologne Center for Genomics, Univ of Bonn, Bonn, Germany; 7Pediatrics II, Univ Children’s Hospital Essen, Essen, Germany; 8Dept of Pediatric Urology, VU Univ Medical Center Amsterdam, Amsterdam, Netherlands; 9Dept of Clinical Chemistry and Clinical Pharmacology, Univ of Bonn, Bonn, Germany; 10Dept of Neonatology, Children Hospital Univ of Bonn, Bonn, Germany; 11Howard Hughes Medical Institute, Chevy Chase, MD.

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) account for approximately 50% of children with end-stage renal disease, taking a high toll on affected individuals from 244 CAKUT families. Mutations in 20 genes have been identified in the LN GWAS. In both glomerular and tubulointerstitial compartments, PDGFRA (fold-change 2.57 and 2.40, respectively) and COL4A1 (fold-change 2.61 and 2.2x10^-10, respectively) were also associated with LN (P=0.037 and 2.2x10^-10, respectively). This work is the first large-scale genome wide investigation of LN and provides evidence of multiple biologically plausible LN susceptibility loci. Consistent with a functional role in LN, PDGFRA and associated pathway members showed significant inductions in intra-renal mRNA levels in LN cases compared to controls. Funding: NIDDK Support

FR-PO708


Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are developmental disorders that involve a spectrum of renal structural malformations. They occur in 1 in 500 live births and comprise the major cause of end-stage renal disease in childhood. There are 15 genes reported in the Human Gene Mutation Database with mutations responsible for CAKUT. However, a large proportion of cases remain unexplained. We aim to identify novel rare mutations in candidate genes that play a role in kidney cell differentiation and elucidate their involvement in CAKUT etiology.

Methods: We employ a targeted next generation sequencing approach in 50 Dutch CAKUT patients. Enrichment methods allow us to capture and analyze in parallel the protein-coding regions of 208 candidate genes and 36 miRNAs. The genes selected were previously shown to have experimental evidence for their role in human isolated or syndromic CAKUT or were demonstrated to be involved in disrupted nephrogenesis in transgenic animals or cell models. For data analysis we used in-house mapping and variant calling methodology.

Results: Sequencing results from the first 60 patients with severe kidney dysplasia showed that the average read depth is 210X. Approximately 200 variants were called per individual. Further variant prioritization based on variant frequency data from dbSNP and Genome of the Netherlands, evolutionary conservation, and in-silico predictions resulted in a list of potentially pathogenic mutations. Variants were validated by Sanger sequencing. Conclusions: This study shows that targeted sequencing approach and variant prioritization method is efficient in identifying gene mutations in a large cohort of sporadic CAKUT cases. By this approach, previously reported causal mutations in known CAKUT genes were successfully identified. Interestingly, the majority of the novel and promising pathogenic variants identified, were unique for each patient. Hence, CAKUT might be even more heterogeneous in their etiology than expected. Functional studies to test the impact of novel mutations on protein function and kidney development are currently on-going.

FR-PO709

Whole Exome Sequencing in 3 Brothers with Posterior Urethral Valves Alina Hilger,1 Gabriel C. Dworschak,3 Daw-yang Hwang,1 Peter Nuernberg,3 Stefanie Weber,3 Goedeke Beckers,3 Michael Ludwig,2 Friedhelm Hildebrant,1,2 Heiko M. Reutter.1,7 1Institute of Human Genetics, Univ of Bonn, Bonn, Germany; 2Dept of Medicine, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 3Cologne Center for Genomics, Univ of Bonn, Bonn, Germany; 4Dept of Pediatric Urology, VU Univ Medical Center Amsterdam, Amsterdam, Netherlands; 5Dept of Clinical Chemistry and Clinical Pharmacology, Univ of Bonn, Bonn, Germany; 6Dept of Neonatology, Children Hospital Univ of Bonn, Bonn, Germany; 7Howard Hughes Medical Institute, Chevy Chase, MD.

Background: Posterior urethral valves (PUVs) are the most common cause of lower urinary tract obstruction leading to severely compromised renal function. The incidence is 1 in 4,000 live male births. In 8-10 000 newborns each year in the US and 527A

Results: After applying the filtered step 5 variants in the genes COL6A5, GATA3, MIER3, LRP27 and PHLP1 were chosen to be possibly disease causing. Conclusions: This study suggests that different genotypes can be involved in the development of PUVs, however no conclusion can be drawn about the effect on the disease.

Conclusion: The current screening and segregation analysis of parents and affected of 70 PUV patients from Germany and the US for the presence of these variants should identify the disease causing gene.

Funding: Government Support - Non-U.S.

FR-PO710

Defective Transport and Epithelial Differentiation: Genetics of Key Events in Nephropathic Cystinosis Claudia Ragugi,1 Alessandro Luciani,2 Corinne Antincaic,1 Olivier Devuyst.2 UCL, Brussels, Belgium; 2UZH, Zurich, Switzerland; 3INSERM, Paris, France.

Background: Nephropathic cystinosis (NC), a lysosomal storage disease caused by mutations in the lysosomal cystine transporter cystinosin (CTS), is characterized by generalized proximal tubule (PT) dysfunction that progresses, if untreated, to end-stage renal disease. The pathogenesis of defective PT cellular transport in NC remains unclear.

Methods: In order to investigate the early events involved into PT dysfunction, we performed biochemical profile on a new line of C57BL/6 Ncr KO mice, which accumulate cystin in the kidney and shows signs of tubulopathy. Endocytic uptake and differentiation

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

527A
and proliferation markers were assessed on primary PT cells (mPTC) derived from aforementioned mice.

Results: Metabolic studies revealed that Ctns KO mice presented with a progressive PT dysfunction with low-molecular-weight proteinuria, glucosuria and phosphaturia, before structural damage and in absence of renal failure. These changes were related to decreased expression of multi-ligand receptor complex megalin/cubulin and to increased dephosphorylation (ZONAB transcription factor) and proliferation (PCNA and Cyclin D1) rates. Studies on mPTC confirmed the reduced expression of endocytic receptors, with decreased uptake of specific ligands, resulting from an abnormal transcription program involving a loss of integrity of tight junctions, modified distribution of ZO-1 and release of ZONAB. The mPTC also showed increased markers of proliferation and oxidative stress, as observed in Ctns KO kidneys. These changes could be rescued by overexpression of wild-type CTNS.

Conclusions: These data reveal that the loss of CTNS function in PT cells triggers an early chain of events leading to cell differentiation and transport defects, before structural damage. They may provide new targets for interventions which, in turn, could alleviate the burden caused by the urinary loss of vital metabolites in patients with NC.

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

FR-PO711

Increased Urinary Loss of Podocytes and Proximal Tubular Epithelial Cells in Nephropathic Cystinosis

Ekaterina A. Ivanova, 1 Fanny Oliveira Arcolino, 1 Maria Pia Rastaldi, 2 Elena N. Levchenko. 1 Univ Hospitals Leuven & Katholieke Universiteit Leuven, Leuven, Belgium; 2Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy; ‘Fondazione IRCCS Policlinico & Fondazione D’Amico, Milano, Italy.

Background: Cystinosis is an autosomal recessive disorder caused by mutations in the CTNS gene that encodes a lysosomal cystine transporter in proximal tubular and renal cortex in high cystine levels in the lysosomes. Cystinosis is associated with severe renal dysfunction progressing towards end-stage renal failure. We hypothesized that increased urinary loss of podocytes and proximal tubular epithelial cells might underlie renal dysfunction in cystinosis.

Methods: We used urine samples from healthy donors (n=9) and cystinosis patients (n=14). Urine samples were characterized for the presence of mRNA of podocyte and proximal tubular epithelium (PTEC) markers (CD2A2, podocin/cx, CD13 and AQP1) by qRT-PCR (mean expression values calculated as Ct normalized by creatinine). Conditionally immortalized podocyte and PTEC cell lines were generated from freshly voided urine of healthy volunteers and cystinosis patients.

Results: We demonstrated in cystinosis a significant increased level of podocytophagy and a higher number of PTECs voided into urine. In addition, urine samples from cystinosis patients showed more viable podocytes and PTECs suitable for in vitro culture in comparison to healthy donors. As expected, cystinosis podocyte and PTEC cell lines accumulated cystine. Using viable podocytes and PTEC extracted from urine of both healthy donors and cystinosis patients, we established several conditionally immortalized cell lines and characterized them by the expression of the podocyte markers, including CD2A2, synaptopodin, and nephrin for podocytes and CD13 and AQP1 for PTECs. Cystinosis podocytes demonstrated increased motility in wound-healing assay as compared to the control. Also, the actin cytoskeleton, as shown by phalloidin and alpha-actinin staining, and cell adhesion sites were altered in cystinosis cells.

Conclusions: Our data demonstrate increased urinary loss of podocytes and PTECs in cystinosis. Decreased adhesion to the extracellular matrix might be one of the mechanisms underlying renal damage in this disorder.

Funding: Private Foundation Support

FR-PO712

Endosomal/Lysosomal Dysfunction in Kidney Proximal Tubular Epithelial Cells Deficient for Lyosomal Cystine Transporter Cystinosin

Ekaterina A. Ivanova, 1 Maria Giovanna De Leo, 1 Antonietta De Mattia, 2 Elena N. Levchenko. 1 Univ Hospitals & Katholieke Universiteit, Leuven, Belgium; 2Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy; ‘Bambino Gesu Children’s Hospital, Rome, Italy.

Background: Nephropathic cystinosis is a lysosomal storage disorder caused by a deficiency of cystinosin (CTNS), the lysosomal cystine/\-co-transporter. The disease is characterized by lysosomal cystine accumulation with renal Fanconi syndrome being an early event in the renal proximal tubular injury with cystine accumulation in the epithelial cells. However, the disease is not limited to the kidney and patients suffer from various complications of disease. Cystinosin is encoded by the CTNS gene on chromosome 16q13.1.

Methods: We performed a detailed characterization of endosomal compartments and endocytosis in PTC obtained from urine of a healthy volunteer and a cystinosis patient involved in the study. We found that endocytosis in PTC from both groups was not restored after treatment with cysteamine, suggesting that cystinosin has additional important roles in controlling the reabsorptive function of renal proximal tubular cells (PTC). Here we have explored the role of cystinosin in endocytic membrane trafficking.

Results: We studied endocytosis and degradation/recycling of various cargo proteins, including a ligand of megalin RAP. Surface binding of megalin ligand GST-RAP was assessed on primary PT cells (mPTC) derived from aforementioned mice.

Results: Metabolic studies revealed that Ctns KO mice presented with a progressive PT dysfunction with low-molecular-weight proteinuria, glucosuria and phosphaturia, before structural damage and in absence of renal failure. These changes were related to decreased expression of multi-ligand receptor complex megalin/cubulin and to increased dephosphorylation (ZONAB transcription factor) and proliferation (PCNA and Cyclin D1) rates. Studies on mPTC confirmed the reduced expression of endocytic receptors, with decreased uptake of specific ligands, resulting from an abnormal transcription program involving a loss of integrity of tight junctions, modified distribution of ZO-1 and release of ZONAB. The mPTC also showed increased markers of proliferation and oxidative stress, as observed in Ctns KO kidneys. These changes could be rescued by overexpression of wild-type CTNS.

Conclusions: These data reveal that the loss of CTNS function in PT cells triggers an early chain of events leading to cell differentiation and transport defects, before structural damage. They may provide new targets for interventions which, in turn, could alleviate the burden caused by the urinary loss of vital metabolites in patients with NC.

Funding: Private Foundation Support

FR-PO714

Mutations in HA01 Encoding Glycolate Oxidase Cause Isolated Glycolic Aciduria

Yaoyao Frischvogel, Avraham Zeharia, Ruth Belototsky. Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel.

Background: Perturbations in glyoxylate metabolism are associated with excessive oxalate synthesis, as oxalate is the product of glyoxylate oxidation. Glycolic aciduria has been regarded as a hallmark of primary hyperoxaluria type 1 (PH1) manifesting with kidney stones, nephrocalcinosis and kidney failure. Mutations in HA01, encoding glycolate oxidase, the enzyme catalyzing the oxidation of glycollate to glycolic acid, have been investigated as a possible cause of non-type 1 type II PH.

Methods: Urinary organic acid profile performed by gas chromatography-mass spectrometry. Direct DNA sequencing was used for mutation screening in the HA01 gene. Results: Two brothers, both with a similar urinary oxalate excretion did not carry bi-allelic mutations in HAO1. The genetic nature of triple A in this kindred, was recently identified to the mitochondrial abnormality.

Conclusions: Loss-of-function mutations in the HA01 gene, encoding glycolate oxidase, are responsible for asymptomatic isolated glycolic aciduria without hyperoxaluria.

Funding: Clinical Revenue Support

FR-PO715

Muscle Involvement in Dent Disease 2

Yo Han Ahn, Eujin Park, Jiwon M. Lee, Hee Gyung Kang, IL-Soo Ha, Hae Il Cheong. Dept of Pediatrics, Seoul National Univ Children’s Hospital, Seoul, Korea.

Background: Dent disease is an X-linked recessive renal tubulopathy mostly caused by CLCN5 mutations (type 1). However, some patients have OCR1L mutations (type 2), known to be associated with Lowe syndrome. It is somewhat difficult to differentiate these two diseases by clinical features only. Several studies have shown differences in serum muscle enzyme levels between Dent disease 1 and 2.

Methods: Patients with Dent disease 1 (Group 1, n=24), Dent disease 2 (Group 2, n=5) and Lowe syndrome (Group 3, n=16) were included. The serum levels of 3 muscle

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

Underline represents presenting author/disclosure.

528A
enzymes were measured; creatinine kinase (CK), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST). Serum levels of alanine aminotransferase (ALT) were also measured as a control. The median of the serum levels of the enzymes in each group to test the validity of the serum levels as a biomarker to predict the genotypes.

Results: All of the patients in Group 2 showed no clinical symptoms of muscle involvement except for one patient having muscle hypotonia of both upper extremities. The serum levels of the enzymes in each group are shown in Table 1. When we compared Between Groups 1 and 2, the positive and negative predictive values of the abnormal levels of the enzymes were also shown in Table 1. Serum levels of AST were normal in all of the patients. Table 1. The serum levels of the enzymes in each group and the predictive values (PV) of the levels.

<table>
<thead>
<tr>
<th>Serum levels of the enzymes Comparison between Groups 1 and 2</th>
<th>Group 1</th>
<th>Group 2</th>
<th>PV</th>
<th>PV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>37 (13-84)</td>
<td>25 (10-80)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.82</td>
<td>0.60</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>285 (181-595)</td>
<td>293 (43-319)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.82</td>
<td>0.60</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>34 (13-84)</td>
<td>34 (13-84)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.82</td>
<td>0.60</td>
</tr>
<tr>
<td>CK (U/L)</td>
<td>293 (43-319)</td>
<td>293 (43-319)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.82</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Conclusions: Measurement of the serum levels of muscle enzymes in patients with Dent disease can provide useful information to predict genotypes, even though the patients do not have overt clinical signs of muscle involvement. Muscle involvement maybe a cardinal finding in patients with OCR1LI mutations regardless of the phenotype.

Funding: Government Support - Non-U.S.

FR-PO716

Urinary 2,8-Dihydroxyadenine Excretion in Patients with APRT Deficiency: Effect of Allopurinol andFebuxastot Therapy Hrafnhildur Linnet Runosdottir,1 Vidar O. Edvardsson,2,3 Margret Thorsteinsdottir,2,3 Runolfur Palsson.2,3 1University of Iceland; 2Landspitali - The National Univ Hospital of Iceland; 3ArcticMass, Reykjavik, Iceland.

Background: Adenine phosphoribosyltransferase (APRT) deficiency results in excessive urinary excretion of poorly soluble 2,8-dihydroxyadenine (DHA), causing nephrolithiasis and/or chronic kidney disease. Treatment with allopurinol has been used as a therapy. A reliable method for therapeutic monitoring is lacking. We evaluated urinary DHA excretion in patients with APRT deficiency using ultra-performance liquid chromatography-electrospray tandem mass spectrometry (UPLC-MS/MS).

Methods: UPLC-MS/MS was used to measure the concentration of DHA in 24 hr and random urine samples from 28 patients with APRT deficiency, before and after treatment with allopurinol or the alternative agent febuxostat. Urine samples from healthy subjects were used as controls. The pH of the urine specimens was adjusted to 10, using 20 mM NaOH, before all precipitates were filtered off. The urinary excretion of DHA in random urine samples was expressed as DHA-to-creatinine ratio (ng/mmol). Data are expressed as median and range.

Results: In 20 healthy controls, the median DHA-to-creatinine ratio was 0.4 (0.2-0.8) ng/mmol. In untreated patients with APRT deficiency, the median 24 hr urinary excretion of DHA was 1750 (1045-2700) µg/hr (n=5) and the median DHA-to-creatinine ratio in random urine samples was 272 (85-374) ng/mmol (n=8). In patients treated with allopurinol, the median 24 hr urinary excretion of DHA was 848 (47-2393) µg/hr (n=33) and the median DHA-to-creatinine ratio was 126 (2.5-865) ng/mmol in random urine samples (n=12). In patients treated with febuxostat, the median 24 hr urinary excretion of DHA was 293 (43-319) µg/hr (n=3) and the median DHA-to-creatinine ratio in random urine samples was 74 (5-246) ng/mmol (n=4).

Conclusions: Marked reduction in urinary excretion of DHA was observed after pharmacotherapy was initiated. Febuxostat may be a more effective agent than allopurinol. These preliminary data suggest that the UPLC-MS/MS assay greatly enhances monitoring of pharmacotherapy in patients with APRT deficiency.

Funding: NIDDK Support, Other NIH Support - National Center For Advancing Translational Sciences (NCATS)

FR-PO717

Kidney Function and Chronic Kidney Disease in Patients with APRT Deficiency Hrafnhildur Linnet Runosdottir,1 Runolfur Palsson.2,3 Vidar O. Edvardsson.2,3 1University of Iceland; 2Landspitali - The National Univ Hospital of Iceland, Reykjavik, Iceland.

Background: Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder of purine metabolism, characterized by nephrolithiasis and/or chronic kidney disease (CKD). Despite an estimated heterozygote carrier rate of 0.4-1.2%, only a handful of cases have been identified in many countries, including the US. The aim of this study was to estimate the prevalence of APRT deficiency based on frequencies of mutated APRT alleles in genomic databases.

Methods: We searched for 47 reported APRT mutations in two large databases of genome sequences available in the public domain, the 1000 Genome Project (n=1092) and the NHLBI GO Exome Sequencing Project (n=6503). Minor allele frequencies (MAF) <0.01% were determined and the heterozygote carrier frequency defined as the sum of pathogenic alleles. The prevalence rate of homozygous genotypes was calculated using the Hardy-Weinberg principle.

Results: In the two databases combined, 5 mutations were detected with MAF <0.01% that were predicted to have pathogenic effects on the protein function. The rare pathogenic APRT alleles are shown in the Table.

<table>
<thead>
<tr>
<th>No.</th>
<th>Position</th>
<th>MAF (%)</th>
<th>Homozygous frequency (%)</th>
<th>Base change</th>
<th>Allele change</th>
<th>Location</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48876532</td>
<td>0.0005</td>
<td>0.00000025</td>
<td>C→T</td>
<td>A→G</td>
<td>codon 455</td>
<td>S152C</td>
</tr>
<tr>
<td>2</td>
<td>48876532</td>
<td>0.0005</td>
<td>0.00000025</td>
<td>C→T</td>
<td>A→G</td>
<td>codon 455</td>
<td>S152C</td>
</tr>
<tr>
<td>3</td>
<td>48876532</td>
<td>0.0005</td>
<td>0.00000025</td>
<td>C→T</td>
<td>A→G</td>
<td>codon 455</td>
<td>S152C</td>
</tr>
<tr>
<td>4</td>
<td>48876532</td>
<td>0.0005</td>
<td>0.00000025</td>
<td>C→T</td>
<td>A→G</td>
<td>codon 455</td>
<td>S152C</td>
</tr>
<tr>
<td>5</td>
<td>48876532</td>
<td>0.0005</td>
<td>0.00000025</td>
<td>C→T</td>
<td>A→G</td>
<td>codon 455</td>
<td>S152C</td>
</tr>
</tbody>
</table>

Considering only rare pathogenic variants yielded a homozygous frequency of 0.0005×0.0001=0.000000118558%, suggesting an overall disease prevalence in the range of 1:8000 to 1:17,000.

Conclusions: These data indicate a prevalence of APRT deficiency in the range of 1 in 8,000 to 1 in 17,000. Thus, APRT deficiency appears to be a seriously underrecognized cause of kidney stones and CKD.

Funding: NIDDK Support, Other NIH Support - National Center For Advancing Translational Sciences (NCATS)

FR-PO719

Estimated Incidence of Primary Hyperoxaluria Using Population Allele Frequencies of Disease Variants Katharina Hopp,1 Andrea G. Cogal,1 Hakon Hakonarson,2 Dawn S. Milliner,1 Peter C. Harris. 1Mayo Clinic; 2Children’s Hospital of Philadelphia.

Background: Primary Hyperoxaluria (PH) is a rare recessive condition characterized by oxalate buildup plus ESRD and caused by mutations to AGXT (PH1), GRHPR (PH2), and HOGA1 (PH3). Clinical prevalence is estimated at 1 to 3 per million but the true disease frequency is unknown.

Methods: We have used allele frequencies reported in the NHLBI Exome Sequencing and the 1000 Genome Project to better estimate the incidence rate (IR) and carrier frequency (CF) of PH. This is based on published pathogenic PH alleles and data obtained within Mayo’s RKSC PH Registry. Additionally, we scored the likely pathogenicity of non-synonymous variants with a minor allele frequency (MAF) >0.01% using in silico tools. Variant scoring as highly likely pathogenic were considered as PH mutant alleles.

Results: Based on published pathogenic variants an overall PH CF of ~1:20 was determined. Including predicted mutations the CF/IR increase to ~1:20. The PH prevalence in the African American (AA) and in European American (EA): AA: CF ~1:129, IR ~1:66,200; EA: CF ~1:129, IR ~1:66,200, due to common EA alleles, AGXT p.G170R (MAF 0.1%, CF 1:492) and HOGA1 c.700+5G>T (MAF 0.3%, CF 1:166). The AGXT p.R289H variant is the most prevalent AA allele and accounts for ~41% of AA mutant alleles (MAF 0.2%, CF 1:289; EA CF 1:196). When separated by type, PH1 and PH3 have comparable allele frequencies (PV) of 0.2%, CF 1:165). The PH2 may provide a better estimate of CF (~1:462) and IR (~1:851,037), since its rarity limits the number of mutations seen in the clinic. Interestingly, within the RKSC PH Registry, PH3 is 8 times more prevalent than PH1, highlighting a great underdiagnosis of PH3, presumably due to its milder phenotype.

Conclusions: PH is more common than previously estimated, suggesting that the disease is underdiagnosed/non-penetrant, especially in the case of PH3. NIDDK Support, Other NIH Support - NACTS.
Sustained Pyridoxine (VB6) Response in Primary Hyperoxaluria Type 1 (PH1) Recipients of Kidney Alone Transplantation (KTx) 


Background: PH1 patients homozygous for the G170R mutation develop normal or near normal urine oxalate (Uox) with VB6. The purpose of this study was to examine the efficacy of long-term VB6 in G170R homozygous patients after KTx.

Methods: G170R homozygous patients enrolled in the Rare Kidney Stone Consortium PH Registry who underwent KTx were included. Patients were maintained on VB6 post-KTx. Uox was monitored.

Results: G170R homozygous patients underwent KTx between 9.9-11.1. Median age was 39 yrs (range 22-67), 80% were female and 80% received LD KTx. One patient was on VB6 prior to ESRD. Median follow-up was 8.2 yrs (range 1.6-13.4). Median VB6 dose was 7.7 mg/kg/d (range 5.4-9.4). At end of follow-up, 4 grafts were functioning and 1 graft (patient 5) failed due to rejection.

Funding: NIDDK Support, Other NHI Support - National Center For Advancing Translational Sciences (NCATS)

FR-PO722

Acute Intermittent Porphyria: An Underdiagnosed Cause of Chronic Tubulo-Interstitial Nephritis 

Alexandre Karra,1 Nicolas Pallét,2 Eric Thévet,3 Hervé Pay2 1Nephrology, Hôpital Européen Georges Pompidou, Paris, France; 2Biochemistry, Hôpital Européen Georges Pompidou, Paris, France; 3Centre Français des Porphyries, Hôpital L. Mourier, Colombes, France.

Background: Acute Intermittent Porphyria (AIP) is a rare inherited disorder of heme biosynthesis. This autosomal dominant disease is frequent (1/1600 in Western Europe) but most cases are asymptomatic or undiagnosed. Chronic kidney disease (CKD) is frequent among patients with AIP, but there is a large epidemiological study to determine the prevalence of kidney dysfunction in this population.

Methods: In collaboration with the French National Reference Center for Porphyria, a large cross-sectional study was conducted among 415 AIP patients with proven heme and porphyrin analysis. A complete absence of available laboratory data, including a serum creatinine measurement. Renal Insufficiency (RI) was determined as an estimated GFR<60 ml/min/1.73m2 (according to MDRD).

Results: RI prevalence in the entire AIP study population was 26.5%. Distribution of RI patients in different CKD stages was: CKD 3a in 53%, CKD 3b in 38%, CKD 4 or 5 in 9%. RI was more frequent in female (35%) than in male (9%) patients (P 5.44), in symptomatic (48%) than in asymptomatic (9%) patients (OR 9.33). Prevalence of kidney disease increases with age: among female AIP patients, prevalence of MDRD<45 is 0% before the age of 40 yrs, 14% between 40 and 60 yrs, 28% after the age of 60. These risk factors are cumulative, yielding a 65% prevalence of RI among the 52 female symptomatic AIP patients aged >60. Patients with RI have a mean proteinuria of 0.39±0.3 g/kg, and are hypertensive in 93% of cases. Renal biopsy, when performed, shows mainly tubulo-interstitial lesions. For the 12 patients that reached ESF, the mean age of dialysis initiation was 58±11. Six patients underwent kidney transplantation, without recurrence of tubulointerstitial nephritis on the renal allograft.

Conclusions: Renal involvement is frequent in AIP, especially among female patients. As AIP symptoms are uncommon and non-specific, a screening for a deficiency of heme metabolism should be performed in all patients with unexplained chronic tubulo-interstitial nephropathy.

Funding: NIDDK Support

FR-PO724

A Novel Homozygous FAH R237Q Missense Associated with Chronic Form of Tyrosinaemia Type 1 

Jie Ding, Fang Wang, Yong Yao, Yanqin Zhang. Dept of Pediatrics, Peking Uni First Hospital, Beijing, China.

Background: Autosomal-recessive tyrosinaemia type I, characterized by liver and renal tubular damage and neurological crises, is caused by a defect in the enzyme fumarylacetoacetate hydratase (FAH). The aim of this study was to characterize FAH gene mutation in a Chinese boy with chronic form of tyrosinaemia type I and his family.

Methods: An 8-year-old boy of unrelated healthy Chinese parents developed X-type legs at the age of 4. There was no history of neonatal jaundice and he had never been transfused. At age 8, physical examination showed this patient had hepatomegaly, 4 cm below the costal margin in the right midclavicular line. Moreover, the skeletal deformities were noted, such as ribs valgus, X-type legs, and thickening of the wrists. The results of the laboratory tests performed were as follows: aspartate aminotransferase was normal, alkaline phosphatase 1671 U/L (<750 U/L), and AFP 566.1 ng/ml (0–20 ng/ml). In plasma, there was normal level of tyrosine and phenylalanine, but decreased phosphorus (0.38 mmol/L; 1.45–2.1 mmol/L), Urinary succinylacetone, 4-hydroxyphenylpyruvate

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

Underline represents presenting author/disclosure.

530A
and 4-hydroxyphenylflavate were elevated. Aminociduria, phosphaturia and distal renal tubular acidosis were also detected. Abdominal MRI examination revealed diffuse hepatic parenchymal nodules and enlarged bilateral kidneys. Morphology and size were normal in the spleen. In addition, skeletal X-ray showed bone changes of rickets. All exons of FAH with adjacent intron–exon junctions were analyzed using direct sequencing.

Results: DNA analysis in our patient and his younger brother (clinically asymptomatic at the age of 5 months) revealed a homzygous G>A transition at nucleotide 39 of the FAH gene that leads to a R237Q substitution in the resulting protein. The carrier status of both the parents was revealed by sequencing the respective PCR product. The mutation R237Q was not detected in 100 Chinese control chromosomes.

Conclusions: Our report extends the phenotypic and genotypic spectrum of tyrosinaemia type I.

Funding: Government Support - Non-U.S.

FR-PO725

The Efficient Use of Oxygen in the Kidney Is Impaired in Claudin-2 Deficient Mice

William J. Welch,1 Lei Pei,2 Glenn Solis,1 Lynn Magenheimer,2 Alan S.L. Yu.1 1Medicine, Georgetown Univ, Washington, DC; 2The Kidney Institute, Univ of Kansas Medical Center, Kansas City, KS.

Background: The proximal tubule (PT) is responsible for 65-70% of reabsorption of the glomerulat filtrate, much of it driven by active transeptular transport processes requiring ATP and oxygen. However, a portion of PT transport is facilitated by passive paracellular movement of ions and fluid through tight junctions. Claudin-2, an integral membrane protein expressed in tight junctions of the PT functions as a paracellular cation channel and mediates Na+ movement from the lumen to the peritubular space.

Conclusions: Our data suggest that aldosterone may signal via SGK1 to upregulate claudin-4 expression and thereby decrease paracellular Na+ permeability in the collecting duct. Indeed, the majority of newly synthesized NKCC2 proteins is trapped in the ER and destined for ER associated degradation (ERAD). The aim of the present study was to identify the protein partners specifically involved in ERAD of NKCC2.

Methods: Protein-protein interactions were investigated by the yeast two-hybrid system (Y2H) and co-immunoprecipitation assay (Co-IP). The expression of NKCC2 protein was monitored in transiently transfected OKP and HEK cells, using immunoblot and confocal imaging.

Results: Using the Y2H, we identified ancient ubiquitous protein 1 (AUP1), as a specific binding partner of NKCC2. AUP1 is a member of a protein family that contains the coupling of ubiquitin conjugation to ER degradation domain (CUE). Co-IP assay showed that endogenously expressed AUP1 interacts mainly with NKCC2 immature forms. Accordingly, immunocytochemistry analysis showed co-localization of the proteins mainly in the ER. Co-expression of AUP1 and NKCC2 increased the expression of NKCC2 protein as well as its mature form. These data suggest that paracellular movement of Na+ is an important pathway for PT reabsorption of Na+.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO726

Aldosterone Upregulates Claudin-4 Expression and Decreases Paracellular Na+ Permeability in the Renal Cortical Collecting Duct

Madhumitha Rajagopal, Alan S.L. Yu. Internal Medicine, Univ of Kansas Medical Center, Kansas City, KS.

Background: Aldosterone upregulates Na+ reabsorption in the renal cortical collecting duct by increasing transepithelial Na+ transport. Whether it also regulates paracellular transport pathways is largely unexplored. Paracellular permeability is known to be mediated by tight junction membrane proteins called claudins. We used the murine cortical collecting duct cell line (mpkCCDc14), to study the effect of aldosterone on paracellular Na+ permeability and the role of claudins.

Methods: We treated mpkCCDc14 cells with aldosterone or vehicle. In the presence of apical amiloride, which blocks transepithelial Na+ permeability, the transepithelial resistance (TER) reflects paracellular ion permeability. We measured TER with an electronic voltmeter and mounted cell sheets on an Ussing chamber to calculate paracellular Na+ and Cl- permeabilities. We used immunoblotting to measure changes in claudin expression.

Results: Aldosterone treated cells had 51.5 ± 4.3% higher TER than vehicle treated cells (9147 ± 383 Ω.cm² compared to 6564 ± 295 Ω.cm²). These cells also showed a 45.5 ± 2.8 % lower paracellular Na+ permeability (Pma), than vehicle treated cells (p = 0.005). Of the claudins known to be expressed in the collecting duct, aldosterone caused a 3.5 fold increase in protein expression of claudin-4 (which behaves as a Na barrier and Cl pore) but did not change expression of claudin-3, -7, -8 or -10. The aldosterone-mediated increase in TER was almost completely reversed by treatment with the steroid receptor antagonist, RU486. Treatment with SGK1 inhibitor, GSK650394 significantly decreased TER in both aldosterone- and vehicle-treated cells suggesting a role for SGK1 in modulating the decrease in Pma.

Conclusions: In summary, our data suggests that aldosterone might signal via SGK1 to upregulate claudin-4 expression and thereby decrease paracellular Na+ permeability in the collecting duct. A decrease in paracellular Na+ permeability would reduce back-flux of actively reabsorbed Na+, significantly enhancing net Na+ reabsorption.

Funding: NIDDK Support

FR-PO727

AUP1 Promotes Polyubiquitination and ER-Associated Degradation of NKCC2

Elie Seaayfan, Sylvie Demaretz, Nadia Defontaine, Kamel Laghmani. INSERM UMR872; CNRS ERL 7226; Univs Paris V, Paris VI, Paris, France.

Background: Mutations in the apical Na-K-2Cl co-transporter, NKCC2, cause type I Bartter syndrome (BS1), a life-threatening kidney disease. Yet the mechanisms underlying the regulation of NKCC2 trafficking in renal cells are scarcely known. We have previously shown that export from the ER constitutes the limiting step in the maturation and cell surface expression of NKCC2. Indeed, the majority of newly synthesized NKCC2 proteins is trapped in the ER and destined for ER associated degradation (ERAD). The aim of the present study was to identify the protein partners specifically involved in ERAD of NKCC2.

Methods: Protein-protein interactions were investigated by the yeast two-hybrid system (Y2H) and co-immunoprecipitation assay (Co-IP). The expression of NKCC2 protein was monitored in transiently transfected OKP and HEK cells, using immunoblot and confocal imaging.

Results: Using the Y2H, we identified ancient ubiquitous protein 1 (AUP1), as a specific binding partner of NKCC2. AUP1 is a member of a protein family that contains the coupling of ubiquitin conjugation to ER degradation domain (CUE). Co-IP assay showed that endogenously expressed AUP1 interacts mainly with NKCC2 immature forms. Accordingly, immunocytochemistry analysis showed co-localization of the proteins mainly in the ER. Co-expression of AUP1 and NKCC2 increased the expression of NKCC2 protein as well as its mature form. These data suggest that paracellular polyubiquitination and increased the amount of total NKCC2 protein. 

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO728

Regulation of NKCC2 Activity by Inhibitory SPAK Isomorfs: KS-SPAK Is a More Potent Inhibitor Than SPAK2

James A. McCormick. Medicine (Nephrology and Hypertension), Oregon Health & Science Univ, Portland, OR.

Background: The WNK-SPAK/OSR1 pathway plays an important role in the regulation of ion homeostasis, and the maintenance of extracellular fluid volume and blood pressure. SPAK and its phosphorylated splice variant, OSR1, interact with NKCC1, NKCC2 and NCC. Two putative inhibitory SPAK isoforms have been identified, Kidney-Specific SPAK (KS-SPAK) which lacks the majority of the full-length SPAK kinase domain, and SPAK2, which only lacks the initial portion of the kinase domain. Both isoforms are highly expressed in kidney, but their functional relevance is unclear.

Methods: We tested the ability of KS-SPAK and SPAK2 to inhibit the activity of NKCC1 and NKCC2 in Xenopus oocytes. 86Rubidium uptake experiments were performed under hypotonic low chloride (160 mMOSM), isotonic (210 mMOSM), or hypertonic (340 mMOSM) conditions.

Results: While KS-SPAK strongly inhibited activity of NKCC2 at all tonicitides (by 60-72%), SPAK2 only inhibited its activity, mildly, under hypotonic low chloride conditions (18%). Since it was reported that SPAK2 strongly inhibits NKCC1 activity, we compared the effects of KS-SPAK and SPAK2 on NKCC1 and NKCC2 under hypotonic low chloride conditions, which maximally activate full length SPAK/OSR1. KS-SPAK inhibited uptake by both cotransporters to a similar degree (84% and 88% respectively). In contrast, SPAK2 exerted a significantly greater effect on NKCC1 (77% inhibition) than on NKCC2 (23% inhibition). Truncation of SPAK2 revealed that deletion of the catalytic loop resulted in an inhibitory effect on NKCC2 similar to that of KS-SPAK (61% and 65% inhibition respectively). For KS-SPAK, mutagenesis studies showed that a WNK phosphorylation site in KS-SPAK, but not SPAK2, is required for its ability to inhibit NKCC2 activity, but residues involved in its interactions with cation cotransporters (D238 and L252) are required for its inhibitory effect. Finally, coinmunoprecipitation experiments showed that both KS-SPAK and SPAK2 associated with NKCC2.

Conclusions: These data reveal that while both KS-SPAK and SPAK2 interact with NKCC2, SPAK2 is a relatively weak inhibitor of NKCC2 activity. This difference may be physiologically important.

Funding: NIDDK Support, Private Foundation Support

FR-PO729

Salt Loading Alters Renal Expression of Tamm-Horsfall Protein, Na+, K+, 2C1 Transporter and Cyclooxygenase-2

James M. Bates, Satish Kumar. Dept of Medicine/Nephrology Section, Univ of Oklahoma HSC and VA Medical Center, Oklahoma City, OK.

Background: The American diet contains more salt than recommended. The thick ascending limb of the loop of Henle (TAL) plays a critical role in renal sodium handling. It has constitutive expression of Na+, K+, 2C1 cotransporter (TACC2) and Tamm-Horsfall protein (THP) and inducible expression of cyclooxygenase-2 (COX-2). We investigated the effect of high salt on NKCC2, phosphorylated NKCC2 (pNKCC2) and COX-2 in THP-deficient (THP −/−) and wild-type (THP +/+) mice.

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

Underline represents presenting author/disclosure.

531A
The Sodium Chloride Cotransporter and Epithelial Sodium Channel Associate in a Complex in the Distal Convoluted Tubule

Robert S. Hoover, Hui-fang Bao, Brandi M. Wynne, Rickta Mallick, Douglas C. Eaton, Abinash C. Mistry, Emory Univ School of Medicine, Atlanta, GA.

Background: The sodium chloride co-transporter (NCC) and the epithelial sodium channel (ENaC) are two key sodium transporting proteins in the distal tubule of the mammalian kidney. We previously demonstrated that these proteins associate.

Methods: We utilized confocal microscopy, immunoprecipitation, and immunoblotting to assess the interaction between NCC and the subunits of ENaC.

Results: Utilizing a recently defined model of the mammalian DCT (mDCT15 cells) that natively express DCT2 proteins, including NCC and the alpha, gamma and beta subunits of ENaC, we demonstrated this association. We immunoprecipitated NCC utilizing our immunopurified polyclonal anti-NCC antibody. Immunoblotting the immunoprecipitated sample for alpha ENaC revealed clear presence of alpha ENaC. Lysate for mDCT15 cells also demonstrated expression of alpha ENaC. Immunoprecipitation with resin only and vector only expressing (9.1% ± 1.9) cells.

Conclusions: NCC and ENaC co-immunoprecipitate, both in a cell culture model and in native kidney tissue. This data demonstrates that these proteins associate in a sodium transporting complex. This novel association between NCC and ENaC that may lead to salt-sensitive hypertension through activating their substrates Na-(K)-(2)Cl co-transporter (NKCC2), COX-2 and THP-2. The data were statistically compared by Student’s t-test and two-way analysis of variance.

Results: In the THP** mice, membrane-bound THP increased on HS (NS THP** = 0.233 ± 0.07 vs THP** = 0.45 ± 0.1, P = 0.021). Membrane-bound NKCC2 was elevated in THP** mice on NS and (NS THP** = 0.07 ± 0.06 vs THP** = 0.18 ± 0.03, P = 0.005, HS THP** = 0.03 ± 0.005 vs THP** = 0.63 ± 0.013, P = 0.015 ), and decreased by HS in both THP* and THP** mice (genotype factor significance, F = 15.45, P = 0.0008; salt factor significance, F = 17.62, P = 0.0004, no interaction). Membrane-bound pNKCC2 was similar between THP* and THP** mice on NS and lower in THP* and THP** mice on HS (NS THP* = 0.78 ± 0.15 vs THP** = 0.70 ± 0.13, P = 0.3, HS THP* = 1.68 ± 0.31 vs THP** = 0.84 ± 0.27, P = 0.03). It was increased by HS in THP** mice (NS 0.78 ± 0.15 vs HS 1.68 ± 0.31, P = 0.013). Membrane-bound COX-2 was reduced in THP** mice on NS and similar between THP* and THP** mice (NS THP* = 0.4 ± 0.10 vs THP** = 0.2 ± 0.03, P = 0.015, HS THP* = 0.1 ± 0.1 vs THP** = 0.34 ± 0.04, P = 0.3). It was increased by HS in THP** mice (NS 0.2 ± 0.03 vs HS 0.34 ± 0.04, P = 0.03). 

Conclusions: Renal expression of THP is increased with chronic salt loading suggesting a role for it in sodium handling. More studies are needed to define the interactions among THP, NKCC2 and COX-2 in TAL.

Funding: Clinical Revenue Support

FR-PO730

The Sodium Chloride Cotransporter and Epithelial Sodium Channel Contribute to Salt-Sensitive Hypertension through Activating their Substrates

Brandon M. Wynne, Alexia L. Mattheyses, Abinash C. Mistry, Emory Univ School of Medicine, Atlanta, GA.

Background: The sodium chloride cotransporter (NCC) and the epithelial sodium channel (ENaC) are both primary mechanisms for sodium reabsorption and have been found to be expressed apically in the late distal convoluted tubule (DCT2). Hyperactivity of sodium reabsorption by either protein can produce increases in blood pressure. Classically, these transporters have been thought to work independently of each other. However, regulatory systems such as aldosterone and angiotensin II for both NCC and ENaC contain appreciable overlap. Preliminary data from this laboratory suggests an interaction as shown by co-immunoprecipitation. Thus, we hypothesized that NCC and ENaC may be co-localized intracellularly, as well as interacting with each other.

Methods: To test this hypothesis, COS-7 cells were co-transfected with vectors containing either: GFP-tagged NCC and/or mCherry-tagged subunits of ENaC α or β. Co-localization experiments were performed along with fluorescence resonance energy transfer (FRET) (Tykon 1AR, Emory Integrated Cellular Imaging Core).

Results: Transfection of COS-7 cells with GFP-tagged NCC and one subunit of mCherry-tagged ENaC α or β revealed significant intracellular co-localization of NCC with each ENaC subunit. Furthermore, using FRET acceptor photobleaching technology in cells co-transfected (NCC+/α or β), NCC/mCherry vector only or ENaC α only transfected cells, we observed a significant increase (p = 0.05, ANOVA) in EGPF fluorescence following mCherry photobleaching. Cells co-transfected with NCC and ENaC α or β exhibited more than a 23% increase in EGPF fluorescence, as compared to NCC/mCherry vector only expressing (9.1% ± 0.7) cells.

Conclusions: These novel data suggest an intimate association and possible interaction between NCC and the α and β subunits of ENaC, which may influence our understanding of salt transport in the distal nephron.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO731

Augmented Calcium-Binding Protein 39 (Cab39) Expression in Renal Tubule Contributes to Salt-Sensitive Hypertension through Activating N(5K)/CC

Shrei Sanyal, Sung-Sen Yang, Yu-wei Fang, Min-hua Tseng, Chih-jen Cheng, Robert S. Hoover.

1Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, Taipei, Taiwan; 2Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan.

Background: Enhanced SPK and ORS1 kinases phosphorylation in vivo by WNK4 may lead to salt-sensitive hypertension through activating their substrates Na(+)K(+)2Cl(-) cotransporter [NKKCC]. Recently, it was shown that a ubiquitously expressed Cab39 protein could stimulate N(5K)/CC through activating SPK/ORS1 but independent of WNK4/14 in vivo study. The purpose of this in vivo study is to uncover the physiological role of Cab39 on the regulation of SPK/ORS1 and N(5K)/CC, especially in the renal tubules.

Methods: We generated and analyzed the kidney tubule-specific cadherin gene promoter driven flag-tagged mouse Cab39 transgenic (Tg) mice fed with normal rodent chow. At age of 10-12 wks, phenotype including blood pressure as well as serum electrolytes were measured with or without 0.9%NaCl in tap water ad libitum.

Results: We obtained 8 strains of Cab39 Tg mice. However, offspring could not be got from the Cab39 Tg mice with the abundance of flag-tagged mCab39 over 50% of embryos. Among 300 offspring (Cab39 Tg) Cab39. Thus we chose a strain with the mildly overexpressed abundance of the flag-Cab39 (25% ±6%) in this study. With tap water, the Cab39 Tg mice were phenotypically normal but a slightly increased p-SPAK/OSR1, p-NKCC2 and p-NCC in the kidneys was found. When these mice drunk 0.9%NaCl water for 5 days, a significant reduction in urine output and salt excretion. The reduction in urine output of dKO mice as a result of HCTZ treatment was accompanied by a significant drop in their BP. WT mice did not display any significant effect on their BP in response to HCTZ treatment. HCTZ did not have a significant effect on BP of pendrin- or NCC-KO mice, both of which have normal vascular volume, but it increased the urine output in pendrin-KO mice, indicating the important role of pendrin in compensatory salt absorption in response to NCC inhibition/ablation.

Conclusions: 1. HCTZ reduces blood pressure largely via extra-renal effects that are exaggerated in volume-depleted states, and that these effects are independent of NCC inhibition.

Funding: NIDDK Support, Veterans Affairs Support, Government Support - Non-U.S.
FR-PO734

Regulation of NCC by Angiotensin II in Response to Low K Diet by Liu, 1 Richard A. Coleman, 1 P. Richard Grimm, 2 Eric J. Delprie, 2 Paul A. Welling, 2 James B. Wade.1 and Luis Antonio Reyes Castro, 2 Juliette Hadchouel, 3 Elena Zambrano, 2 Gerardo Gamba.1

Background: Low K diet stimulates the renal NaCl cotransporter (NCC) by an unknown mechanism. Since the STE20/SPS-1-related proline-alanine-rich protein kinase (SPAK) can function to stimulate NCC by phosphorylation of specific N-terminus sites, we investigated if the response of NCC to low K diet is mediated by SPAK and in associated with changes in angiotensin II.

Methods: Using phospho-specific antibodies in Western blot and immunolocalization studies of wild type (WT) and SPAK -/- mice fed a low K or control diet for 4 days, we examined the effect of low K diet on expression and phosphorylation of NCC and SPAK. Levels of angiotensin II and aldosterone were measured by enzyme immunoassay.

Results: In WT, we found that Low K diet more than doubled total NCC expression and phosphorylation of NCC at the T58 site. This was associated with an increase in total SPAK expression in cortical homogenates and an increase in phosphorylation of SPAK at the S383 activation site. By contrast, Low K diet had no effect on NCC or pNCC in SPAK knock-out mice. The increased NCC abundance and phosphorylation with low dietary potassium occurred concomitantly with an increase in angiotensin II but not aldosterone.

Conclusions: These findings indicate that SPAK is a critical mediator of increased pNCC in dietary K restriction. The findings support the idea that low K increases angiotensin II to increase SPAK-dependent phosphorylation of NCC. Such a response would limit Na/K exchange in CNT/CD2 segments to limit urinary K loss with Low K diet.

Funding: NIDDK Support

FR-PO735

Ovarian Steroids Recover the NaCl Cotransporter Activation/Phosphorylation in Gonadectomized Female Rats by Lorenzo Comor Rozas, Luis Antonio Reyes Castro, 1 Juliette Hadchouel, 1 Elena Zambrano, 2 Gerardo Gamba.1

Background: The thiazide-sensitive NaCl cotransporter NCC is subjected to sexual dimorphic regulation in rats. One study showed that response to thiazide diuretics was higher in female than in male rats (JASN, 1994) and another revealed, in the distal convoluted tubule, that NCC expression of ovariocectomized rats is increased by estradiol (JCI, 1998). Little is known, however, about the mechanisms and the role of other female hormones.

Methods: We analyzed in rats the NCC activity by urinary response to bendroflumethiazide (BFTZ), as well as the total and phospho-T58 NCC, total and phospho-S383-SPAK expression, using specific antibodies, in proteins from kidneys of control and gonadectomized male and female rats, four weeks after sham or gonadectomy. Wild type and prolactin receptor knockout (PRLR-/-) female and male mice were also studied. Serum radioimmunoanalysis confirmed the absence of sex hormones in gonadectomized animals. To assess if ovarian hormones or prolactin restore the activity/phosphorylation of NCC, ovariocectomized rats were treated with 30 μg/kg of 17-flulandrosterol or 50 μg/kg of progesterone i.p for three weeks, or one adenohypophysis was transplanted into the renal capsule to produce hyperprolactinemia.

Results: The urinary response to BFTZ was higher in female than in male rats. No difference was observed in total NCC expression, but phospho-T58 NCC was significantly higher in female than in male rats. This was associated with increased expression and p-T583 SPAK in female rats. The differences were eliminated by ovarioectomy. No effect of ovarioectomy on NCC and SPAK expression/phosphorylation was observed. NCC phosphorylation in ovariocectomized rats was recovered by 17-β-estradiol and progesterone administration. Hyperprolactinemia did not recover NCC phosphorylation. In addition, the higher NCC phosphorylation in female rats persisted in PRLR-/- animals.

Conclusions: We conclude that sexual dimorphic increase of NCC phosphorylation in female rats is dependent on ovarian steroid hormones, with little to no participation of prolactin.

Funding: Government Support - Non-U.S.

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

FR-PO736

Clinical Significance of Urinary Thiazide-Sensitive NaCl Cotransporter (NCC) Measurement by Newly Developed Enzyme-Linked Immunosorbent Assays by Kiyoshi Isobe, Takayasu Mori, Eisei Sohara, Tatemitsu Rai, Sei Sasaki, 1 Luis Antonio Reyes Castro, 1 Juliette Hadchouel, 1 Elena Zambrano, 2 Gerardo Gamba. 1

Background: Patients with advanced chronic kidney disease (CKD) can benefit more from thiazide- and thiazide-like diuretics (TLD) than from loop diuretics (LD) or aldosterone antagonists, but the reasons for this are unknown. The thiazide-sensitive NaCl cotransporter (NCC) is the major NaCl transporter in the distal convoluted tubule (DCT) and is involved in NaCl absorption. We developed highly sensitive enzyme-linked immunosorbent assays (ELISAs) for urinary total NCC (tNCC) and its active form, phosphorylated NCC (pNCC). Urinary pNCC was correlated with the estimated glomerular filtration rate (eGFR) and was undetectable when eGFR was less than 16.8 ml/min/1.73 m2, which is consistent with the clinical observation that thiazide is effective in patients with such low eGFR. pNCC was found to be negatively correlated with the fractional excretion of sodium. These data in CKD patients further validate that the ELISA systems for urinary NCC are valuable tools for estimating NCC activity in vivo. Moreover, an link between serum phosphorus and urinary NCC was observed.

Conclusions: Thus, the measurements of NCC, especially pNCC, in human urinary exosomes would provide novel information about the status and the regulation of NCC in the human kidney.

Funding: Government Support - Non-U.S.

FR-PO737

Unscrambling the Molecular Mechanism of Calcineurin Inhibitors-Induced Hypertension after Kidney Transplantation by Pedro San-Cristobal, 1 Marleen L.A. Kortenoeven, 2 Robert A. Fenton, 3 Joost Hoenderop, 4 René J. Bindels. 1 Physiology, Radboud Univ Nijmegen Medical Centre, Nijmegen, Netherlands; 2 Biomedicine, Aarhus Univ, Aarhus, Denmark.

Background: To survive, end stage renal disease patients must immediately undergo either: a) dialysis treatments or b) kidney transplantation. Transplantation is currently the best method of treatment. Calcineurin inhibitors (CNI) are the foundation of immunosuppressive management after transplantation. CNI diminish the graft rejection rate, but have serious side-effects leading to a phenotype similar to Pseudohypothyroidism II. Overactivity of the thiazide-sensitive NaCl cotransporter (NCC) is the postulated mechanism of action. Indeed, patients with CNI-induced hypertension exhibit features that fit with an augmented activity of NCC.

Methods: We developed a unique procedure to isolate a highly enriched preparation of fluorescein labelled distal convoluted tubules (DCT) from transgenic mice employing an advanced tubular sorter. Using primary cultures of these isolated segments, a reproducible methodology to measure CNI-mediated 22Na+ reabsorption in DCT cells was established. Furthermore, we demonstrated that incubation with 5 μM CNI (Cyclosporine A or Tacrolimus) significantly stimulates the thiazide-dependent 22Na+ transport across the primary DCT cultures. The recorded response to CsA was higher compared to control groups treated with hypertonicity, or angiotensin II (NCC stimulatory maneuvers). In line with our hypothesis, 100 μM hydrochlorothiazide added to the media prevented the CNI enhanced response. Furthermore, time courses from 1.5 to 24 hr showed similar enhanced 22Na+ transport. Finally, in mouse kidney lysates CsA phosphorylated NCC in a dose and time response.

Conclusions: This study supports the hypothesis that CNI-induced hypertension is caused by a rise in NCC activity involving a phosphorylation of the amino-terminal domain at Thrreonine 533A. In parallel, a produce a molecular hallmark of the mechanism involved in CNI-induced hypertension. This could be the first step towards designation and implementation of future clinical trials to develop new guidelines for transplanted patients.

Funding: Government Support - Non-U.S.

FR-PO738

KLHL3 Modulates Kidney-Enriched WNK Kinase Isoforms to Modulate NCC by Chong Zhang, 1 Nick Meermriet, 1 Andrew Terker, 1 Maria Chavez-Canales, 2 Gerardo Gamba, 1 Juliette Hadchouel, 1 David H. Ellison, 1 Chao-Ling Yang. 1 Nephrology & Hypertension, Oregon Health & Science Univ, Portland, OR; 2Paris Cardiovascular Research Center, INSERM-U970, Paris, Namibia; 3Molecular Physiology Unit, Universidad Nacional Autónoma de México, Mexico City, Mexico.

Background: Mutations of two components of the cullin-RING ligase complex, Cul3 and KLHL3, cause familial hyperaldememic hypertension (FHH). It has been reported that WNK1 and WNK4 bind to KLHL3, fostering ubiquitination and degradation of the proteasome. It has been postulated that the FHH-causing KLHL3 or Cul3 mutations impair the ability to ubiquitinate WNKs, leading to accumulation of WNK1 and WNK4, activating NCC.

Methods: We used transient transfection in HEK293 cells followed by western blotting. We also used overexpression in Xenopus oocytes, with measurement of 22Na uptake.

Results: Surprisingly, KLHL3 did not affect endogenous WNK1 and WNK3 in HEK293 cells, although it degraded WNK4 strongly. Alternative splicing generated different isoforms of WNK Kinases in a tissue-specific manner, so we compared effects of WNK1, KS-WNK1, and a WNK1 D11, an isofrom highly expressed in the kidney. We also tested forms of WNK3expressed preferentially in brain (B-WNK3) and kidney (K-WNK3). Like WNK4, K-WNK3 and WNK1 D11 were degraded more than 70% at the protein level, whereas L-WNK1 was unchanged. We have reported WNK kinase form signaling complex via protein interaction and phosphorylation to regulate NCC activity. In the mammalian and Xenopusoocyte expression system, WNK4 inhibits NCC, whereas WNK1 and WNK3 activate it. Since WNK isoforms, regulated by KLHL3, are all expressed in the DCT, mutations of KLHL3 must affect not only WNK4, but also WNK D11 and K-WNK3. In agreement with this hypothesis, co-expression of wild type KLHL3 reduced Na uptake in oocytes expressing NCC. In contrast, FHH-mutant KLHL3 stimulated Na uptake to more than 150%, suggesting that the mutations are not simply loss of function.

Conclusions: KLHL3 exerts differential effects on renal and extrarenal WNK isoforms; FHH-mutant KLHL3 mutations may exert dominant effects on NCC activity.

Funding: NIDDK Support, Veterans Affairs Support
Acidic Motif in WNKs Are Crucial Components for the Binding with KLHL3
Akihito Ohta,1 Shiniichi Uchida,1 Sei Sasaki,1 Dario Alessi,2 1Dept of Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan; 2MRC Protein Phosphorylation Unit, College of Life Sciences, Univ of Dundee, Dundee, United Kingdom.

Background: Pseudohypoaldosteronism type II (PHAII) is an autosomal-dominant disorder characterized by hyperkalemia, metabolic acidosis, and hypertension. WNK1 and WNK4 gene mutations were reported to cause PHAII. Lifton and another group identified KLHL3 and CUL3 mutations in PHAII, suggesting these two proteins may also form CRL3 complex that regulates blood pressure. After these reports, we started to search for KLHL3-interacting partner and analyze how these KLHL3-CUL3 complex are related to the pathogenesis causing PHAII.

Results: We generated Wild-type KLHL3 and mutant KLHL3 expressing 293 cell lines and immunoprecipitated KLHL3 interacts with CUL3 and WNKs. Some mutant mutations causing PHAII lost the binding with WNKs but WT-KLHL3 could bind with WNKs in 293 cell. To further analyze which parts of WNK1 interact with KLHL3, WNK1 fragments were co-transfected in WT-293 cell lines and found WNK1-479-667 fragment containing coiled-coil domain could bind WT-KLHL3. WNK1 fragments mutated in E633K, D655A and Q636E which are same sites reported in PHAII WNK4 patients, also transfected in KLHL3 cell and immunoprecipitated mutated WNK1 fragments could lose binding to KLHL3. Transfected sites in not only WNK4 but also WNK1 are important for the KLHL3 interaction. To narrow the site which parts interact between WNK1 and KLHL3, small WNK1 fragments in WNK1 (479-667) were transfected and found that acidic motif in WNK1 should be crucial for the binding with WT-KLHL3. WNK1 acidic motif mutation or deletion motif are conserved in other WNKs WNK1-WNK4 (N529K), WT-KLHL3 or PHAI1I mutant (N529K) KLHL3 were transfected in WNK2, WNK2 293 cell lines and found WNK2 or WNK3 could bind WT-KLHL3 but not mutant KLHL3 (N529K).

Conclusions: These results indicate that acidic motif in WNKs are crucial components for the binding with KLHL3 and speculate that abolishing the ability to interact between WNKs and KLHL3 in PHAII, modulating the ubiquitination WNK isoforms cause that the accumulation of WNKs which leads to abnormal sodium absorption in kidney causing hyperkalemia.

Funding: Pharmaceutical Company Support - AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck KgA, Janssen Pharmaceuticals and Pfizer., Government Support - Non-U.S.

FR-PO740
Low Salt Intake Decreased Transcription and Protein Level of KLHL3 in Mouse Kidney
Koichiro Susi, Eisei Sohara, Moko Zeniya, Tatemitsu Rai, Sei Sasaki, Shiniichi Uchida. Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: WNK-OSR1/SPAK-NaCl cotransporter (NCC) signal cascade is important for regulating salt balance and blood pressure in the body. It is well known that low salt diet activates and high salt diet inhibits this cascade, leading to regulation of sodium reabsorption through NCC. Recently, we found that Cullin3-KLHL3 E3 ligase complex that regulates blood pressure. After these reports, we started to search KLHL3-interacting partner and analyze how these KLHL3-CUL3 complex are related to the pathogenesis causing PHAII.

Methods: Male C57BL/6J mice fed high-salt, normal or low-salt diet were sacrificed after overnight fast, rats were fed a 2% K+ meal for 3 hours) increased both total and membrane NCC expression via decreasing NCCp, and membrane NCC protein expression in HEK293 cells transfected with GFP-NCC and the identity of the protease(s) involved.

Funding: JSDK Support

FR-PO743
Aldosterone Modulates NCC via Altering Its Interaction with 14-3-3
Xiuyan Feng,1 Yiqian Zhang,1 Matthew Lee,1,2 Guangping Chen,1,3 Dingying Gu,1 Hui Cai,1,2 1Renal Div, Dept of Medicine, Emory Univ School of Medicine, Atlanta, GA; 2Dept of Physiology, Emory Univ School of Medicine, Atlanta, GA; 3Dept of Nephrology, The 2nd Affiliated Hospital, Wenzhou Medical Univ, Wenzhou, Zhejiang, China; 4Renal Section, Atlanta VA Medical Center, Decatur, GA.

Background: 14-3-3 gamma, a multifunctional protein, binds to and regulates a large number of cellular substrates, including epithelial sodium channel (ENaC). Previous data have shown that 14-3-3 is involved in aldosterone-mediated ubiquitination of ENaC, leading to increase in ENaC activity.

Methods: Cell cultures, transfection, immunoprecipitation and western blot analysis were used in the study.

Results: To determine whether 14-3-3 is involved in aldosterone-mediated regulation of NCC, we have tested the effect of 14-3-3 gamma on NCC protein expression. We found that 14-3-3 gamma down-regulated total NCC and membrane NCC protein expression in a dose-dependent manner in HEK293 cells consistently transfected with GFP-NCC and 14-3-3 gamma plasmids. Aldosterone treatment (10 μM, for 3 hours) increased both total and membrane NCC protein expression in HEK293 cells transfected with GFP-NCC and 14-3-3 gamma, while decreasing interaction of NCC with 14-3-3 gamma. We also found that aldosterone increased both total and membrane NCC expression via decreasing NCCp.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Conclusions: These data suggest that aldosterone increases NCC expression through decreasing binding of 14-3-3 gamma to NCC, and therefore decreasing NCC ubiquitination.

Funding: Veterans Affairs Support, Private Foundation Support

FR-P0744

RNA Profiling Reveals Compensatory Up-Regulation of Intercalated Cell Transcripts in SPAK-Null Mice Having a Gitelman-Like Phenotype. E. Eric, Delboy, 1 Ian A. Welling, 1 Physiology, Univ of Maryland School of Medicine, Baltimore, MD, 2Anesthesiology, Vanderbilt School of Medicine, Nashville, TN.

Background: An adaptive increase in salt reabsorption preserves salt balance when the thiazide-sensitive sodium-chloride cotransporter (NCC) is lost in Gitelman Syndrome or NCC phosphorylation is lost in Ste20/SPAK-related proline-alanine-rich protein kinase (SPAK) null mice. To explore the mechanism of adaptive salt reabsorption, global-transcriptome analysis of the renal cortex from WT and SPAK-null animals was performed.

Methods: RNA was extracted from the cortex of SPAK-null and WT littermate mice. microarray analysis was performed using Affymetrix GeneChip (Mouse Gene 1.0 ST) containing probes of all mouse genes and analyzed on an Affymetrix GeneChip 3.000 system. Quality control analysis, Robust Multi-array Average, and Linear Model for Microarray based differential expression analysis were subsequently performed. The altered expression of highlighted genes was verified by RT-PCR.

Results: Statistical analysis indicated that 176 genes were down-regulated and 263 genes were up-regulated significantly in the SPAK-null cohort compared to WT. Interconnected cell (ICs) markers, transporters and enzymes were especially prevalent, including pendrin, the sodium-dependent chloride bicarbonate exchanger, anion-exchanger 4, carbonic anhydrase 4 and 15, and the B1-, C2-, G3-, and D2-subsutents of the V-type H⁺-ATPase. Significantly, these transport components represent a system recently proposed to facilitate thiazide-sensitive sodium-chloride reabsorption in the β-ICs. These changes were paralleled by an increase in transcript abundance of the β- and γ-subunits of ENaC.

Specific distal nephron fate factors and signaling elements were also significantly up-regulated, highlighting potential molecular pathways that underlie the adaptive process.

Conclusions: Transcriptome-profiling reveals interconnected cell sodium-chloride transport is up-regulated to preserve sodium balance in the absence of NCC phosphorylation.

Funding: NIDDK Support

FR-P0745

Chemical Library Screening for WKN Signaling Inhibitors by Using Fluorescent Correlation Spectroscopy. Takasavari Mori, Eriko Kikuchi, Eisei Sohara, Tatemitsu Rai, Sei Sasaki, Shinichi Uchida. Dept of Nephrology, Graduate School of Medical and Dental Sciences, Bunkyo-ku, Tokyo, Japan.

Background: We have shown that WNK oxidative stress-responsive 1 (OSR1)/STE20/SPS1-related proline-alanine-rich protein kinase (SPAK)-Slc12a transporters cascade regulates blood pressure by controlling vascular tone as well as renal NaCl excretion. Therefore, agents that inhibit this signal cascade could be a new class of antihypertensive drugs. Since the binding of WNk to OSR1/SPAK kinases was postulated to be important for signal transduction, we sought to discover inhibitors of WNK-SPAK binding by screening drugs. Since the binding of WNK to OSR1/SPAK kinases was postulated to be important for signal transduction, we sought to discover inhibitors of WNK-OSR1 binding by screening drugs. We have previously reported that aldosterone increases open probability of the β1-ENaC, and therefore decreasing NCC ubiquitination. The thiazide-sensitive sodium-chloride cotransporter (NCC) is lost in Gitelman Syndrome or NCC phosphorylation is lost in Ste20/SPAK-related proline-alanine-rich protein kinase (SPAK) null mice. To explore the mechanism of adaptive salt reabsorption, global-transcriptome analysis of the renal cortex from WT and SPAK-null animals was performed.

Results: Aldosterone increases open probability of the β1-ENaC, and therefore decreasing NCC ubiquitination. The thiazide-sensitive sodium-chloride cotransporter (NCC) is lost in Gitelman Syndrome or NCC phosphorylation is lost in Ste20/SPAK-related proline-alanine-rich protein kinase (SPAK) null mice. To explore the mechanism of adaptive salt reabsorption, global-transcriptome analysis of the renal cortex from WT and SPAK-null animals was performed.

Conclusions: Transcriptome-profiling reveals interconnected cell sodium-chloride transport is up-regulated to preserve sodium balance in the absence of NCC phosphorylation.

Funding: NIDDK Support

FR-P0747

Biphasic Regulation of the Epithelial Sodium Channel by Inflammation and the IKK/NF-κB Pathway. Hui Li, Eric D. Morrell, Robert S. Edinger, Nuria M. Pastor-Soler, Kenneth R. Hallows. Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: The kidney collecting duct epithelial sodium channel (ENaC) is critical for the normal regulation of volume and blood pressure but also responds to pathologic conditions such as sepsis-induced inflammation. We have previously shown that the inflammatory mediator Ikβ kinase-β (IKKβ) stimulates ENaC by phosphorylating the ubiquitin ligase Nedd4-2. Others have observed that the downstream mediator NFκB inhibits ENaC. To define the time course and mechanisms of ENaC regulation by this inflammatory stimulus, we treated polarized epithelial kidney cell cultures with TNFα, IKK modulators, and also NFκB activators of this pathway, or IKK inhibitor and measured ENaC whole-cell and surface expression levels and currents.

Methods: Mouse polarized kidney cortical collecting duct (mCkcc1) and primary airway epithelial cells were cultured on Transwells and then treated with 100 ng/ml LPS or TNFα prior to measurements. Amiloride-sensitive short-circuit currents were measured in Ussing chambers or with an epithelial volt-ohmmeter. Immunoblots, cell surface biotinylation assays and co-immunoprecipitations were performed to measure changes in ENaC whole-cell and apical surface expression and binding to Nedd4-2. Confocal microscopy was performed on immunofluorescently labeled ex vivo kidney slices to examine changes in ENaC subcellular localization in response to IKK modulation.

Results: ENaC activity increased at 1 h but decreased by 18 h in response to activation of the IKK/NF-kB pathway by TNFα treatment in primary airway epithelial cells. This decrease correlated with decreased α-ENaC and mineralocorticoid expression. Overexpression of ENaC, cells with either TNFα or LPS similarly decreased ENaC currents and also β- and γ-ENaC apical surface expression. TNFα acutely decreased the binding of Nedd4-2 to β-ENaC, an effect that was reversed by treatment with IKK inhibitor. Finally, acute TNFα treatment of kidney slices induced apical translocation of β-ENaC, which was blocked in the presence of IKK inhibitor.

Conclusions: Biphasic regulation of the ENaC by the IKK/NF-κB pathway may help integrate the response of ENaC and epithelial salt transport to hormonal and inflammatory stimuli.

Funding: NIDDK Support

FR-P0748

ENaC Inhibition Stimulates Conductive H + and Cl Secretion in the Mouse Cortical Collecting Duct. Masayoshi Nanami. 1 Hui-fang Bao, 2 Alan Mark Weinstein, 3 Takeshi Nakashizu, 2 Douglas C. Eaton, 4 Susan M. Wall. 4 Medicine and Physiology, Emory Univ School of Medicine, Atlanta, GA; 4Medicine, Weill Medical College of Cornell Univ, New York, NY; 4Medicine, Hyogo College of Medicine, Nishinomiya, Japan.

Background: Inhibiting the epithelial Na+ channel (ENaC) reduces C1 secretion in the cortical collecting duct (CCD). Since ENaC does not transport C1, the purpose of this study was to determine how ENaC modulates C1 absorption in the CCD in vitro.

Methods: Wild type or cortical duct-specific ENaC null mice consumed a NaCl-replete diet or diet with aldosterone administered by minipump. C1 currents were perfused in vitro in the presence and absence of an ENaC inhibitor (benzamil, 3 mM) in the luminal fluid. Results: Application of an ENaC inhibitor (benzamil, 3 mM) to the luminal fluid unmasks conductive H+ and C1 secretion. Benzamil-sensitive HCO3- and C1 flux were reduced or abolished with the application of the non-selective C1 channel blocker, DIDS, or the H+/H-coexchanger, bafilomycin to the perifusate. Similarly, ENaC gene ablation unmasks DIDS-sensitive C1 secretion. Single channel recordings of intercalated cell amilipmic membrane in split open CCDs demonstrated a stellare-sensitive C1 channel with properties that resembles CIC-5.

Conclusions: 1) In CCDs from aldosterone treated mice, most C1 absorption is benzamil-sensitive, 2) Benzamil application stimulates stellare- and bafilomycin-sensitive conductive secretion of C1 and H+; and 3) an intercalated cell apical membrane C1 channel may mediate benzamil-sensitive C1 secretion.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
FR-PO749
An Exon Deletion Activates the Epithelial Sodium Channel Jiejing Chen
Thomas R. Kleyman, Shaohui Sheng. Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Epithelial Na+ channels (ENaC) have essential roles in the regulation of extracellular fluid volume and blood pressure. The three ENaC subunits typically present in functional channel complexes in epithelia are encoded by their corresponding multi-exon genes that have a similar architecture. Common isoforms of all three human ENaC subunits (α, β, γ) are translated from mature mRNAs that are similarly spliced with inclusion of 13 exons. While the channel pore is formed by amino acid residues encoded by exons 2 and 13, ten exons (3 through 12) encode the large extracellular region.

Methods: We examined whether exons 3 through 12 were required for functional ENaC expression by generating series of exon deletions. Human ENaCα with in-frame deletions of individual exon sequences in α subunit cDNAs were expressed in Xenopus oocytes and their functional properties were examined by two-electrode voltage clamp.

Results: Deletion of any of these exon-encoding sequences eliminated channel activity, with the exception of exon 11 that encodes the knuckle domain. Cells expressing channels with an α subunit exon 11 deletion showed 4-fold greater amiloride-sensitive currents than oocytes expressing wild type (WT) channels. The increased channel activity primarily reflected an increased channel open probability (5-fold greater than WT), as both levels of surface expression and single channel current were similar to WT. Surprisingly, deletion of exon 11 from either the β or γ subunit diminished channel activity, reflecting a reduced level of surface expression.

Conclusions: Our results suggest that the α subunit knuckle domain regulates channel gating.

Funding: NIDDK Support

FR-PO750
Specific Inactivation of the Epithelial Sodium Channel (ENaC) in Connecting Tubule: Effect on Sodium and Potassium Homeostasis Soren Brandt Poulsen,1 Jeppe Praetorius,1 Lance Miller,2 Raoul D. Nelson,2 Edith Hummler,3 Birgitte M. Christensen.1, 3Aarhus Univ; 1Univ of Utah School of Medicine; 3Univ of Lausanne.

Background: In the kidney, ENaC is crucial for Na+ reabsorption, but it is also involved in the excretion of K+. ENaC is expressed in the late distal convoluted tubule, connecting tubule (CNT), and collecting duct (CD), where it is tightly regulated by the steroid hormone aldosterone. Inactivation of the αENaC subunit in the CD does not disturb Na+ /K+ balance in mice (Rubera et al, JCI 2003). However, αENaC deletion in both the CNT and CD causes symptoms of pseudoaldosteronism type 1 as evidenced by disturbance in Na+ and K+ balance on standard and challenging diets (Christensen et al, JASN, 2010).

Methods: To further investigate the significance of αENaC in the CNT, mice with Cre-recombinase expressed under the control of the V-ATPase B1-subunit promoter (these mice also express Cre in a portion of the CNT cells, Miller et al, KI, 2009) were crossed with floxed Scnn1a mice (Hummler et al, Genesis, 2002). Thus, KO mice with a deletion of αENaC in part of the CNT were generated.

Results: Results revealed that at baseline level (standard diet), KO mice showed no difference in urinary Na+ and K+ excretion, urine output, water intake, blood K+, osmolality or aldosterone compared to controls. On low Na+ diet (7 days), however, KO mice showed increased urinary Na+ excretion (on day 5 and 6) but no difference in blood K+ (sampled on day 7). When challenged with high K+ diet (2 days), KO mice decreased their food intake, lost weight, and excreted less K+ through the urine (on day 1 and 2; P < 0.05). Moreover, they showed a lower water intake and urine output (on day 1; P < 0.05).

Conclusions: All baseline levels were unchanged in KO mice deficient for αENaC in part of the CNT, but on challenging diets the KO mice appeared with a phenotype. The phenotypes was however less severe compared to mice with αENaC deleted in both the CNT and the CD. This may suggest that expression of αENaC both in the CNT and the CD are important for Na+ and K+ balance.

Funding: Private Foundation Support

FR-PO751
Effects of Long-Term Aldosterone Administration on mRNA Expression Levels in the Renal Distal Nephron Examined by FACS and RNA Sequencing Soren Brandt Poulsen, Jeppe Praetorius, Robert A. Fenton, Birgitte M. Christensen. Aarhus Univ.

Background: Renal sodium reabsorption and potassium excretion in the distal convoluted tubule 2 (DCT2) and connecting tubule (CNT) are tightly regulated by aldosterone. Previously, microarrays have been used to investigate the regulatory role of aldosterone. However, the emergence of next generation sequencing (RNA sequencing) offers improved sensitivity by employing sequence-based approaches directly determining the mRNA sequence, thus making it possible to generate a more complete catalog of aldosterone regulated genes in this study, we used FACS sorting and RNA sequencing to identify genes in the DCT2 and CNT not previously known to be regulated by aldosterone.

Methods: We used a mouse model expressing EGF driven by the TRPV5 gene promoter, i.e., the mice expressed EGF in DCT2 and CNT cells. The mice were administrated saline (n = 7) or 100 μg aldosterone/kg body weight (n = 7) for six days. Following, a population of EGF positive cells (DCT2 and CNT) was generated using FACS sorting (purity ~90%). The cell population was sequenced using an Illumina HiSeq 2000 (yield: ~40 mio paired end 100 bp reads). Finally, data was analyzed using the tophat pipeline (Trapnell et al, Nature Protocols, 2012).

Conclusions: In this model, one of the most significant changes was the 2-fold upregulation of Sgk1 (p = 0.058; αENaC: p = 0.147). Furthermore, RNA sequencing showed an increase in Sgk1 (p = 0.002) and a decrease in Nedd4-2 (p = 0.011), proteins known to be involved in ENaC regulation. In conclusion, we have used a new genetic mouse model expressing EGF in the late aldosterone-sensitive distal nephron. These mice are a powerful tool to study the molecular mechanisms that regulate the ENaC expression.

Funding: Private Foundation Support

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

FR-PO752
The Role of Epithelial Sodium Channel ENaCα and the Apical CI/HCO3-, Exchanger Pendrin in Compensatory Salt Absorption in the Distal Nephron in NCC (Na-CI Cotransporter) KO Mice Mina Patel-Chamberlin,1 Kamyar A. Zadehi,2,3 Sharon L. Barone,2,3 Manoocher Soleimani,2,3 1Dept of Internal Medicine, Univ of Cincinnati; 2Research Services, Veterans Administration.

Background: Lack of NCC function does not cause significant salt wasting under basal conditions. NCC KO mice have increased expression of ENaC and pendrin, suggesting enhanced compensatory salt absorption in the distal nephron. Pendrin/NCC double knockout (KO) mice develop profound salt wasting compared to wild type (WT), NCC KO or Pendrin KO mice, demonstrating the important role of pendrin in compensatory salt absorption in NCC KO mice. We hypothesize that the inhibition of ENaC or down regulation of pendrin can cause significant salt wasting in NCC KO mice.

Methods: WT and NCC KO mice were treated with daily injection of amiloride, an ENaC inhibitor, or acetazolamide (ACTZ), a carbonic anhydrase inhibitor (CAI), for 6 days. Animals were subjected to balanced studies. At the end of studies, kidneys were harvested and examined for proteins and mRNAs of interest. Blood samples were collected for electrolytes and acid base analysis.

Results: There was an ~80% increase in urine output (UO) in NCC KO compared to WT mice after amiloride treatment (0.74ml vs. 1.29ml, p<0.02). Salt excretion increased and urine osmolality decreased more significantly in NCC KO vs WT mice after amiloride treatment (p<0.02). Daily treatment with ACTZ resulted in ~85% reduction of pendrin expression in both WT and NCC KO mice at 6 days of treatment. However, the diuretic response was more exaggerated in NCC KO mice (1.1 ml/day before 2.3 after ACTZ) (p<0.01) vs. WT mice (1.05 ml/day before 1.30 after ACTZ).

Conclusions: 1. ENaC plays a important role in salt reabsorption in NCC KO mice. 2. NCC plays an important role in salt reabsorption in the setting of carbonic anhydrase inhibition, which is associated with increased delivery of salt from the proximal tubule and the down regulation of pendrin. We propose that the combined inhibition or inactivation of NCC and ENaC or NCC and carbonic anhydrase can provide a strong diuretic regimen, particularly in salt retaining conditions (e.g. congestive heart failure and nephrotic syndrome).

Funding: NIDDK Support, Veterans Affairs Support

FR-PO753
Albumin-Induced Oxidative Stress Prevents Aldosterone-Induced Expression of ENaC in Collecting Ducts of Nephrotic Rats Kamkar Mohammad Udayan, Gaëlle Bricaud, Alain Douzet. Centre de Recherches des Cordeliers, Paris, France.

Background: Porcine aminomucinose (PAN) nephritic rats show high plasma aldosterone and retain sodium via stimulation of ENaC and Na+ATPase in the late aldosterone-sensitive distal nephron. PAN nephrotic rats with clamped aldosteronemia (adrenalectomy plus supplementation with constant infusion of aldosterone and dexamethasone) do retain sodium although ENaC is not induced. We evaluated the role of aldosterone in the regulation of ENaC expression.

Methods: Experiments were performed either in cortical collecting ducts (CCD) from control and PAN nephrotic rats or in mCCD cells (mCCDs). Production of reactive oxygen species (ROS) was evaluated through the nuclear labeling with dihydro-ethidium (DHE), and gene expression was quantified by RT-PCR.

Results: In mCCDs, apical addition of albumin induces aldosterone, and the production of ROS. Albumin-induced accumulation of ROS was prevented by dynasore, an inhibitor of endocytosis, by apocynin, an inhibitor of NADPH oxidase, and by N acetyl cysteine (NAC), an ROS scavenger. Addition of H2O2 (0.5-1 mM) altered the basal level of reactive oxygen species (ROS) in CCDs. Production of reactive oxygen species (ROS) was prevented by apocynin, an inhibitor of NADPH oxidase, and by N acetyl cysteine (NAC), an ROS scavenger. Addition of H2O2 (0.5-1 mM) altered the basal level of reactive oxygen species (ROS) in CCDs.

Conclusions: Luminal endocytosis of albumin in collecting ducts of nephrotic rats triggers oxidative stress, via activation of NADPH oxidase, which counterbalance aldosterone-induced expression of ENaC.

Funding: Government Support - Non-U.S.

Poster/Friday

Nα+, K+, and CI- Transporters in Health and Disease

536A
FR-P0754

Apical Shear-Stress Regulates Sodium Transport in Principal Cells of the Collecting Duct  Thomas Fernandez,1,2 Alexandra Chassot,1,2 Pierre-Yves F. Martin,1,3 Eric Feraillé,1,3 1Service of Nephrology, Univ Hospital of Geneva, Geneva, Switzerland; 2Dept of Physiology and Cellular Metabolism, Univ of Geneva, Geneva, Switzerland.

Background: Sodium (Na) transport in renal tubules is tightly controlled and plays a central role in homeostasis of the body extracellular fluid volume. In addition to the classical neuro-endocrine regulatory inputs (incl. RAA system), other local factors such as apical shear stress introduced by tubular lumen flow may participate to Na homeostasis.

Methods: We designed an in vitro experimental setting to explore the effect of apical flow on a cellular model of collecting duct (CD) using the well-described mouse CD cell line mCDCC11 grown on polycarbonate filters. Directional flow was generated using an orbital shaker delivering a shear stress of 2 dynes/cm² simulating physiological urinary flow rates.

Results: We observed a delayed and sustained 40% decrease of the amiloride-sensitive Na current in cells subjected to flow. This was correlated with a significant decrease of ENaC subunits and SGK1 mRNA expression. The flow-mediated Na reduction was not prevented by PKD1 or RIPIA silencing, suggesting a role of the primary cilium as a mechanosensor in this mechanism. On the other hand, whole-genome transcriptional analysis of wild-type mCDCC11 cells subjected to flow suggested a role for PKA signaling and PKA substrates phosphorylation including CREB was increased by flow. This was further confirmed by PKA inhibition that partially prevented the flow-mediated decrease of Na transport in vitro as well as the downregulation of ENaC subunits mRNA expression.

Conclusions: These results are in line with physiological adaptation reported after unilateral nephrectomy in rodents in which a larger tubular fluid delivery is observed together with a renal arterial flow fractional decrease of 8%. We propose that the shear stress-mediated adaptive mechanism is involved in the homeostasis of extracellular fluid volume after nephron reduction.

FR-P0755

Primary Cilia Influence the Roles of TRPM3 and TRPV4 in Renal Epithelial Cell Adaptation to Acute Hypersmolar Stress Brian J. Siroky,1 Bradley P. Dixon,1 Raven Gail Comer,1 Nancy Kleene,2 John J. Bissler.1 1Nephrology and Hypertension, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Cancer and Cell Biology, Univ of Cincinnati, Cincinnati, OH.

Background: Ability of renal epithelial cells to adapt to changes in extracellular osmolality is critical to cell volume regulation. Primary cilia sense environmental conditions including osmolality and hypertonicity, but whether cilia participate in osmotic response in renal epithelial cells is not known. Transient receptor potential (TRP) channels TRPV4 and TRPM3 are osmoreponsive. TRPV4 localizes to cilia in certain cell types, while cellular localization of TRPM3 is not known. We investigated the role of cilia in the adaptive response of renal epithelial cells to acute osmotic stress, and whether TRPV4 and TRPM3 are involved.

Methods: TRPV4 and TRPM3 expression was determined in ciliated (176-5) and nonciliated (176-5A) murine renal epithelial cells by RT-PCR, and TRPV4 localization was observed by immunocytochemistry. Cells were challenged with 16 hours of osmotic stress mediated by 600mM NaCl in the medium. TRPV4 expression was confirmed by immunoblotting.

Results: Ciliated and nonciliated cells expressed TRPV4 and TRPM3. TRPV4 was observed in apical and basolateral membranes of both cell types, but was absent from cilia of 176-5 cells. Hypersmolar stress induced both Bgl1 and Arx1b induction expression in both cell lines. In contrast, induction of these genes was attenuated in ciliated cells compared to ciliated cells. Presence of TRPV4 agonist abrogated Bgl1 and Arx1b induction in nonciliated cells only. Presence of TRPM3 agonist attenuated Bgl1 and Arx1b induction primarily in ciliated cells.

Conclusions: These results suggest that cilia mediate osmotic response in renal epithelial cells, and that TRPM3 is involved in this mechanism. Furthermore, in the absence of cilia, TRPV4 appears to mediate the attenuated osmotic response.

Funding: NIDDK Support, Private Foundation Support

FR-P0756

P2Y12 Receptor Blockade Reverses Lithium-Induced Lowered Urinary Concentration in Male Mice Yue Zhang,1 Noel G. Carlson,1 Bellamkonda K. Kishore,1 Carolyn M. Eccelbarger2 1Univ of Utah & VA Medical Center, Salt Lake City, UT; 2Georgetown Univ, Washington, DC.

Background: Lithium therapy is associated with the development of impaired water handling through to NDI in about 60% of patients prescribed lithium. Lithium down-regulates the expression and synthesis of aquaporin 2 (AQP2), reducing ducting collect tubular water reabsorption. We have previously shown that amiloride, blocking ENaC mediated lithium uptake in the principal cells, partially attenuates NDI after 3 weeks of therapy (1). However, the long-term (5 months) effect of amiloride in this model has not been studied.

Aim: To investigate the long-term effects of amiloride on chronic lithium induced nephrogenic diabetes insipidus in an established rat model.

Methods: Male wistar rats were divided into control, lithium alone and lithium plus amiloride groups (n=6 per group). Lithium was provided in rat chow (60 mmol/kg food) for 6 months and amiloride was introduced in drinking water (0.2 mmol/l) following the establishment of NDI one after month of lithium treatment and continued for 5 months. Following metabolic studies the rats were euthanised and kidneys processed for histology, immunohistochemistry and western blotting.

Results: Amiloride partially restored the urinary concentration from 199±14 mosmol/kg (lithium alone) to 612±72 mosmol/kg (lithium + amiloride) vs controls 2258±182 mosmol/kg.

This effect was accompanied by a decreased urine output (lithium alone 174±31 µl/min/kg vs lithium + amiloride 54±8 µl/min/kg) and control 11±4 µl/min/kg). AQP2 water channel expression examined by western blotting and immunohistochemistry showed a significant decrease (40.37±2%; p < 0.01) in the lithium alone treated rats and it was restored (88.7 ± 16%; p < 0.01) with amiloride administration.

Conclusions: This study demonstrates a persistent partial recovery from NDI with amiloride over 6 months in lithium treated rats. This has potential clinical significance for the management of patients with lithium-induced NDI.


Funding: Government Support - Non-U.S.

FR-P0757

Pharmacological Blockade of P2Y12 Receptor Reverses Lithium-Induced Lowered Urinary Concentration of NKC22, NCC and α-ENaC Protein Abundances in Mice Yue Zhang,1 Noel G. Carlson,1 Bellamkonda K. Kishore,1 Carolyn M. Eccelbarger2 1Univ of Utah & VA Medical Center, Salt Lake City, UT; 2Georgetown Univ, Washington, DC.

Background: P2Y12, is an ADP-activated G-protein coupled receptor (R) that inhibits adenylyl cyclase activity, potentially reducing cellular cAMP levels. We found that P2Y12-R protein is expressed in the rodent kidney, and its irreversible blockade by clopidogrel (CLPD; Plavix®), significantly increased urinary concentration and vasopressin (AVP) and AQP2 protein abundance in the kidney, and ameliorated lithium (Li)-induced diabetes insipidus (DI) in rodents. Since Li also affects renal sodium transport, here we examined the effect of CLPD on Li-induced alterations in renal sodium transporters/channels in mice.

Methods: Groups of mice (B6D2 strain; n = 5-7/group) were fed Li-added diet (40 mmol/kg chow) with or without addition of CLPD (80 mg/kg bw/day) to drinking water. Mice were fed either regular diet or with CLPD. After 14 days, major renal sodium transporter, channel, and exchanger expressions were measured by immunoblotting in cortex (Cx) and medullary (Md) fractions. Urinary AVP and AQP2 levels were quantified.

Results: The most striking finding was upregulation of the abundance of the thick ascending limb (TAL) Na-K-2Cl cotransporter (NCC2) by CLPD treatment alone (30% and 137%, respectively in Md and Cx). In the presence of Li, CLPD restored the moderate down-regulation of NKC22 (19 and 52%, respectively in Cx and Md) to control levels. In addition, in Li-treated mice, CLPD restored the abundance of the thiazide-sensitive Na transporter (NCC) and α-subunit of the epithelial sodium channel (ENaC) in Md. Li-induced increases in urinary AVP and P2E2 were either augmented (P < 0.01) or reversed (P < 0.01), respectively, by CLPD.

Conclusions: CLPD was able to reverse Li-induced down-regulation of major apical proteins involved in sodium reabsorption in the TAL through collecting duct (CD). This effect was not solely the result of increased AVP levels, but appears to be due to re-sensitization of the TAL and CD to AVP action, aided by the reversal of Li-induced increased P2E2 levels. Thus, P2Y12-R antagonism may be a promising approach for the treatment of Li-induced DI.

Funding: Veterans Affairs Support, Private Foundation Support
FR-P0759
Physiological Roles of Moesin, a Crosslinker between Membrane Proteins and Actin Cytoskeleton in the Electrolytes and Water Reabsorption Ryo Hatano, Kotoko Kawaguchi, Shinji Asano. Dept of Molecular Physiology, Ritsumeikan Univ, College of Pharmaceutical Sciences, Kusatsu, Shiga, Japan.

Background: Moesin is a member of ERM (ezrin-radixin-moesin) family protein, which is known to function as a crosslinker between membrane proteins and actin cytoskeleton. Moesin is expressed in several tissues including kidney, liver, lung, and intestine. The moesin family protein is mainly expressed in the endothelial cells and epithelial cells as proximal tubule cells, although the physiological importance in the kidney still remains unclear. Recently, Carmonso et al. reported that moesin but not radixin interacts with the intracellular C-terminal region of Na+/K-2CT cotransporter (NKCC2) (Bio Cell, 104(2), 156-161, 2012). They reported that moesin regulated the expression of NKCC2 in cultured cells, although it is not clear whether moesin regulates the apical surface expression of NKCC2 directly or indirectly. However, it is reported that moesin deficient mice did not exhibit apparent phenotypes in vivo (Doi Y et al. The Biol Chem. 274(4): 2315-2321, 1999).

Methods: In the present study, we investigated the physiological roles of moesin in the functional regulation of NKCC2 using moesin deficient mice.

Results: In wild type (WT) mice kidney, relatively low level of moesin was expressed in the thin ascending segment of Henle (TALH) compared to endothelial cells and brush border membrane of proximal tubules, and it is co-localized with NKCC2 at apical membrane of TALH. In moesin deficient mice, the apical localization of NKCC2 was disturbed in the TALH. Furthermore, the metabolic cage studies revealed that moesin deficient mice exhibited the urinary losses of electrolytes as Na⁺, K⁺, and Cl⁻ whereas daily urine volume were not different between WT and moesin deficient mice.

Conclusions: These results suggest that moesin plays important role in the regulation of electrolytes/water homeostasis in the kidney. Further experiments are required to reveal the detailed mechanism how moesin regulates the apical membrane localization of NKCC2.

FR-P0760
Relation between BK-α/J4-Mediated K Secretion and ENaC-Mediated Na Reabsorption Donghui Wen, Ryan J. Cornelius, Dianelys Rivero, Steven C. Sansom. Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE.

Background: The BK-α/J4 channel is located in the intercalated cells (IC) of the distal nephron and mediates K secretion when mice are on a high K, alkaline diet. The present studies were conducted to determine whether BK-α/J4-mediated K secretion was dependent on ENaC-mediated Na reabsorption from principal cells.

Methods: Wild type (WT) and BK-α/J4 knockout mice (B4KO) were adapted to a low Na, high K, alkaline diet (LNaHK) for 7-10 days to maximize Na reabsorption-driven K secretion in the aldosterone sensitive distal nephron. At the end of diet treatment, we gave a 12 hr bolus of vehicle, hydrochlorothiazide (HTZ, 50 mg/kg) or amiloride (5 mg/kg; ENaC inhibitor). Plasma and urine [Na⁺], [K⁺], [amiloride] and osmolality were measured using a flame photometer, HPLC, and osmometer, respectively. Luminal [K⁺] and [Na⁺] in the terminal cortical collecting duct (CCD) were calculated via the formulas: [U]K⁺/[U]Na⁺ × P[OSM] or [U]Na⁺/[U]OSM.

Results: The calculated concentration of amiloride in the lumen of the terminal CCD, determined by HPLC and the plasma and urine osmolalities, was at least 20 μM, which would typically inhibit ENaC-mediated Na reabsorption. We found that HTZ, which enhanced Na excretion in WT on a control diet, did not affect Na handling in mice on LNaHK. However, amiloride significantly enhanced Na excretion, reduced plasma [Na⁺], and evoked volume depletion in WT and B4KO on LNaHK. The amilor-sensitive K secretion to NaCl ratio (kNa/K), calculated from the luminal [K⁺] and [Na⁺] in vehicle and amiloride-treated mice, was 1.5 in WT and 0.49 in B4KO, which was close to a value of 0.54 found in WT on a control diet.

Conclusions: We conclude that the high -kNa/Na in WT, compared with B4KO, on LNaHK demonstrates a mechanism for BK-α/J4-mediated K secretion in intercalated cells that is driven by ENaC-mediated Na reabsorption in principal cells, by a mechanism likely involved in recycling of Na from plasma to lumen.

Funding: NIDDK Support

FR-P0761
WNK1 Attivates BK Channel Activity through MAPK ERK1/2 Signaling Pathway Yingli Liu,1 Xiang Song,2 Weihui Ni,,1 Yanli Shi,1 Hui-Fang Bao,2 He-ping Ma,2 Douglas C. Eaton,2 Jieqiu Zhuang,3 Hui Cai.1,2,4

Background: WNK4 was also found to inhibit BK channel activity remains not entirely clear. We have investigated the effect of WNK1 on BK channel activity using cell attached single channel blot analysis.

Methods: We have investigated the effect of WNK1 on BK channel activity using cell attached single channel recording technique, cell cultures, transfection, siRNA knock-down and western blot analysis.

FR-P0762
Dietary K Changes Modulate BKα Protein Abundance through MAPK Signaling Pathway Yanhui Shang,1 Shanyi Wang,2 Matthew Lee,3 Xiuyan Feng,1 Yingli Liu,1 Dingying Gu,1 Hui Cui.1,2,3 Renal Div, Dept of Medicine, Emory Univ School of Medicine, Atlanta, GA; Dept of Physiology, Emory Univ School of Medicine, Atlanta, GA; Dept of Nephrology, The First Affiliated Hospital, Wenzhou Medical Univ, Wenzhou, Zhejiang, China; Dept of Nephrology, The Second Affiliated Hospital, Wenzhou Medical Univ, Wenzhou, Zhejiang, China; Renal Section, Atlanta VA Medical Center, Decatur, GA.

Background: Dietary K loading has been shown to increase urinary K excretion. High K diet has been shown to suppress renin-angiotensin system, whereas low K diet stimulates renin-angiotensin system. High K diet increased BKα protein expression in rabbit cortical collecting duct (CCD) cells. Inhibiting ERK1/2 and p38 was found to increase BKα channel activity in rat CCD cells. However, exact mechanism on how dietary K changes modulate BKα channel activity remains not entirely clear.

Methods: Mice metabolic cage study, cell cultures, transfection, western blot analysis were used for the studies.

Results: To investigate the mechanism on how the dietary K changes affect BKα abundance, we have fed mice with low K (deficient diet), normal K (1.0 %) and high K (10 %) diets for 10 days. After 10 days of dietary K challenges, mice fed with high K diet exhibited a high urinary K excretion, whereas mice fed with low K diet exhibited a low urinary K excretion. We have found that high K diets increased BKα protein abundance (200.03 ± 96.41, n=9, vs normal K group 100.00 ± 28.25, n=8, p=0.01), whereas low K diets decreased BKα abundance (54.39 ± 35.62, n=6, vs normal K group 100.00 ± 12.24, n=6, p=0.01). High K diet decreased p38 phosphorylation, whereas low K diet increased p38 phosphorylation. We also found that angiotensin II (Ang II) treatments decreased BKα protein expression in a dose-dependent manner in HEK293 cells transiently transfected with myc-BKα plasmids.

Conclusions: These data suggest that dietary K changes modulate BKα protein abundance possibly via altering Ang II-mediated p38 MAPK signaling pathway.

Funding: Veterans Affairs Support, Private Foundation Support

FR-P0763
The BK Channel Localizes to Lipid Rafts in the Apical Membrane of the Corticocollecting Duct Rolando Carrizzo-Gayton, Carlos Schreck, Marcello D. Carattino, Thomas R. Kleymann, Lisa M. Satlin.1 Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY; Medicine, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: The Ca²⁺ and stretch-activated BK channel, present in principal (PC) and intercalated (IC) cells but more abundant in IC, mediates flow-induced K secretion (FIKS) and the enhanced K secretion observed in response to dietary K loading in the cortical collecting duct (CCD). BK channel activity is regulated by membrane cholesterol (Pharmacol Ther 135:133-150, 2012). Studies by others have shown in non-renal cells that (i) BK channels localize to sphingolipid-cholesterol-rich lipid rafts (LRs) and (ii) channel activity is regulated by the composition and/or integrity of LRs. We hypothesized that BK channels in the CCD localize to LRs which provide a structural foundation for signaling complexes that regulate channel activity.

Methods: Single CCDs from NZW rabbits were microperfused in vitro for immunofluorescence labeling of endogenous BKα (the pore forming subunit of the BK channel) and caveolin 1 (Cav-1), a protein marker of LRs, and visualized by confocal microscopy. Monolayers of MDCK C7 and C11 cells (PC and IC models, respectively) were transfected with myc-tagged BKα and assayed for colabeling of c-myc and Cav-1. LRs were isolated from MDCK cells by sucrose density fractionation and analyzed by western blotting (WB) for c-myc and Cav-1. CoIP was also performed using total membrane for c-myc-BKα and Cav-1.

Results: Endogenous apical BKα colocalizes with Cav-1 in the native CCD. MDCK C11 cells express more recombinant BKα than C7 cells, but in both cell lines, the channel colocalizes with Cav-1. Immunodetectable recombinant BKα and Cav-1 were identified in the same sucrose fraction, corresponding to the migration pattern of LRs.

Conclusions: The data suggest that the BK channel in the CCD localizes to LRs which provides a structural foundation for signaling complexes that regulate channel activity.

Funding: Veterans Affairs Support, Private Foundation Support

FR-P0764
Na+, K+, and Cl- Transporters in Health and Disease Underlie presents author/disclosure.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO764

Regulatory Adaptation of ROMK Channel in Thick Ascending Limb

Yuliia Sharkovsky, Alexandra Böhlöck Böhlick, Kerim Mutig, Sebastian C. Bachmann.
Institute of Vegetative Anatomy, Charité Universitätsmedizin Berlin, Berlin, Germany.

Background: The renal outer medullary potassium channel (ROMK) plays a critical role in the regulation of potassium recycling across the apical membrane in thick ascending limb (TAL) of Henle’s loop, providing K availability for the action of the luminal Na-K-2Cl cotransporter (NKCC2).

ROMK localization along rat TAL has previously revealed a cellular heterogeneity. Some cells demonstrated strong ROMK signal in the apical plasma membrane, whereas others exhibited little or no immunoreactivity. This study aimed to characterize the expression and regulation of ROMK in the TAL after short- or long-term stimulation of transport by vasopressin (AVP).

Methods: Vasopressin-deficient Brattleboro rats were treated with the vasopressin V2 receptor-selective agonist desmopressin (dDAVP) using osmotic minipumps for 7-hour (short-term) or 24-hour periods (long-term study). Biosynthesis and cellular distribution of ROMK were studied in the kidneys.

Results: Double immunofluorescence labeling in Brattleboro rats showed an interminent ROMK-immunoreactivity pattern in the apical membrane of TAL, whereas the expression of NKCC2 was intact or that compensation elsewhere (ie in TAL) had occurred. In short-term treated rats, ROMK-positive cells were increased by 21% in cortical and by 35% in medullary TAL. Measuring the ROMK-positive perimeter of TAL profiles, there were increases by 21% and 14%, respectively. Western blot revealed no significant difference of ROMK abundance in the cortex and an 1.7-fold-increase in the medulla for long-term study.

Conclusions: These data reveal a new resource for the study of the TAL segment and its associated transporter function. Further studies are needed to address whether any of the newly identified gene changes play roles in regulation of transsepithelial NaCl transport.

Funding: Other NIH Support - NHLBI

FR-PO765

Renal Potassium Conservation Is Impaired in a Kidney-Specific Kir4.1 Knock Out Mouse

Daniel A. Gray, Emily Lambert, Wilson Nino, Jonathan Tran, Anita de Oliveira Silva.
Nephrology, Univ of Rochester.

Background: Mutations in the Kir4.1 potassium channel underlie the SeSAME/ED Symposium; a neurorenal condition characterized by hypokalemia, hypomagnesemia, metabolic alkalosis. The generalized Kir4.1 knockout mouse lives only to 2-3 wks of age. To better understand the pathophysiology of this syndrome, we therefore developed a kidney-specific Kir4.1 knockout mouse (ksKO).

Methods: The ksKO mice were generated by first creating a mouse expressing the cadherin 16 promoter, which drives Ckex recombinase expression in the distal nephron (P. Igarashi) with a generalized Kir4.1 heterozygote. Offspring that were Kir4.1 heterozygous were then crossed with a floxed Kir4.1 mouse, Kir4.1fl/−/− (K. McCarthy). Offspring included the ksKO (Kir4.1fl/−/−) and associated controls. Blood, obtained by cardiac puncture, and urine, from bladder aspiration, were analyzed in a reference lab. Significance (∗) was taken at p<0.05.

Results: ksKO mice grew normally to adulthood. Kir4.1 protein expression (by immunofluorescence) in the distal nephron was markedly reduced but not abolished. Under baro- and diet stress, ksKO mice showed metabolic alkalosis but not hypokalemia or hypomagnesemia. They had normal urine volume, sodium concentration, and urine, from bladder aspiration, were analyzed in a reference lab. Significance (∗) was taken at p<0.05.

Conclusions: Kir4.1, which underlies basolateral K recycling and cells from adjacent segments were trimeled and the DCT1 segments were pooled yielding 300-500 cells per sample. Deep sequencing was done on an Illumina HiSeq 2000 sequencer after RT-PCR amplification. Expression levels were calculated in ‘reads per kilobase exons per million reads’ (RPKM).

Results: After mapping to the rat reference genome (rL4), transcripts corresponding to a total of 5171 distinct genes were identified in 6 DCT1 samples. Compared to RNA-seq data in all other tubule segments revealed that 58 transcripts were unique to the DCT1. These included 3 protein kinases (Pik3r1, Pik3r5, and Pik4) and 7 G-protein coupled receptors (Gpr39, Gpr37, Gpr39, Gpr41, Gpr42, and Gpr47). Further, transports (Slc2a12, Slc29a2, [nucleoside transporter], and Slc39a2 [zinc ion transporter]) and 1 transcription factor (Zfp189). Of more than 100 protein kinases expressed, the 10 most abundant were Wnk1, Cdk1, Slk1, Bshk, Fasth, Map262, Punkt, Pik1, Pdk2, Wnk1 and Slk1, and expressed in the collecting duct (DCT1) and its associated transporter function. Further studies are needed to address whether any of the newly identified gene names play roles in regulation of transepithelial NaCl transport.

Funding: Other NIH Support - NHLBI

FR-PO766

Use of Serum Total Protein (TP) to Correct for Colloid-Related Bias of Serum Sodium (Na) Measured by the Indirect Ion-Selective Electrode (ISE) Method

Pratima Ghamarine,* Isabelle Ayoub,* Robert H. Barth,* Philip Goldwasser,* SUNY Downstate; *VA NY Harbor Healthcare System, Brooklyn, NY.

Background: When the serum colloid level is lower than normal, the usual indirect ISE method (dNa) tends to be artificially high—compared with direct ISE (dNa) used in gas panels—while above normal serum colloid results in the opposite. Studies disagree on whether a linear equation using TP (as a proxy for serum colloid) can be used to predict iNa - dNa (iNa). Jones & Twomey (07) found dNa fell by 2 ± 1.2 mg/dL increase in TP. While Dimensesi (05) found the TP effect to be nonlinear.

Methods: To test this, we (i) paired chemistry and gas panels obtained < 20 minutes apart (median=5 min.) in a retrospective cohort of all patients (pts) admitted to our critical care units during a 1 year period, (ii) calculated iNa using the TP method of ON (TP, adjusting for dNa). Limiting each to one pairing and excluding hemolyzed or turbid samples left 228 na+ (dNa) pairs.

Results: Significant differences [mean ± se] were found between the panels (dNa: 1.8± 0.1 mEq/L, p<0.10; dNa: -5.9±1.9 mEq/L, p<0.02) indicating bias. TP ranged from 2.1-10.1 g/dL. Na+ correlated significantly with TP (-0.28±0.13, p<.002), and not at all with iNa + dNa (r=0.05). The trend of Na+ means versus TP groups, categorized into 5 groups, is shown.

Funding: Veterans Affairs Support

FR-PO767

Renal Effects of Caveolin-1 Deletion


Background: Caveolin-1 (Cav1) is essential for caveolae biogenesis. These cholesterol-rich subdomains of lipid rafts microdomains are involved in signal-transduction, vesicular trafficking, and functional modulation of plasma membrane proteins. Little is known about the role of the caveolea in the kidney. In this study we tested the hypothesis that caveolea interfere with renal NaCl- and water reabsorption.

Methods: To evaluate the role of caveolea in the kidney, Cav1-deficient (Cav1−/−) mice were evaluated for their physiologic kidney performance, kidney morphology, biochemical profile of renal transporters, and renal vascular contractility.

Results: In wildtype (WT) mouse kidneys, Cav1 was strongly expressed in the distal convoluted tubule (DCT2) and collecting ducts. No Cav1 expression and no caveolae were detected in kidneys from Cav1−/− mice. Immunoblotting evaluation of distal epithelial salt transporters and water channels revealed decreased levels of phosphorylated Na-CI cotransporter in DCT2 (-40%) and of Na-K-ATPase (-33%) in the collecting duct upon Cav1 disruption. Functional analysis of renal interlobar arteries showed significantly decreased contractile response of Cav1−/− mice to phenylephrine. Concomitant inhibition of NO production by L-NAME has suppressed the differences between WT and Cav1−/− indicating that Cav1 expression is critical for renal transporters, and renal vascular contractility.

Funding: Veterans Affairs Support

FR-PO768

RNA-Seq Identification of Transcriptome of Native DCT1 Cells

Jae Wook Lee, Chung-Lin Chou, Fahad Saeed, Mark A. Knipper. NIH.

Background: Complete transcriptomes have been identified for the inner medullary collecting duct, medullary thick ascending limb, and proximal tubule cells because they can be biochemically isolated from kidney in large enough numbers for DNA microarray analysis. However, only limited data from SAGE experiments exist for the DCT1 cell type.

Methods: Here, we use deep-sequencing technology (RNA-seq) to identify the transcriptome of native rat DCT cells manually microdissected from collagenase-treated rat kidneys. The microdissection used a high resolution optical system capable of discriminating cell types. The DCT1 segment was carefully identified and cells from adjacent segments were trimmed away. The DCT1 segments were pooled yielding 300-500 cells per

Funding: NIDDK Support

FR-PO769

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

Underline represents presenting author/disclosure.

539A
Conclusions: Our data suggest that Cav1 promotes renal reabsorption of water and electrolytes by inhibiting eNOS and facilitating the function of the distal epithelial transporters.

FR-PO769

Total Body Adiposity Is Associated with Inflammation and Vitamin D in Chronic Kidney Disease

Maria Ines Barreto-Silva,1 Márcia R.S.G. Torres,1 Carla C.S. Lemos,2 Simone Vargas Da Silva,2 Rachel Bregman.2 (Nutrition, State Univ of Rio de Janeiro; 1Nephrology, State Univ of Rio de Janeiro; 2Pharmacology, State Univ of Rio de Janeiro, Brazil)

Background: High body adiposity, inflammation and vitamin D 25(OH)D deficiency may contribute to poor outcome in chronic kidney disease (CKD) patients.

Methods: CKD patients under multidisciplinary treatment were evaluated. Total body adiposity was evaluated by X-ray absorptiometry - (DXA-total-BF); %; central body fat evaluated by DXA trunk fat (%); and by anthropology (waist circumference, waist-to-hip-ratio; waist-to-height-ratio). Body mass index (BMI; kg/m2) was estimated. Serum levels analysis for: leptin, high molecular weight adiponectin (HMWAdipo), C-reactive protein, interleukin-6, tumor necrosis factor alpha (TNFα), interferon-gamma and 25(OH)D.

Results: One hundred patients (56% men) under treatment for at least 1 year were studied. Results as mean±SD: age=66±12 years, estimated glomerular filtration rate (eGFR)=29±13 ml/min (CKD-EPI), BMI=25±4. Total body adiposity: visceral fat (VBF); %; waist circumference, waist-to-hip-ratio. Body mass index (BMI; kg/m2) was estimated. Serum levels analysis for: leptin, high molecular weight adiponectin (HMWAdipo), C-reactive protein, interleukin-6, tumor necrosis factor alpha (TNFα), interferon-gamma and 25(OH)D.

Conclusion: Total body adiposity is associated with inflammation and vitamin D deficiency and should be a target in the nutritional treatment of this population.

FR-PO770

Renal Inflammation and Injury Induced by Cisplatin Are Regulated by Magnesium Status

Malvika H. Solanki, Prodyot K. Chatterjee, Madhu Gupta, Xiangying Xue, Christine N. Metz. Center for Immunology and Inflammation, The Feinstein Institute for Medical Research, Manhasset, NY.

Background: Cisplatin-induced acute kidney injury (AKI) occurs in 1/3 of patients taking cisplatin. The risk of cisplatin-AKI increases with age and is higher among females. Cisplatin impairs renal handling of magnesium (Mg) and Mg deficiency is common among US adults. Because Mg deficiency is associated with enhanced inflammation, we examined the effects of Mg deficiency and supplementation on inflammation during cisplatin-AKI.

Methods: Older female C57BL/6 mice (10/group, 10mo old) were fed either normal (100% Mg) or Mg-deficient (10% Mg) diets. After 2wks, saline or cisplatin (12mg/kg, ip) was injected. An additional group of Mg-deficient mice was supplemented with MgCl2, in water and MgSO4, s.c prior to cisplatin. Mice were euthanized 48hrs post-cisplatin. Blood urea nitrogen (BUN) levels and renal inflammatory markers (mRNA and protein) were measured. Renal neutrophil infiltration was measured by Leder staining and myeloperoxidase (MPO) levels. Renal STAT3 and ERK1/2 expression/activation were analyzed by Western blotting.

Results: Mg deficiency elevated BUN levels and increased markers of inflammation (Ccl2, Ccl4, Cxc10 and Tnfα-mRNA and Cxcl2, Ccl2, IL-6, IL-10 and Cxcl10 protein) following cisplatin compared to 100%Mg-cisplatin controls (p<0.05). Renal neutrophil infiltration and MPO levels were higher in cisplatin treated Mg-deficient mice when compared to controls (p<0.01). Mg-deficient mice treated with cisplatin exhibited enhanced renal STAT3 protein expression/phosphorylation, as well as ERK1/2 phosphorylation compared to controls (p<0.05). Mg replacement reversed cisplatin-induced renal damage and inflammation and cisplatin-mediated STAT3 and ERK1/2 activation, two pathways involved in cisplatin-mediated inflammation. These findings support investigating the effects of Mg status before and during cisplatin therapy on renal outcomes in patients.

Conclusions: Mg-deficient mice exhibit increased renal inflammation in response to cisplatin treatment. Magnesium deficiency may contribute to both cisplatin-induced renal inflammation and patient outcomes. These findings support investigating the effects of Mg status before and during cisplatin therapy on renal outcomes in patients.

FR-PO771

Effect of Brazilian Nut Supplementation on Nr2 and NK-B Expression in Hemodialysis Patients

Ludmila Fmf Cardozo,1 Liliana M. Pedruzzi,1 Milena Barzca Stockler-pinto,1 Julio Belalme Dalleprane,2 Juliana M.S. Siqueira,1 Olavo M. Cabral,3 Maurilo Leite,3 Denise Mafra.1 1Post Graduation Program in Cardiovascular Sciences, Federal Fluminense Univ (UFF), Niterói, Rio de Janeiro (RJ), Brazil; 2Institute of Nutrition, State Univ of Rio de Janeiro (UERJ), RJ, Brazil; 3Nefrologia Clinic, Niterói, RJ, Brazil; 4Div of Nephrology, Federal Univ of Rio de Janeiro (UFRJ), RJ, Brazil.

Background: Previous studies in our laboratory showed that the supplementation of 1 unit of Brazilian nut (Bertholletia excelsa, family CARYOPHYLLACEAE) is effective to improve serum levels of calcium, magnesium, sodium, potassium, and cholesterol in type 2 diabetes patients. Because Mg deficiency and supplementation on inflammation may be a target in the nutritional treatment of this population.

Methods: Ten patients (50% men; 55±13;8.9ys; BMI 24±2.1; 2kg/m2) were studied. They received 1 nut (5g; courtesy: Agriculture Arauanã) a day for 3 months. Blood samples were obtained after 12h fasting and the peripheral blood mononuclear cells were isolated before and after supplementation. Quantitative Real-Time PCR analysis was performed using 7500 Real-Time PCR System (Applied Biosystems) to evaluate the levels of mRNA expression encoding Nr2 and NK-B.

Results: After nut supplementation, the NK-B expression decreased from 1.92±0.64 to 0.71±0.36 (p<0.001) and the Nr2 expression increased from 0.60±0.09 to 1.45±0.27 (p<0.001). These data suggest that the consumption of only one Brazilian nut per day during 3 months can activate Nr2 and diminish inflammation by reducing NK-B expression in HD patients.

Conclusions: It is the first report to confirm the TLR-19 and NF-κB in HD patients. Supported by: CAESP, Faperj, CNpq.

FR-PO772

Nr2/NK-B Equilibrium Is Altered in Hemodialysis Patients

Ludmila Fmf Cardozo,1 Liliana M. Pedruzzi,1 Milena Barzca Stockler-pinto,1 Julio Belalme Dalleprane,2 Juliana M.S. Siqueira,1 Olavo M. Cabral,3 Maurilo Leite,3 Denise Mafra.1 1Post Graduation Program in Cardiovascular Sciences, Federal Fluminense Univ (UFF), Niterói, Rio de Janeiro (RJ), Brazil; 2Institute of Nutrition, State Univ of Rio de Janeiro (UERJ), RJ, Brazil; 3Nefrologia Clinic, Niterói, RJ, Brazil; 4Div of Nephrology, Federal Univ of Rio de Janeiro (UFRJ), RJ, Brazil.

Background: Reactive oxygen species (ROS) activate NF-kB that regulates the transcription of several genes, including pro-inflammatory cytokines. Oxidative stress and inflammation are frequent findings in patients with Chronic Kidney Disease (CKD), and considered mediators of cardiovascular disease. Several studies address the strategies to halt this process, including the activation of the transcription nuclear E2-related factor 2 (Nr2), which regulates the expression of detoxifying enzymes. The aim of this study was to evaluate the expression of Nr2 and NK-B in CKD patients on hemodialysis.

Methods: Twenty hemodialysis patients (65% men, BMI 23.6±0.3 kg/m2, time of dialysis 4±6 months, DM 21.4%, 54.9±15.2yrs) from Nefrologia Clinic in Niterói, RJ, Brazil, were compared to 11 healthy individuals (45.5% men, BMI 23.8±1.9 kg/m2, 50.9±8.0 yrs). Blood samples were drawn after 12h fasting, and the peripheral blood mononuclear cells were isolated. Quantitative Real-Time PCR analysis was performed using 7500 Real-Time PCR System (Applied Biosystems) to evaluate the levels of mRNA expression encoding Nr2 and NK-B.

Results: The HD patients had lower expression of Nr2 (0.58±0.35) when compared to healthy individuals (1.13±0.64, p<0.05). By contrast, the NF-kB expression were 2 fold in HD patients (2.18±0.6, when compared to healthy individuals (1.04±0.22, p<0.0001). The HD patients presented NF-kB expression inversely correlated with Nr2 levels (r=-0.54, p<0.01) and this correlation was positive for the healthy individuals (r=0.85, p<0.001).

Conclusions: The results show that HD patients present an increased NF-kB and reduced Nr2 expression, which is the opposite of healthy individuals. NF-kB may participate in the negative regulation of Nr2 expression in these patients. Supported by: CAESP, Faperj, CNpq.
Methods: We performed a CoQ10 dose escalation study (2 weeks each of 300, 600, 1200, and 1800 mg/day) in 20 chronic hemodialysis patients to test the hypothesis that CoQ10 therapy reduces oxidative stress. F2-isoprostanes, isofuran, and high-density lipoprotein (HDL) apolipoprotein A1 (apoA-1) oxidation were measured to assess oxidative stress and CoQ10 to determine dose, concentration, and response relationships.

Results: Plasma CoQ10 levels increased in a linear fashion from 704 ± 286 ng/mL at baseline to 4033 ± 1637 following 1800 mg/day, and plasma isofuran concentrations, a marker of oxidative stress reported to be associated with mitochondrial dysfunction, decreased from 141 ± 67.5 pg/mL at baseline to 72.2 ± 37.5 following 1800 mg/day (P<0.003 vs. baseline and P<0.001 for the effect of dose escalation, Figure, Panel A). In addition, reduced plasma isofuran concentrations correlated with increased plasma concentrations of CoQ10 (P=0.02, Figure, Panel B). Plasma F2-isoprostane concentrations and HDL apoA-1 oxidation did not change during the study.

Conclusions: Short-term daily CoQ10 supplementation significantly decreased plasma isofuran concentrations in a dose-dependent manner but did not affect HDL oxidation. This might indicate improved mitochondrial function and decreased oxidative stress in hemodialysis patients treated with CoQ10.

Background: Hepcidin, the iron regulatory hormone, regulates renal handling of iron and that hepcidin expression is modulated by the P2X7 receptor in podocytes. The trapping of lipid-laden podocytes in the glomerulus is a critical but reversible step in glomerulosclerosis. Recently, an alternative pathway of lipid metabolism through the lysosomal degradative pathway of autophagy is described and now termed lipophagy. However, whether and how this pathway is involved in the progression of lipid-induced nephropathy remains unclear.

Methods: In this study, we demonstrate the first evidence that Rho kinase (ROCK) pathway plays a critical role in lipophagy in podocytes treated with oxidative low density lipoprotein (LDL). Oxidative low density lipoprotein treated podocytes, which consequently activates, and results in a marked increase of reactive oxygen species production. Interestingly, this process is reversed by ROCK inhibition evidenced by increased lipophagy which associated to low phosphorylated Akt and actin-related protein 2 levels. Furthermore, pharmacological inhibition of ROCK in high fat diet mice exhibits a significantly ameliorated albuminuria and mesangial matrix accumulation compared to control. The renoprotective effect of fasudil, a ROCK inhibitor, on high fat diet mice is attributed to decreased lipid retention and improved lipophagy in kidney.

Results: Our data suggests a previously unknown contribution of ROCK to lipid-induced nephropathy. Constitutive inhibition of ROCK may be a major protective strategy to ameliorate lipid-overload in podocyte and lipid-related loss of renal function.

Conclusions: Constitutive inhibition of ROCK may be a major protective strategy to ameliorate lipid-overload in podocyte and lipid-related loss of renal function.

FR-PO776

P2X7 as a Potential Target for Improved Glycemic Control in Diabetes

Diana Marks,1 Ballard Seddique,2 Gregory Fong,1 Frederick W.K. Tam,2 Edward S. Debsam,1 Robert J. Unwin,1 Centre for Nephrology, Univ College London, London, United Kingdom; 2Dept of Medicine, Imperial College London, London, United Kingdom.

Background: Dynamic regulation of GLUT2 at the enterocyte brush border membrane (BBM) provides a high capacity route for post-prandial dietary glucose absorption; however, GLUT2 is permanently expressed at the BBB in diabetes and probably contributes to hyperglycemia and development of diabetic complications, including nephropathy. Our study investigated the putative role of the P2X7 receptor in regulating intestinal GLUT2 expression in vivo.

Methods: Wild-type (WT) and P2X7-/- mice were anaesthetized and 10cm segments of proximal small intestine were cannulated in vivo. These were perfused with Krebs buffer containing 75mM glucose, oxygenated with 95%O2:5%CO2, to create segmental flow at a rate of 1ml/min. The intestine was removed and placed in an organ chamber at 37°C and allowed to equilibrate for 30 minutes. Serosal fluid was collected after an additional 30 minutes (control period) and 30 minutes after the solution was switched to one containing 10mM glucose or 10mM Phloretin (Phl), a competitive inhibitor of GLUT2 (experimental period). Glucose concentration was measured using a glucose oxidase assay.

Results: In WT animals, glucose absorption was decreased by switching the perfusate to 10mM glucose, indicating rapid loss of GLUT2 expression after removing the high glucose stimulus. The reduction in transport induced by phloretin confirmed the contribution of GLUT2-mediated transport at 75mM glucose. In contrast, in P2X7-/- mice glucose absorption was unaffected by reducing glucose concentration.

Conclusions: These data suggest a role for P2X7 receptor in controlling GLUT2 expression at the enterocyte BBB and provide evidence that this pathway may be a novel target to improve glycemic control in diabetic patients.

Funding: Private Foundation Support

FR-PO777

Docosahexaenoic Acid Counteracts Palmitate-Induced Proteolytic Signaling in Myotubes

Myra Woodworth-Hobbs,1 2 Matthew B. Hudson,1 Jill Rahnert,1 Bin Zheng,1 Harold A. Franch,1 Russ Price,1,3 1Dept of Medicine/Nephrology, Emory Univ, Atlanta, GA; 2Nutrition and Health Sciences, GDBBS, Emory Univ, Atlanta, GA; 3Atlanta VAMC, Decatur, GA.

Background: Rho kinase (ROCK) plays a role in muscle insulin resistance and dysregulated protein metabolism in cultured skeletal muscle, resulting in debilitating muscle atrophy. The saturated fatty acid palmitate (PA) induces muscle insulin resistance and dysregulated protein metabolism in cultured skeletal muscle, resulting in debilitating muscle atrophy. The saturated fatty acid palmitate (PA) induces muscle insulin resistance and dysregulated protein metabolism in cultured skeletal muscle, resulting in debilitating muscle atrophy.

Methods: C2C12 myotubes were treated with 500mM PA and/or 100mM DHA for up to 24h. The rate of protein degradation was measured by monitoring the release of radiolabeled phenylalanine into the culture media, and the expression of mRNAs and proteins involved in atrophic signaling pathways were measured by quantitative real time PCR and western analysis, respectively.

Results: PA increased the rate of protein degradation by 31% (P<0.05 vs. all other groups), while co-treatment with DHA completely prevented the response. Akt is a key modulator of protein balance that inhibits the FoxO3 transcription factors which regulate "atrogene" expression. PA reduced the activation state of Akt (phospho:total Akt) by 24%-40% at timepoints ranging from 2h-24h (P<0.05 vs. control) and increased the nuclear and cytoplasmic protein levels of FoxO3 by 40%. PA also increased the mRNA levels of three FoxO3 target genes, the E3 ubiquitin ligases MuRF-1 and atrogin-1/MAFbx and the autophagy modulator Bnip3. DHA attenuated the effects of PA on Akt, FoxO3, and all three atrogens.

Conclusions: These data indicate that PA induces myotube atrophy by inducing the ubiquitin-proteasome and autophagic proteolytic systems and that DHA counters the catabolic effects of PA by improving Akt signaling.

Funding: NIDDK Support, Other NIH Support - NIGMS - 1K23GM102676-01

FR-PO777

P2X7 as a Potential Target for Improved Glycemic Control in Diabetes

Joanne Marks,1 Ballard Seddique,1 Gregory Fong,1 Frederick W.K. Tam,2 Edward S. Debsam,1 Robert J. Unwin,1 Centre for Nephrology, Univ College London, London, United Kingdom; 2Dept of Medicine, Imperial College London, London, United Kingdom.

Background: Dynamic regulation of GLUT2 at the enterocyte brush border membrane (BBM) provides a high capacity route for post-prandial dietary glucose absorption; however, GLUT2 is permanently expressed at the BBB in diabetes and probably contributes to hyperglycemia and development of diabetic complications, including nephropathy. Our study investigated the putative role of the P2X7 receptor in regulating intestinal GLUT2 expression in vivo.

Methods: Wild-type (WT) and P2X7-/- mice were anaesthetized and 10cm segments of proximal small intestine were cannulated in vivo. These were perfused with Krebs buffer containing 75mM glucose, oxygenated with 95%O2:5%CO2, to create segmental flow at a rate of 1ml/min. The intestine was removed and placed in an organ chamber at 37°C and allowed to equilibrate for 30 minutes. Serosal fluid was collected after an additional 30 minutes (control period) and 30 minutes after the solution was switched to one containing 10mM glucose or 10mM Phloretin (Phl), a competitive inhibitor of GLUT2 (experimental period). Glucose concentration was measured using a glucose oxidase assay.

Results: In WT animals, glucose absorption was decreased by switching the perfusate to 10mM glucose, indicating rapid loss of GLUT2 expression after removing the high glucose stimulus. The reduction in transport induced by phloretin confirmed the contribution of GLUT2-mediated transport at 75mM glucose. In contrast, in P2X7-/- mice glucose absorption was unaffected by reducing glucose concentration.

Conclusions: These data suggest a role for P2X7 receptor in controlling GLUT2 expression at the enterocyte BBB and provide evidence that this pathway may be a novel target to improve glycemic control in diabetic patients.

Funding: Private Foundation Support

FR-PO777

Iron Metabolism in Kidney and Erythropoietin Synthesis: A Case of Hepcidin

Karin Zoubia,1 Boualem Moulouel,1 Dounia Houamel,1 Laurent Goaya,1 Paris Diderot Univ, INSERM U773, Paris, France; 2Paris Diderot Univ, INSERM U773, Paris; 3Paris Diderot Univ, INSERM U773, Paris.

Background: Erythropoietin (EPO) is produced exclusively in renal interstitial fibroblasts. Of interest, it has been shown that the production of EPO is regulated by iron but the mechanism of this regulation remains unclear. We have recently shown that hepcidin, the iron regulatory hormone, regulates renal handling of iron and that hepcidin knockout mice (hepc-/--) exhibited a marked iron deposition within the thick ascending limb of Henle. In this study we investigated whether EPO synthesis is monitored by the intrarenal hepcidin-dependant regulation of iron. Indeed, EPO-producing fibroblasts that are immersed in a faintly vascularized environment and their iron content may be modulated by the degree of iron reabsorption in the tubular cells.

Conclusions: These data suggest a role for P2X7 receptor in controlling GLUT2 expression in the enterocyte BBM and provide evidence that this pathway may be a novel target to improve glycemic control in diabetic patients.

Funding: Private Foundation Support

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

Underline represents presenting author/disclosure.

541A
Methods: Iron deposits in renal fibroblasts were analysed by electron microscopy (EM). After iron restricted diet (ID) renal and serum EPO were quantified by RT-qPCR and ELISA.

Results: in hepc- mice, EM analysis showed significant iron deposits in interstitial fibroblasts.

EPO mRNA was reduced in hepc- mice as compared to WT. ID induced the expression of EPO in WT but not in hepc- mice. Similar data were obtained after phlebotomy suggesting that iron deposits in interstitial fibroblasts may impair renal EPO production.

Hepcidin mRNA level in liver was decreased in ID mice versus controls. However, when cells were incubated with hepcidin, EPO synthesis remained unchanged suggesting no direct effect of the hormone on renal fibroblasts.

Conclusions: Our data indicate that hepcidin, by controlling renal tubular iron transport, may exert a feedback control on EPO production. Thus a crosstalk between depletion of interstitial fibroblasts and therefore EPO production.

Our data indicate that hepcidin, by controlling renal tubular iron transport, may exert a feedback control on EPO production. Thus a crosstalk between depletion of interstitial fibroblasts and therefore EPO production.

Background: Conformation of fructose has been implicated in the development of renal and impaired kidney function, but the mechanisms are not fully understood. Because females may be more sensitive to certain electrolyte disturbances such as hyponatremia, we tested the impact of chronic fructose feeding on electrolyte homeostatic mechanisms in the kidney.

Methods: Young (2-month) male and female (F) mice (129/Sv background) were offered ad libitum access to either a corn-starch based control (C) or a high fructose (HFr, 66% fructose) diet as purified chow and plain drinking water for 15 weeks (n = 6/sex/diet). Diets contained similar amounts of sodium (Na+), potassium (K+), and chloride (Cl-).

Conclusions: These findings suggest that hepcidin expression is associated with decreased prevalence of kidney disease. The reason for this is unknown and warrants further study.

Background: The aim of this study was to investigate the relationship between OBS, albuminuria, eGFR <60 ml/min/1.73m2 (CKD), and End Stage Renal Disease (ESRD) in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study.

Conclusions: Our data indicate that hepcidin, by controlling renal tubular iron transport, may exert a feedback control on EPO production. Thus a crosstalk between depletion of interstitial fibroblasts and therefore EPO production.

Effects of Kefir on Cytokines and Nitric Oxide Production, by Peritoneal Macrophages of Streptozotocin-Induced Diabetic Rats. Fabiana R. Maciel,1 Gabrieli S. Simões,1 Edvaldo T. Pires,1 Marcelo Macedo Rogerio,1 Cristina Bogus,1 Maricela Oliveria,1 Thaimes Fernandes,1 Guilherme Nogueira,1 Margaret Mouru,1 Elisa MS Higa,1 Medicine, UNIFESP, Sao Paulo; Nutrition, School of Public Health, USP Sao Paulo,1 Biochemical Technology - Pharmaceuticals, USP Sao Paulo.

Certificates: FR-PO778

Effects of Kefir on Cytokines and Nitric Oxide Production, by Peritoneal Macrophages of Streptozotocin-Induced Diabetic Rats. Fabiana R. Maciel,1 Gabrieli S. Simões,1 Edvaldo T. Pires,1 Marcelo Macedo Rogerio,1 Cristina Bogus,1 Maricela Oliveria,1 Thaimes Fernandes,1 Guilherme Nogueira,1 Margaret Mouru,1 Elisa MS Higa,1 Medicine, UNIFESP, Sao Paulo; Nutrition, School of Public Health, USP Sao Paulo,1 Biochemical Technology - Pharmaceuticals, USP Sao Paulo.

Background: The extensive production of reactive oxygen species in diabetes mellitus is due to hyperglycemia, and the oxidative stress decreases immune response. Careful control of glycemic status is known to minimize the diabetic complications. Kefir (K) is a fermented dairy product, which presents immunomodulatory properties.

Methods: Male adult Wistar rats received injection of streptozotocin (45mg/kg, I.V.). DM was defined as glycemia ≥200mg/dL. The animals were allocated in 4 groups (n=4 each): control (CTL); CTLK; DM; DMK. They received K, or its vehicle at 1.8 mL/day for 21 days.

Results: DMK when compared to DM presented decreased levels of glycemia (mg/dL) (925±69 vs 555±92), TNF-α (μg/mL) (178±19 vs 109±20), IL-1β (μg/mL) (101±14 vs 70±5) as well as the NO (μM) (102±9 vs 66±5), p<0.05.

Conclusions: Probiotic supplementation resulted in attenuation of the classic symptoms of diabetes, with decrease in glycemia and increased levels of IL-10, TNF-α, IL-1β and NO. These results suggest that K could be an adjuvant therapy in DM, resulting in a better control of the metabolic parameters, with potential to modulate the immune response, improving the immunocompetence of diabetic patients.

FR-PO780

Sex Differences in Dietary-Fructose-Induced Renal Hypertrophy and Electrolyte Abnormalities in Mice. Nikhil Sharma, Lijun Li, Shehr-bano Awan, Alison Yunghans, Carolyn M. Ecelbarger. Dept of Medicine, Georgetown Univ; Washington, DC.

Methods: Young (2-month) male and female (F) mice (129/Sv background) were offered ad libitum access to either a corn-starch based control (C) or a high fructose (HFr, 66% fructose) diet as purified chow and plain drinking water for 15 weeks (n = 6/sex/diet). Diets contained similar amounts of sodium (Na+), potassium (K+), and chloride (Cl-).

Conclusions: Our data indicate that hepcidin, by controlling renal tubular iron transport, may exert a feedback control on EPO production. Thus a crosstalk between depletion of interstitial fibroblasts and therefore EPO production.

FR-PO778

Oxidative Balance Score (OBS) Is Associated with Chronic Kidney Disease (CKD). Titilayo O. Ilori,1 Young Sun Ro,1 Orlando M. Gutierrez,4 Soyeon Joyce Bogsan,3 Marice Oliveira,3 Thamires Fernandes,1 Guilherme Nogueira,1 Margaret Mouru,1 Elisa MS Higa,1 Medicine, UNIFESP, Sao Paulo; 2Biochemical Technology - Pharmaceuticals, USP Sao Paulo.

Method: We tested the impact of chronic fructose feeding on electrolyte homeostatic mechanisms in the kidney.

Results: in hepc- mice, EM analysis showed significant iron deposits in interstitial fibroblasts. After iron restricted diet (ID) renal and serum EPO were quantified by RT-qPCR and ELISA.

Results: in hepc- mice, EM analysis showed significant iron deposits in interstitial fibroblasts. After iron restricted diet (ID) renal and serum EPO were quantified by RT-qPCR and ELISA.

Results: in hepc- mice, EM analysis showed significant iron deposits in interstitial fibroblasts. After iron restricted diet (ID) renal and serum EPO were quantified by RT-qPCR and ELISA.

Results: in hepc- mice, EM analysis showed significant iron deposits in interstitial fibroblasts. After iron restricted diet (ID) renal and serum EPO were quantified by RT-qPCR and ELISA.
**Methods:** We examined the association between heavy metal concentration, dietary intakes and estimated GFR using data from the Korean National Health and Nutritional Examination Survey 2011. For the present study, the analysis was restricted to 1,753 adult participants who were aged 18-18 years and provided serum heavy metals levels, eGFR and diet survey.

**Results:** The mercury, cadmium and lead were negatively associated with eGFR and positively correlated with age (r = 0.064; p = 0.018) and beef intake (r = 0.076; p = 0.004). The lead was independently associated with age (r = 0.338; p = 0.001), eGFR (r = 0.048; p = 0.005), shellfish (r = 0.054; p = 0.022), pork (r = 0.081; p = 0.003) and beef intake (r = 0.101; p = 0.001).

**Conclusions:** Age, GFR and dietary intake were associated with level of heavy metals. Shellfish intake may increase heavy metal levels, beef and pork intake may decrease cadmium levels. Therefore, attention to heavy metals is necessary in elderly chronic kidney disease patients needing protein restriction.

**FR-PO783**

**Altered Renal Lipid Metabolism Results in Lipotoxicity and Progression of Human Diabetic Nephropathy and Obesity Related Glomerulopathy**

Michal Herman-Edelstein,1 Moshe Levi,2 Pnina Scherzer,1 Amalia Gettszain Bakhshi,3 Uzi Gaffer.1

**Background:** Animal models link ectopic lipid accumulation to renal dysfunction, but whether this process occurs in the human kidney is uncertain. To this end we investigated whether there is altered renal triglyceride and cholesterol metabolism resulting renal lipid accumulation and lipotoxicity in human diabetic nephropathy (DN) and obesity related glomerulopathy (ORG).

**Methods:** Lipid staining and the expression of lipid metabolism genes were studied with cross-sectional CT images using the software (Fat index view, The Aquilion™ TSX-101A, TOSHIBA, Japan). We then followed all of the patients for the next 12±1 [5-15] months, and repeatedly assessed nutritional parameters.

**Results:** In 16 obese patients with stages 3-4 CKD were randomized to either laparoscopic sleeve gastrectomy (SG) weight loss surgery or best medical care (BMC), including dietary & physical activity modifications. Body weight, fat mass, adipokines, insulin resistance (HOMA-IR) & quality of life (QOL) scores were measured. Differences between groups were examined at 12 months with ANOVA corrected for baseline values or by Hodges-Lehmann median difference.

**Conclusions:** eGFR significantly underestimated eGFR in obese patients with CKD. Weight loss surgery may reduce hyperfiltration & insulin resistance, & improve adipokine & QOL in obese patients with stages 3-4 CKD.

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

**FR-PO785**

**Kidney Function, Adipokines, and Quality of Life after Weight Loss Surgery in Obese Patients with Stages 3-4 Chronic Kidney Disease: A Randomized Controlled Pilot Study**

Helen L. MacLaughlin,1 Wendy L. Hall,2 Amee G. Patel,3 Rochelle Maree Blacklock,4 Iain C. Macdougall3

**Background:** Obesity is an independent risk factor for chronic kidney disease (CKD). Weight loss surgery is associated with improvements in eGFR, whereas GFR decline was no longer significant in multi-variable regression after adjusting for age and weight. We aimed to determine if the effect of weight loss on eGFR is sustained over time.

**Methods:** We performed a randomized controlled trial of 100 overweight and obese patients with stages 3-4 CKD and eGFR < 60 mL/min x 1.73 m² randomized to SG or BMC. Study visits included dietary intake, physical activity, body composition, quality of life, and markers of adipokines (adiponectin, resistin, leptin). Changes in GFR were analyzed using the Cockcroft-Gault and MDRD formulae.

**Results:** There was no difference in baseline characteristics between the groups. At 12 months, SG had a greater weight loss (7.2±5.6% vs. 2.1±5.0%, p < 0.001), significantly more adiponectin (med diff 19.3 mg/L; 95% CI 11.9, 26.7) and leptin (med diff 17.5; 95% CI 10.8, 24.2) and significant decrease in resistin (med diff -0.43 ng/mL; 95% CI -0.80, -0.06). In multi-variable regression, 7 mmol/h higher baseline U-urea related to 0.011 mg/dL more positive S-cr change (95%CI=0.006/0.016) and -0.07 mL/min more negative eGFR change per year (95%CI=−0.110/−0.038).

**Conclusions:** In middle-aged adults, higher protein intake is associated cross-sectionally with higher GFR but longitudinally with faster GFR decline over-time.

**Funding:** Government Support - Non-U.S.
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.

Conclusions: These findings suggest that initiation of maintenance HD therapy increased abdominal adiposity while decreased thigh muscle volume over 1 year, indicating the accelerated sarcopenic obesity in incident HD patients.

FR-PO787 The Beneficial Effects of Body Weight Reduction in Overweight Patients with Proteinuric Immunoglobulin A Nephropathy: A Randomized Controlled Trial Pyawan Kittisilam, Talersuksan Kankanabuch, Wiwat Chancharoenthana, Keerati Pradditpornsilp, Somchai Eiam-ong, Kriang Tungsanga. Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: The study was conducted to examine the effects of body weight (BW) reduction on proteinuria in overweight and biopsy-proven IgA nephropathy (IgAN) patients. (body mass index, BMI-23 kg/m²) with persistent proteinuria ≥1 g/day. Methods: 26 overweight IgAN patients were randomized into 2 groups: 1) control- usual dietary intake (n=13) and 2) low-calorie, a 500 kcal/d subtraction from basal energy expenditure, and normal protein diet (n=13). Patients were treated with the maximal doses of ACEI/ARB and other anti-hypertensive agents to control BP at the level of less than 130/85 mmHg. At baseline and 6-month treatment, anthropometric measurement, dietary food record, urine protein concentration (APA), plasma adipokines (leptin, adiponectin & resistin) and interleukin (IL)-6 as well as laboratory parameters were assessed. (NCT01773382)

Results: There were no significant differences in baseline characteristics and demographics, including BP, BMI, renal function, 24-hour urine protein, normalized PNA (nPNA), and plasma cytokines. After 6 months, nPNA and dietary protein intake were not different, indicating comparable protein intake. Total daily calorie intake were significantly lower in the low-calorie diet group (1,307±171 vs. 1,772±315 kcal/d, p<0.01). There were significant reductions in BW (3.9±2.6 kg, p<0.001) and 24-hour urine protein (0.6±0.4 g/d, p<0.001) in the low-calorie diet group. BP and renal function parameters were not different. In the low-calorie diet group, patients with BW reduction of more than 5% had significantly lower plasma levels of leptin (46.5±27.6 vs. 19.3±7.8, p=0.02) but higher adiponectin than the control group (18.6±14.7 vs. 3.1±21.2%, p=0.03).

Conclusions: 6-month BW reduction is independently associated with significantly decreased proteinuria in overweight IgAN patients. This effect may be partly mediated by changes in adipokine levels. Further studies are required to examine the long-term effect of BW reduction in IgAN.

Funding: Government Support - Non-U.S.


Background: Patients with diabetes, obesity, and chronic kidney disease (CKD) are generally physically inactive which may be an important contributor to their high mortality rate. Whether higher daily caloric intake has a beneficial or detrimental effect on ability to exercise in this population is unknown.

Methods: We examined baseline data from a VA funded randomized controlled trial (NCT01036490) to assess physical activity in 26 overweight IgAN patients (body mass index, BMI>23 kg/m2) with persistent proteinuria (> 200 mg/day for at least 3 months). Data from the baseline symptom-impaired baseline physical function, self-reported physical activity level, and physical function (SF-36) were collected and assessed. Malnutrition can be found also in pre-ESRD patients. Since the nutritional status of MHD patients is a major determinant of long-term outcome of renal patients, there is a need for simple inexpensive method to analyze body composition and body function in MHD patients.

Results: A high prevalence of MS (30.3%) was observed. Table 1 shows the studied variables according to the number of components of the MS. LowACR correlated with BMI (r=0.23, p<0.0001), MS components (r=0.22 p<0.0001), CKD-EPI (0.16, p=0.03), age (r=0.12, p=0.001), and systolic blood pressure (SBP, r=0.09, p=0.005). In a stepwise multiple regression model, LowACR as the dependent variable, the final model identified, age, CKD-EPI, and MS components as the independent variables explaining the variance of the LowACR (model R=0.36).

Conclusions: In conclusion, the measurement of body cell mass seems an adequate tool to evaluate muscle mass and nutritional status of renal patients.

Funding: Veterans Affairs Support

FR-PO791 Calibration of the Brief Food Frequency Questionnaire among Patients on Dialysis Cynthia Delgado,1 Patricia Ann Ward,2 Glenn M. Chertow,3,7 Lindsey Storer,1 Lorien S. Dalrymple,4 Torin Block,2 George A. Kayser,2,5 John Kornak,4,5 Barbara A. Grimes,6 Nancy G. Kutner,2 Kirsten L. Johansen.1,7 NutritionQuest Berkley; 6Univ of California, San Francisco; 7USRDS Nutrition Special Studies Center.

Background: Accurately estimating dietary intake is particularly challenging in patients with chronic diseases. The aim of this study was to develop a calibrated equation based on dietary intake restricted by food items from the Block Brief 2000 food frequency questionnaire (BFFQ) using 3-day food diary records among patients on dialysis.

Methods: 1-day food diary data from 146 incident dialysis patients were reviewed and set of intakes. Major dietary components were modeled separately using linear regression. Independent variables were BFFQ-restricted food diary estimates as the average of the 3 days of diaries, restricted to items included in the BFFQ, with the unrestricted 3-day food diary averages as dependent variables.

The measurement of the electrical impedance of the body (BIA) is a simple, rapid, and inexpensive method to analyze body composition and body fluid compartments. Among other parameters, BIA allows to estimate Body Cell Mass (BCM), which is the metabolically active component of fat-free mass and is mainly related to muscle mass.

Aim of this study was to validated the measurement of BCM obtained with single and multifrequency BIA as an indicator of the amount of muscle mass in pre-ESRD and in MHD patients.

Methods: Sixty-two adult renal patients (29 F, 33 M) aged 19-79 years, affected by different kidney disease. Their serum creatinine (Creat) ranged between 0.55 and 2.27 mg/dL and GFR (99nCr-DTPA) between 12 and 32.7 mL/min/1.73 m2. Other 19 anuric MHD patients (7 F, 12 M) aged 26-82 years, dialysis vintage 0.6-15y, mean 7.3 years were evaluated. The values of BCM were obtained using a single frequency and a multifrequency tetrapolar impedance plethysmograph. In CKD patients 24 hour urinary creatinine excretion (24h Ucr) was calculated. In MHD patients 24h Creat Generation was calculated by the increase in serum Creat in the inter-dialytic period.

Results: A very high linear correlation was found between the values of BCM and 24h Ucr (r=0.807). The correlation between BCM and Creat generation was even higher (r=0.894). Similar results were obtained by single and multifrequency BIA. Since Creat is produced by muscle cells 24h Ucr in CKD and Creat Gen in MHD patients equal creatinine production, and both are useful tools to assess the amount of muscle mass.

These data indicate that the value of BCM obtained with BIA is strictly related to the amount of muscle mass, estimated from 24 Ucr in CKD patients and by creatinine generation in MHD patients.

Conclusions: In conclusion, the measurement of body cell mass seems an adequate tool to evaluate muscle mass and nutritional status of renal patients.

Funding: Government Support - Non-U.S.
Results: The BFFQ-restricted diary energy estimate of 1325 ± 545 kcal was 87% of the energy intake in the full food diary (1510.3 ± 510.4, p<0.0001). BFFQ-restricted diary carbohydrate intake was 83% of the full food diary (156.7 ± 78.7 g vs. 190.4 ± 72.7, p<0.0001). The BFFQ-restricted fat intake was 90% of full diary-reported fat intake (50.1 ± 24.1 g vs. 56.4 ± 21.6 g, p<0.0001). Daily protein intake assessments were not statistically different. Associations among BFFQ-restricted diary and unrestricted intake were linear. Final equations did not include adjustments for age, sex, or race because the patterns of associations were not significantly different.

Conclusions: Energy and macronutrient estimates by BFFQ are lower than estimates from 3-day food diaries, but simple calibration equations can be used to approximate total intake from BFFQ responses.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Affairs Support

FR-PO792
Validating a Computer Generated Food Frequency Questionnaire in Children with Hypertension Rossana Baracco, Nancy Fassinger, Mauricio Romero Olivera, Murty Adabala, Amrish Jain, Gaurav Kapur. Pediatrics, Children’s Hospital of Michigan/Wayne State Univ; Detroit, MI.

Background: Lifestyle modifications, including a low sodium diet, are the cornerstone in the management of hypertension (HTN). VioFFQ is a computer generated food frequency questionnaire that collects detailed nutritional intake data and processes it immediately into a user friendly report that helps the healthcare team assess dietary habits and provide counseling. The aim of this study was to validate VioFFQ in children with HTN using 24 hour urine excretion of urea.

Methods: Prospective study of children ages 10 to 19 who were referred for evaluation and management of HTN. Twenty four hour urine was collected for estimating excretion of sodium and urea. The VioFFQ was administered on the morning after the urine collection was done. Pearson correlation was done for intake assessed by the questionnaire and 24 hour urinary measurement of sodium and urea.

Results: Of 50 patients enrolled, 36 completed the study and were included. Of these, 51.4% were African American, 58.3% were male and 58.3% were obese. The medians of age, weight and BMI were 15 (11 – 18), 75.2 kg (42.6 – 131.4) and 27.9 (16.1 – 47.1) respectively. Protein and sodium intake measured by VioFFQ correlated with urine excretion of urea and sodium (r=0.5, p<0.005; r=0.3, p<0.005 respectively). The median sodium intake measured by VioFFQ was 3795 grams (2077 – 12765). Obese and African American patients had higher sodium intake.

Conclusions: VioFFQ is a reliable tool to estimate dietary patterns of sodium and protein intake in children. Obese children have higher intake of sodium as assessed by the survey. As the VioFFQ is picture based, meaningful and easy dietary recommendations can be made regarding dietary changes in children with HTN.

Funding: Private Foundation Support

FR-PO793
Increasing Dietary Fiber Reduces Plasma Levels of Colon-Derived Uremic Solutes in Hemodialysis Patients Tammy L. Sirich,1 Natalie Plummer,1 Thomas H. Hostetter,2 Timothy W. Meyer.1 Medicine, Stanford Univ, Palo Alto, CA; 2Medicine, Case Western Reserve Univ, Cleveland, OH.

Background: Numerous uremic solutes are derived from the breakdown of amino acids by colon bacteria. Two such solutes, indoxyl sulfate (IS) and p-cresol sulfate (PCS), have been associated with adverse outcomes in renal failure. This randomized study tested whether increasing fiber intake would lower the plasma levels of IS and PCS in hemodialysis patients.

Methods: Forty patients on maintenance hemodialysis received either daily supplements of fiber (n=20) or a control starch (n=20) for 6 weeks. Fiber was administered as 18 g/day of resistant starch from high amylose maize. The pre-dialysis plasma levels of IS and PCS were assessed at week 0 and week 6 by liquid chromatography and tandem mass spectrometry. The free, unbound solute concentrations were measured as these are the levels to which body tissues are exposed.

Results: Results showed (mean±sd; *p<0.025 vs Week 6; †p<0.025 Fiber vs Control):

<table>
<thead>
<tr>
<th></th>
<th>IS (mg/dl)</th>
<th>PCS (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>3.6 ± 0.2</td>
<td>27.7 ± 0.15</td>
</tr>
<tr>
<td>Week 6</td>
<td>2.8 ± 0.15</td>
<td>22.2 ± 0.13</td>
</tr>
<tr>
<td>% change</td>
<td>23 ± 39*</td>
<td>24 ± 44†</td>
</tr>
</tbody>
</table>

Increasing fiber intake reduced the plasma levels of IS while the control starch had no effect. Comparison of the % change in plasma levels of IS confirmed a statistically significant effect of increasing fiber intake. Increasing fiber intake also reduced the plasma levels of PCS but the difference between the fiber and control groups did not achieve statistical significance. There were no differences in gastrointestinal or other side effects between the two groups.

Conclusions: Results are in accord with the hypothesis that by providing colon microbes with carbohydrate that escapes digestion in the small intestine, increasing fiber intake reduces microbial production of uremic solutes from amino acids. Increasing fiber intake thus provides a potential means to reduce levels of colon-derived solutes without intensifying the dialysis prescription.

Funding: Other NIH Support - National Center for Complementary and Alternative Medicine (NCCAM)

FR-PO794
Effects of Dietary Phosphorus on Circadian Rhythm of Serum Phosphorus in Chronic Kidney Disease Cheryl A. Anderson,1 Dena E. Rifkin,1 Joachim H. Is,2 Gerard John Smits,3 Geoffrey A. Block.3 1Univ of California San Diego; 2Denver Nephrologist PC.

Background: Effects of dietary phosphorus (P) on circadian rhythm of serum P have been described in healthy individuals, but not in individuals with moderate chronic kidney disease (CKD). We describe the effects of three diets with varying P on circadian rhythm of serum P.

Methods: We conducted a crossover trial in 11 individuals with eGFR 30 – 45 mL/min/1.73m². Participants received 3 different P diets sequentially ("restricted": 750 mg/day + Lanthanum Carbonate 1000 mg (TID), "normal": 1500 mg/day, and "high": 3000 mg/day). Participants ate only foods provided for 7 days, and were then admitted to an in-patient facility for 24-hours of observation followed by a 10-day washout. Serum P was collected every 4 hours starting at 8am during in-patient observation. Mixed effects regression models were used for analyses.

Results: Participants were 91% white, 64% female; with baseline mean(SD) age of 67(14) years, serum P of 3.6(0.5), and eGFR of 36.5 (8.4) mL/min/1.73m². There was a significant diet time interaction on serum P (P<0.05). On normal and high P diets, serum P increased from morning through the afternoon, whereas no diurnal difference was seen on the restricted P diet (Figure). Serum P was lowest and had the least difference by diet at 8am. The largest difference in serum P by diet was observed at 4-8pm.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Affairs Support

FR-PO795
Trajectories of Nutritional Parameters and Formulation of a Composite Nutritional Score in Hemodialysis Patients Michelle M.Y. Wong,1 Stephan Thijssen,1 Len A. Usvyat,2 Peter Kotanko,1 Franklin W. Maddux.2 1Renal Research Institute, New York, NY; 2Fresenius Medical Care North America, Waltham, MA.

Background: Nutritional status is assessed using a combination of multiple parameters in hemodialysis (HD) patients. However, most existing nutritional scores are derived from cross-sectional data and do not consider trajectories of nutritional parameters. Therefore, a cohort study was performed 1) to assess temporal patterns of nutritional parameters using radar plots and 2) to generate a composite nutritional score.

Methods: The patient cohort was derived from the Fresenius Medical Care North America database, and included incident patients who started HD between 2007 and 2011. Serum albumin (Alb), creatinine (Crea), phosphate (P), equilibrated normalized protein catabolic rate (enPCR) and interdialytic weight gain (IDWG) were graphed on radar plots at months 1,3,6,9,15,24 after initiating HD. A composite nutritional score was formulated by converting these five component variables to z scores and generating an additive composite, which was then converted to percentiles. The nutritional score was tracked over two years.

Results: The full dataset comprised 47,238 patients, but not every patient had data available for every parameter each month. Early after HD initiation, albumin, creatinine, phosphate, enPCR and IDWG values indicated poorer nutritional status. Over the first 2
years of HD, each of these nutritional parameters improved, as illustrated on radar plots. The composite nutritional score also improved from the 26th percentile at the start of HD to the 57th percentile at 2 years.

Nutritional Evolution in Incident HD Patients

Conclusions: Serial radar plots are useful tools to assess overall nutritional status by incorporating multiple nutritional parameters and their trajectories over time. In future analyses, trajectories of the composite nutritional score can be applied to predict outcomes in HD patients.

FR-PO796
Does a Low Salt Diet Affect Protein Intake in Chronic Kidney Disease Patients? Eiichiro Kanda,1 Yoshitaka Menuyuki,1 Kaori Sakamoto,1 Tomoya Hirayama,1 Kei Nakajima,1 Yoshihiro Matsumoto,6 Sanae Watanabe,1 Yoshikiko Kanno.1* Dept of Nephrology, Tokyo Kyosai Hospital; 2Saitama Citizens Medical Center; 3Kagawa Nutrition Univ; 4Kitasaito Hospital; 5Josai Univ; 6Shizuoka City Hospital; 7Tokyo Medical University.

Background: Among chronic kidney disease (CKD) patients with severe diet restriction, their compliance to diet restrictions declines. We have reported that protein intake can be estimated on the basis of creatinine-correlated urinary nitrogen (UNC) level of spot urine. In this study, we investigated the relationship between salt intake and UNC as an alternative index of protein intake.

Methods: 132 CKD patients (80 males), who were administered a low salt diet, were enrolled in this prospective cohort study in Japan. Their UCN and urinary sodium (UNa) levels were measured three times at separate outpatient clinics. Salt intake was estimated using the salt intake formula of The Japanese Society of Hypertension Guidelines 2009. The relationship between salt intake and UNC was evaluated on the basis of Pearson’s correlation coefficient (r) with the initial measurement, and generalized estimating equation (GEE) and generalized linear mixed model (GLMM) with repeated measurements. GEE and GLMM were adjusted for age, gender, estimated glomerular filtration rate, proteinuria level, and diuretic use.

Results: The mean age (SD) was 64.6(13.0) years; eGFR 64.1(25.9) ml/min/1.73m²; UP/Cr 91.1(18.9) mg/gCr; UNC 6.97(2.51) g/gCr; estimated dietary protein intake 48.5(8.6) g/day; and salt intake 10.02(3.0) g/day. Salt intake correlated with UNC at the initial measurement (r=0.341, p=0.0005). After adjustment for baseline patient characteristics, a positive longitudinal relationship was indicated by GEE between the salt intake and UNC (beta=-0.346, p<0.0001). The GLMM showed that the increase in salt intake can predict the increase in UNC (beta=-0.346, p<0.0001).

Conclusions: This study showed that UNC is associated with salt intake in CKD patients administered a low salt diet. Because UNC is positively associated with protein intake, it is suggested that a protein intake restriction may be achieved with only salt restriction.

FR-PO797
Fluctuating Protein Intake Is an Independent Risk Factor for the Progression of Chronic Kidney Disease Eiichiro Kanda,1 Masumi Aki,1 Renjiro Kuriyama,1 Masaayuki Yoshida,1 Tatsuo Shigai,1* Tokyo Kyosai Hospital; 2Tokyo Medical and Dental Univ; 3Kokubunji Minamiguchi Clinic; 4Shiigai Clinic.

Background: A low-protein diet prevents the progression of chronic kidney disease (CKD). However, the consistent adherence to a low-protein diet is difficult. We investigated the longitudinal effects of changes in protein intake on the CKD progression in elderly CKD patients.

Methods: CKD patients (n=249, 190 males) administered a low-protein (0.6 to 0.8 g/kg/day) were enrolled in this retrospective cohort study in Japan. Their protein intake was measured every three months. The longitudinal change in protein intake was evaluated by the standard deviation (SD) of their protein intake (protein-intake SD). The endpoint was 25% decline in estimated glomerular filtration rate (eGFR) or starting dialysis. The outcome was evaluated using a time-dependent Cox proportional hazard model adjusted for demographics.

Results: The mean age (SD) was 70.6(7.0) years; eGFR 22.2(14.1) ml/min/1.73m²; protein intake 0.85 (0.22) g/day; protein-intake SD 0.12 (0.07) (median, 0.10; Q1, 0.07; Q3, 0.15). The primary endpoint was observed in 65 patients (26.1%). The patients with high protein-intake SD (>0.10) had a high risk of the renal death: hazard ratio (HR), 1.712 (95%CI 1.050, 2.792); adjusted HR, 2.144 (1.046, 4.391).

Conclusions: Serial radar plots are useful tools to assess overall nutritional status by incorporating multiple nutritional parameters and their trajectories over time. In future analyses, trajectories of the composite nutritional score can be applied to predict outcomes in HD patients.

FR-PO798
Efficacy of Eicosapentaenoic Acid (EPA) on Chronic Kidney Disease (CKD) due to Benign Nephrosclerosis Yoshihiko Inoue,1* Tadahide Maemizu,1 Daisuke Komukai, Kiyoko Inui, Ashio Yoshimura.2 Div of Nephrology, Showa Univ Fujigaoka Hospital, Yokohama, Kanagawa, Japan.

Background: We studied the efficacy of EPA to prevent the progression of both renal impairment and atherosclerotic plaque development in CKD stage 3-4 patients due to benign nephrosclerosis (BNS).

Methods: 31 CKD stage 3-4 patients due to BNS with dyslipidemia were followed for 1 year after the start of EPA treatment. The dosage of 1800 mg/day was newly started. T-cho, LDL-cho, Triglycerides (TG), EPA, arachidonic acid (AA), Dihomo-gamma-linolenic acid (DGLA), docosa hexaenoic acid (DHA), right and left (RL) brachial-ankle pulse wave velocity (baPWV), RL maximum carotid intima-media thickness (max IMT), RL maximum carotid plaque thickness and RL ankle-brachial index (ABI) were studied at before treatment (baseline) and at the end of the study. eGFR and the amount of proteinuria were studied at 1year before the start of treatment, baseline and at the end of the study.

Results: EPA treatment elicited statistically significant increase in EPA (1-year of EPA: 242.2±100.7 μg/ml, baseline: 73.0±39.3 μg/ml, P<0.01), EPA/AA ratio and decrease in TG. RL baPWV and RL max IMT were significantly improved (1-year of right baPWV: 1564.3±333.4 vs. baseline: 1668.1±369.2, 1-year of left: 1597.1±320.2 vs. baseline: 1672.1±378.8 cm/s, 1 year of right max IMT: 0.85±0.26 vs. baseline 0.96 ± 0.35, 1-year of left: 0.80±0.24 vs. baseline 0.92±0.31, P<0.05). eGFR and amount of proteinuria also showed significant improvement at the end of the study (1-year of eGFR: 46.9±13.0 vs. baseline: 43.8±11.1 ml/min/1.73m², P<0.05). Both EPA and DHA levels were significantly low in eGFR exacerbation patients group (n=7) compared with eGFR improvement patients group (n=24) at both baseline and the end of the study. The highest EPA level patients at the end of the study (1-year of EPA: 242.2±100.7 μg/ml, baseline: 73.0±39.3 μg/ml, P<0.01) had a high risk of the renal death: hazard ratio (HR), 2.144 (1.046, 4.391).

Conclusions: EPA may prevent both the development of renal dysfunction and the atherosclerotic change in CKD stage 3-4 patients due to BNS.

FR-PO799
Selenium Supplementation and Antioxidant Outcome Markers in Hemodialysis Patients Elizabeth J. Sussman,1 Carol S. Johnston,2 Kenneth R. Boren,1 Bhupinder Singh.2 Family and Consumer Sciences, California State Univ, Northridge, Northridge, CA; 2School of Nutrition and Health Promotion, Arizona State Univ, Phoenix, AZ; 3Southwest Kidney Institute/DaVita Inc., Tempe, AZ.

Background: Hemodialysis (HD) patients elicit an oxidant-antioxidant imbalance due to renal impairment and atherosclerosis in CKD stage 3-4 patients due to benign nephrosclerosis (BNS).

Methods: 31 CKD stage 3-4 patients due to BNS with dyslipidemia were followed for 1 year after the start of EPA treatment. The dosage of 1800 mg/day was newly started. T-cho, LDL-cho, Triglycerides (TG), EPA, arachidonic acid (AA), Dihomo-gamma-linolenic acid (DGLA), docosa hexaenoic acid (DHA), right and left (RL) brachial-ankle pulse wave velocity (baPWV), RL maximum carotid intima-media thickness (max IMT), RL maximum carotid plaque thickness and RL ankle-brachial index (ABI) were studied at before treatment (baseline) and at the end of the study. eGFR and the amount of proteinuria were studied at 1year before the start of treatment, baseline and at the end of the study.

Results: EPA treatment elicited statistically significant increase in EPA (1-year of EPA: 242.2±100.7 μg/ml, baseline: 73.0±39.3 μg/ml, P<0.01), EPA/AA ratio and decrease in TG. RL baPWV and RL max IMT were significantly improved (1-year of right baPWV: 1564.3±333.4 vs. baseline: 1668.1±369.2, 1-year of left: 1597.1±320.2 vs. baseline: 1672.1±378.8 cm/s, 1 year of right max IMT: 0.85±0.26 vs. baseline 0.96 ± 0.35, 1-year of left: 0.80±0.24 vs. baseline 0.92±0.31, P<0.05). eGFR and amount of proteinuria also showed significant improvement at the end of the study (1-year of eGFR: 46.9±13.0 vs. baseline: 43.8±11.1 ml/min/1.73m², P<0.05). Both EPA and DHA levels were significantly low in eGFR exacerbation patients group (n=7) compared with eGFR improvement patients group (n=24) at both baseline and the end of the study. The highest EPA level patients at the end of the study (1-year of EPA: 242.2±100.7 μg/ml, baseline: 73.0±39.3 μg/ml, P<0.01) had a high risk of the renal death: hazard ratio (HR), 2.144 (1.046, 4.391).

Conclusions: EPA may prevent both the development of renal dysfunction and the atherosclerotic change in CKD stage 3-4 patients due to BNS.
FR-PO801

Changes in Serum Albumin Associated with Decreased Kidney Function, and Its Effects on Mortality in a Nationally Representative Cohort of U.S. Veterans with Non-Dialysis-Dependent CKD

CSaba P Kovácsy,1 Jun Ling Lu,2 Miklos Zsolt Molnar,3 Jennie Z. Ma,3 Joel D. Koppel,3 Kamyar Kalantar-Zadeh.4

1Memphis VA Medical Center; 2Univ of Tennessee Health Science Center; 3Univ of Toronto; 4Univ of Virginia; 5Harbor-UCLA Medical Center; 6Univ of California-Irvine.

Background: Serum albumin (ALB) level is a marker of protein-energy wasting and is inversely associated with increased mortality. However, it is unclear if worsening CKD is associated with progressive decrease in ALB, and if intra-individual changes in ALB affect its association with mortality in patients with non-dialysis dependent (NDD) CKD.

Methods: We examined longitudinally ALB and its association with all-cause mortality in a cohort of 486,157 US veterans with NDD-CKD stages 1-5 and at least 2 ALB measurements, using mixed effects regression models, time-dependent Cox models and joint modeling, adjusted for demographic characteristics, comorbidities and medication use.

Results: Patients had 3,285,026 ALB measurements (median (IQR): 5/patient (3-9)) over 5.9 years median follow-up. The adjusted odds ratio (95% CI) of ALB <3.6 g/dl associated with a 10 ml/min/1.73m2 lower eGFR was 1.09 (1.08-1.10, p<0.001), and individuals experienced an ALB decline at 0.047 g/dl/year (95%CI: 0.046-0.048, p<0.001). 159,761 patients died (mortality rate: 61.4/1000 patient-years (95%CI: 61.0-61.7)). The adjusted mortality hazard ratio (95% CI) associated with each 1 g/dl lower ALB was 3.24 (3.21-3.27, p<0.001, Figure 1).

Conclusions: Thus, hypoalbuminemia worsens over time in patients with NDD-CKD, and progressively lower ALB is associated with increased mortality. The effect of therapeutic interventions to prevent or treat hypoalbuminemia will need to be examined in clinical trials.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO802

Acute Kidney Injury in Shoshin Beriberi – A Case Series

Shashidhar Baikunje,1 Rama S. Prakasha,2 Glaxon Alex.2

1Dept of Nephrology, K. S. Hegde Medical Academy, Mangalore, India; 2Dept of Medicine, K. S. Hegde Medical Academy, Mangalore, India.

Background: Shoshin Beriberi is a rare and unusual metabolic cause of acute kidney injury and literature in this regard is sparse worldwide. Patients often present with evidence of right heart failure, severe shock and metabolic acidosis in addition to renal failure.

Methods: Retrospective analysis of eight cases with above manifestations.

Results: The mean age was 34.8 years and five out of eight were males. Three patients were diabetics. The most common presenting features were edema, breathlessness and oliguria. Mean creatinine on admission was 2.54 mg/dl and mean MDRD eGFR was 36.6 ml/min/1.73m². Mean haemoglobin was 11.9 g/dl, total count 13,412/cu.mm, mild proteinuria was present in seven, RBCs in urine in two and granular casts in four. Abnormal liver enzymes were noted in six of the eight patients, CPK and CK-MB were elevated in four. Echocardiographic evidence of right heart dilatation and pulmonary hypertension were seen in all the cases. Severe metabolic acidosis was noted with mean pH of 7.06 and mean arterial bicarbonate of 5.74mmol/L. Three patients required renal replacement therapy, two needed ventilatory support and four were treated with inotropes. Six patients were treated with broad spectrum antibiotics but the cultures were negative in all except one. IV thiamine was used in seven patients with excellent clinical response and one patient who did not receive thiamine died. There was improvement in acidosis, blood pressure and renal function within 48-72 hours and all the seven of them had normalization of creatinine levels.

Conclusions: Presentation with multisorgan involvement, severe metabolic acidosis, evidence of right heart dilatation with pulmonary hypertension on echocardiogram and dramatic response to IV thiamine were the basis of the diagnosis since the diagnostic tests for thiamine deficiency are rarely used in acute setting. Renal dysfunction has excellent prognosis and the recovery is complete if the condition is suspected and treated promptly.

Funding: Pharmaceutical Company Support - Academy of Nutrition and Dietetics
FR-PO803

Investigation of Carnitine Deficiency in Children Receiving Continuous Renal Replacement Therapy
Kristen Seaberg, Kittida Mistry, Shamin Tuchman, Asha Moudgil.
Nephrology, Children’s National, Washington, DC.

Background: Carnitine deficiency is common in patients receiving chronic hemodialysis (HD) due to inadequate intake, decreased production, and removal during dialysis. The effect of continuous renal replacement therapy (CRRT) on carnitine homeostasis has not been previously studied. We hypothesized that children receiving CRRT may be at risk for carnitine deficiency due to continuous removal, absent intake, and comorbidities related to underlying critical illness.

Methods: Medical records of all patients receiving CRRT at Children’s National between 2011 and 2013 were reviewed for total carnitine (TC) and free carnitine (FC) levels. Patients on carnitine supplementation were excluded. Proportion of carnitine deficiency at baseline, 0.5, 1, 2, and 3 weeks duration on CRRT was assessed. Mean TC and FC levels of children on CRRT were compared to those of a prospective comparison group of children on chronic HD for > 3 months by Student’s t test.

Results: The study group included 27 CRRT patients with mean age 9.9±7.4 years. At initiation of CRRT, 14.3% of children were TC deficient. Deficiency of prevalence increased with duration of CRRT to 54.5%, 72.7%, 75%, and 100% at 0.5, 1, 2, and 3 week time points, respectively. The prevalence of FC deficiency similarly increased with duration of CRRT from 42.9% at baseline to 70%, 75%, 75%, and 100% at 0.5, 1, 2, and 3 weeks. Mean carnitine levels after 1 week on CRRT were significantly lower compared with baseline levels (TC decreased from 41.7 to 20.9 and FC from 27.1 to 14.1 μmol/L, p<0.01). Mean carnitine levels of children on CRRT for 0.5 week was lower compared with levels of 9 children on chronic HD for mean duration of 9.3 months (TC 27.1±17.5 vs 49.5±1.0 and FC 17.5±13.0 vs 29±3.6 μmol/L, p<0.03).

Conclusions: Carnitine levels significantly decrease with longer time on CRRT, and the majority of children on CRRT for 1 week are carnitine deficient. Deficiency is more severe after only 1 week on CRRT in children on chronic dialysis for a mean of 9.3 months. Consequences of carnitine deficiency and possible benefits of supplementation in the critically ill pediatric CRRT population should be investigated.

FR-PO804

The Effect of Serum Zinc on Salt Taste Acuity, Preference and Dietary Sodium Intake in Hemodialysis Patients
Hyun woo Kim,1 So Mi Kim,1 Eun Kyoung Lee,2 Ji Eun Lee.2

Background: High sodium intake has been known for the major cause of fluid overload in hemodialysis patients, leading to increased cardiovascular mortality. High sodium intake is related to low salt taste acuity and high salt preference and zinc status is known to influence taste acuity. We tried to analyze the effect of serum zinc status on salt taste acuity, preference and dietary sodium intake in hemodialysis patients.

Methods: This cross-sectional study enrolled 77 patients, who underwent hemodialysis in the Jeju national university hospital or Dankook university hospital. The patients were divided into two groups based on the level of serum zinc. 26 patients showed normal range and 51 patients showed zinc deficiency. 1-day dietary recall was used to estimate the dietary sodium intake and salt taste acuity and preference were determined by sensory test using variable concentration of NaCl solution.

Results: Baseline characteristic, mean age, sex, cause of ESRD, HTN medication, BP were not different between the two groups. The NaCl solution concentration of both salt taste acuity and preference showed higher tendency in the zinc deficient group than that in the zinc sufficient group (mean NaCl 3% of salt taste acuity: 0.13±0.06 vs. 0.16±0.13, p=0.04, mean NaCl 3% of salt taste preference: 0.48±0.13 vs 0.54±0.10, p=0.07). Although the sodium intake showed high tendency in zinc deficient group, there was no significant difference (2134±937 vs 2546±297 mg/day, p=0.056). But the correlation between the sodium intake and the serum zinc showed the significant negative linear relationship (r=-0.313, p<0.05). Interday weight gain was significantly higher in the zinc deficient group than in those zinc deficient group (2.68±1.02 vs. 3.18±1.02 kg, p=0.04).

Conclusions: We conclude that zinc deficiency may lead to high sodium intake in hemodialysis patients, affecting on the salt taste acuity and preference.

FR-PO805

Inadequate Dietary Intake Correlates with Thiol Markers of Oxidative Stress in Maintenance Hemodialysis Patients (HD)
Paolo Fanti,1 Daniela Giancarini,1 Ranieri Rose,1 Franzini F,1 Khaled Khazim,1 Padam Hirani,1 Sue Cunningham,1 Georgiana Gross,1 Shweta Barwal.1

1Div of Nephrology, UT Health Science Center San Antonio, San Antonio, TX; 2Univ of Siena, Italy; 3Western Galilee Hosp., Israel.

Background: Anorexia and poor nutrition are the most important immediate causes of protein-energy wasting (PEW) in uremia. Oxidative stress (OS) is believed to participate in the pathogenesis of uremic PEW, but it is unclear if direct association exists between poor nutrition and OS in this disease state.

Methods: To test the hypothesis that poor nutrition and OS are linked in uremia, we analyzed the 3-day diet record and the plasma thiols redox of 76 clinically stable HD and 24 age-matched healthy controls (C). 3-day diet record was analyzed with The Food Processor software (ESHA, Salem OR). Analysis of thiol redox included plasma total cysteine (CYS), cysteine (CYSs) and protein thiolation index (PTI) a new marker of OS [Gustarini D, et al. Free Radic Biol Med 53:907, 2012].

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

FR-PO806

The Effect of Oral Vitamin D Supplementation in Non-Dialytic CKD Patients
Sun Moon Kim,1 Soon Kil Kwon,1 Hye-Young Kim,1 Han Ro2 Ji Yong Jung.2

1Internal Medicine, Chungbuk National Univ, College of Medicine; 2Internal Medicine, Gachon Univ of Medicine and Science.

Background: The anti-inflammatory, antifibrotic, and antiproteinuric properties of vitamin D have been defined in studies using active vitamin D analogs. Here, we study the effects of nutritional vitamin D supplementation on bone mineral metabolism and progression of renal disease in chronic kidney disease (CKD) patients.

Methods: We conducted a study in adult, vitamin D deficient [25(OH)D < 30 ng/mL], non-dialytic CKD patients. The patients were classified into oral vitamin D supplementation (cholecalciferol 1,000 IU/day) or not for 6 months. The serum level of 25(OH)D, parathyroid hormone (PTH), calcium, phosphate, alkaline phosphatase, creatinine, and urinary protein excretion were measured serially.

Results: Ninety seven patients were enrolled. The baseline characteristics were not different between vitamin D group vs. control group. Vit D supplementation achieved the improvement in serum 25(OH)D level (vitamin D vs. control, 28.01±12.82 ng/mL vs. 13.50 ± 7.29 at 3 month, p<0.001). 29.49±16.19 vs. 14.17±8.17 at 6 month, p<0.001). This difference was persistent in the subgroup analysis of baseline GFR <30 mL/min/1.73m² vs. GFR 30-60 vs 25(OH)D <15 ng/mL vs. 25(OH)D 15-30. PTH level was decreased in the vitamin D group compared to control group (vitamin D vs. control, 40.2 (26.8 – 72.0) pg/mL vs. 54.2 (38.2 – 101.1) at 3 month, p = 0.013; 38.8 (19.2 – 65.3) vs. 58.1 (39.5 – 137.0) at 6 month, p = 0.014). Vitamin D supplementation increased corrected calcium level compared to control at 3 month, whereas the difference was not significant at 6 month. The level of phosphate, estimated GFR, and random urine protein-to-creatinine ratio were not different. During the study period, four patients in vitamin D group and five in control group started renal replacement therapy. The most common adverse effect was gastrointestinal irritation. There was no case of symptomatic hypercalcemia.

Conclusions: Oral vitamin D supplementation was effective in replenishing vitamin D store in CKD patients. However, we could not find any beneficial effect on renal disease progression.

FR-PO807

The On-Line Hemodiafiltration Improves the Nutritional Status in Hemodialysis Prevalent Patients: A 1-Year, Prospective, Controlled Study
Pablo Molina,1 Belen Vizcaíno,1 Angela Maria Serrato,1 Daniel A. Molina,1 Sandra Beltrán,1 Avila Ana,1 Julia Kanter,1 Mariola D. Molina,2 Jose L. Gorriz,1 Luis M. Pallardo.1

1Dept of Nephrology, Hospital Universitari Dr Peset, Valencia, Spain; 2Dept of Statistics and Operational Research, Universidad de Alicante, Spain.

Background: Compared to conventional haemodialysis, on-line hemodiafiltration (OL-HDF) removes more efficiently uremic toxins, which could attenuate the hypercatabolism and increase the protein anabolism of hemodialysis patients. The present study evaluated the 1-year effect of OL-HDF on nutritional status in prevalent hemodialysis patients.

Methods: This single-center, controlled, intervention study enrolled all high-flux haemodialysis (HF-HD) subjects attending our Unit from 2012 to 2013 (n=33; mean age: 60±17.5 years; women: 42%; median time on dialysis:37(0-133) months). Patients were randomized to receive posodilution OL-HDF (n=17) or to remain on HF-HD (n=16). Changes in multifrequency bioimpedance parameters (primary outcomes) and other biochemical markers were compared in vitamin D group and five in control group started renal replacement therapy. The most common adverse effect was gastrointestinal irritation. There was no case of symptomatic hypercalcemia.

Conclusions: Oral vitamin D supplementation was effective in replenishing vitamin D store in CKD patients. However, we could not find any beneficial effect on renal disease progression.
Comparing with baseline.

Assistance Publique des Hopitaux de Marseille, Marseille, France; 2 Service de bicarbonate concentration in CKD IV-V patients. Further studies are needed to explore the (MDA), ischemia modi-

We performed dosages of (i) anti-oxidant agents: super oxide dismutase (SOD), vitamin C, patients with CKD stage 3 to 5 not on dialysis (CKD NOD) and 38 healthy subjects (control).

in predialysis patients.

for control of hyperphosphatemia. Some studies have showed an increase in bicarbonate

identi-

the renal replacement groups. A decrease in the phosphorus level of 1.11 mg/dL (0.36

tended to be greater in the pre-dialysis patients (3.33 mmol/L p = 0.13) compared with

up was around 13 mo. In each group, patients were divided into two sub-groups according to biopsy results: group 1: major changes were mesangial cell proliferation; group 2: mesangial cell proliferation with focal segmental sclerosis.

Control: There were no differences in blood pressure and renal function changes among the groups with different treatments. In group 1 treated with LH-1, UP dropped from 1.04±0.34 to 0.35±0.21 g/24 h after the treatment; in group 1 treated with LH-1+; UP dropped from 1.08±0.48 to 0.48±0.27 g/24 h. In group 2 treated with LH-1+; UP dropped from 1.08±0.44 to 0.55±0.43 g/24 h after the treatment; in group 2 treated with LH-1+; UP dropped from 1.03±0.39 to 0.33±0.22 g/24 h. There was no statistically significant difference between UPs in group 2 after LH-1 vs. LH-1+. Among patients treated with LH-1+; 6 patients developed upper-respiratory infection followed by exacerbated proteinuria. Five other patients developed fungal and/or skin infections. Another patient showed liver function changes with increased GPT. No side effects were reported for patients treated with LH-1 only.

Conclusion: LH-1 improved proteinuria in IgAN with similar efficacy as LH-1+. Significant side effects were found in LH-1+ group but not in LH-1. These data justify future randomized clinical trials to assess the clinical impact of LH-1 in IgAN treatment.

Funding: Private Foundation Support

FR-PO811

Brachial–Ankle Pulse Wave Velocity Predicts Decline in Renal Function and Cardiovascular Events in Early Stages of Chronic Kidney Disease

Hye Eun Yoon, Sung Jun Kim, Hyeon Seok Hwang, Seok Joon Shin.

Internal Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: In this study, we investigated the predictive capacity of the brachial–ankle aortic pulse wave velocity (baPWV), a marker of arterial stiffness, for the decline in renal function and for cardiovascular events in the early stages of chronic kidney disease (CKD).

Methods: Two hundred forty-one patients who underwent a comprehensive check-up were included and were divided into two groups according to their estimated glomerular filtration rates (eGFR); patients with CKD stages 2 and 3 (30 < eGFR < 90 ml/min/1.73 m2, the eGFR < 90 group; n=117) and those with eGFR > 90 ml/min/1.73 m2 (the eGFR > 90 group; n=124). The change in renal function, the eGFR change, was determined by the slope of eGFR against time. We analysed whether baPWV was associated with eGFR change or predicted cardiovascular events.

Results: baPWV was independently associated with eGFR change in a multivariate analysis of the total patients (β=0.011, p=0.01) and remained significantly associated with eGFR change in a subgroup analysis of the eGFR < 90 group (β=0.008, p=0.028). baPWV was independently associated with cardiovascular events (odds ratio=1.002, p=0.048) in the eGFR < 90 group, but not in the eGFR > 90 group. The receiver operating characteristic curve analysis showed that 1,568 cm/sec was the cut-off value of baPWV for predicting CV events in the eGFR < 90 group (area under curve=0.691, p=0.03).

Conclusions: In patients with early stages of CKD, baPWV was independently associated with the decline in renal function and short-term cardiovascular events.

Funding: Government Support - Non-U.S.
FR-PO812

Inhibitors of Vascular Calcification and Coronary Artery Calcification in ESRD
Ramin Tolouian,1 Sean M. Connery, German T. Hernandez. Texas Tech Univ HSC at El Paso, TX.

Background: Vascular calcification (VC) is an important predictor of cardiovascular mortality in ESRD. Disturbances in mineral metabolism, especially Ca and PO4, have been linked to enhanced calcification of blood vessels but the Ca & PO4 levels do not adequately explain this pathology. Levels of inhibitors of the calcification process, such as Fetuin-A and inorganic pyrophosphate (PiP), are thought to be VC. Therefore, we evaluated the association between Fetuin-A and PiP, and coronary calcification scores in maintenance HD.

Methods: 106 maintenance HD patients were studied (mean ±SD): Age (yr) 58 ±11.2, HD vintage (yr) 4.6 ±3.2, Ca*P (mg/dl) 43 ±11.6, Male 63%, Hispanic 89%, diabetic 72%. Platelet free plasma PiP was measured by radiometric, enzymatic method. Serum Fetuin-A was measured with the UltraEdison ELISA kit (Alpco 43-FETUH-U01) on a Beckman DTX 800 microplate reader. Coronary arterial calcification score (CACS) was measured by sub-second gated helical computed tomography with an Imatron C-150 XL ultra fast CT scanner using a standard CACS protocol: slice thickness 3mm, Density Threshold (HU) 130, Pixel threshold 3, Algorithm Discrete, read by a single, experienced cardiologist.

Results:

There was not statistically significant difference between PiP and Fetuin-A when comparing low-risk CACS (<300) and high risk CACS (≥300) PiP (mm β = 1.56 ±0.49 vs 1.57 ±0.46, Fetuin-A (g/L) 0.67 ±0.24 vs 0.65 ±0.25. Furthermore, there was no significant difference in PiP and Fetuin-A levels between CACS quartiles (p = ns Kruskal-Wallis test). Mean CASC for each quartile were 0.80, 66, 391, and 2,957 respectively. Error bars indicate error of the mean.

Conclusions: There does not appear to be an unadjusted inverse relationship between inhibitors of vascular calcification and CACS our study of HD patients. The possibility of confounding by age, HD vintage, and diabetes needs to be further evaluated.

Funding: Private Foundation Support

FR-PO813

Dietary Habits Are Associated with Proteinuria Independent of Major Cardiovascular Risk
Makoto Kanno,1 Koichi Asahi,1,2 Kenichi Tanaka,1 Yoshimitsu Hayashi,1 Masaki Nakayama,1 Kunitoshi Ikemoto,1 Kunihito Yamagata,1 Kazuhiro Tsutuya,1 Hideaki Yoshida,1 Shouichi Fujimoto,1,2 Tsuyoshi Watanabe.1,2

1Dept of Nephrology, Hypertension, Diabetology, Endocrinology and Metabolism, Fukushima Medical Univ School of Medicine, Fukushima, Japan; 2Steering Committee for “Research on the Positioning of Chronic Kidney Disease (CKD) in the Specific Health Check and Guidance System of Japan”, Fukushima, Japan.

Background: Irregular dietary habits are associated with a number of risk factors for cardiovascular disease (CVD), including obesity, insulin resistance, and dyslipidemia. However, few studies have examined the relationship between these habits and proteinuria or chronic kidney disease (CKD).

Methods: This cross-sectional cohort study examined 181,524 subjects (73,753 men; 107,771 women; mean age, 63.8 years; age range, 40-74 years) who participated in an annual nationwide health checkup system in 2008. We compared prevalence of proteinuria (≥1+ on dipstick test) among participants according to the number of irregular dietary habits (skipping breakfast, dinner within 2 h before bedtime, eating more than 2组长, and eating quickly (EQ)) obtained by questionnaire response. Multivariate logistic regression models were used to adjust for possible confounding factors.

Results: Overall prevalence of proteinuria was 5.9%, and increased significantly from 5.2% to 8.6% with increases in the number of irregular dietary habits. The odds ratio (95% confidence interval) for proteinuria was 1.24 (1.17–1.32) with SB, 1.14 (1.08–1.20) with DbB, 1.08 (1.02–1.15) with SaD and 0.97 (0.93–1.01) with EQ, after adjusting for sex, age, body mass index, metabolic syndrome, hypertension, diabetes, dyslipidemia, estimated glomerular filtration rate, history of stroke, cardiac disease and kidney disease, smoking and exercise habit.

Conclusions: Some irregular dietary habits are associated with proteinuria independent of major CVD risk factors. Future research should investigate whether aggressive intervention regarding daily dietary habits can prevent the development of CVD.

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

FR-PO814

Outcomes Associated with Oral Protein Supplementation during Maintenance Hemodialysis: A Quality Improvement Prospective Interventional Study
Buthayna Dinay, Keyvan Ravakhah, Fazel Dinay. Internal Medicine/Nephrology, St. Vincent Medical Center, Cleveland, OH.

Background: Low serum albumin levels in dialysis patients are associated with increased morbidity & mortality. Dietary protein intake is a cheap and equally effective way of achieving an increase in serum albumin and improve quality of life (QOL).

Methods: A multicenter, prospective, Interventional study included patients from three HD units affiliated with academic and tertiary-care hospitals in Cleveland OH. Patients were adult patients aged > 18 YO and have been treated by HD for at least 6 months. An inclusion criterion was: serum albumin concentration ≥ 3.8 g/dl in HD patients. Exclusion criteria included documented malignancy and any acute illnesses within the last 2 months. From a cohort of 106 patients who were enrolled, 87 were eligible for the analysis. LiquaCel, which provides 16 gm protein and 2.5 gm L-Ariginine per 1 oz. serving, was given to patients with albumin level ≥ 3.8. Blood samples for serum albumin were drawn on the day of midweek HD session. On the same day, the Quality of life Health Survey (QOLHS) Score was evaluated. Patients were evaluated for Serum albumin concentration which was measured monthly for 6 months as primary outcome and they were assessed for QOLHS score obtained before supplementation and at the end of project.

Results: A total of 87 patients were included in the analysis. The mean Baseline QOLHS score was 16.2 and the mean Baseline Albumin was 3.37, when the pre and post protein supplementation data were analyzed using paired t-tests, significant differences were present; the mean increase in serum albumin concentration of 0.9 mg/ml observed (P < .05). The QOLHS score correlated significantly with the serum albumin level at all measurements (baseline: r = -0.37, P = .001; and 6 months: r = -0.46, P < .0001). The QOLHS score was correlated with proteinuria, age, and diabetes needs to be further evaluated.

Conclusions: There does not appear to be an unadjusted inverse relationship between inhibitors of vascular calcification and CACS our study of HD patients. The possibility of confounding by age, HD vintage, and diabetes needs to be further evaluated.

Funding: Pharmaceutical Company Support - Sanofi (Genzyme)

FR-PO815

Effects of Intravenous Ascorbic Acid on Vascular Function and Oxidative Stress in Chronic Kidney Disease
Keith Gills,1 Kathryn K. Stevens,1 Markus P. Schneider,1 Scott Morris,1 Christian Delles,1 Alan G. Jardine,1 Patrick B. Mark,1 Univ of Glasgow, Glasgow, United Kingdom; 2Glasgow Renal and Transplant Unit, Glasgow, United Kingdom; 3Univ of Erlangen-Nuremberg, Erlangen.

Background: Endothelial dysfunction and arterial stiffness may explain premature cardiovascular disease seen in chronic kidney disease (CKD). Antioxidant therapy may improve endothelial dysfunction and reduce cardiovascular risk. We studied the effect of intravenous ascorbic acid (VitC) on oxidative stress and arterial stiffness in hypertensive patients with normal renal function (HTN) and with CKD.

Methods: This was a single-blind crossover study. Patients received both VitC and normal saline (NaCl). At baseline and following each intervention, vascular function, (pulse wave analysis, augmentation index (Aix) and pulse wave velocity) was measured and bloods were drawn for markers of oxidative stress. Rate of reactive oxygen species (ROS) production was measured by electron paramagnetic resonance and total antioxidant capacity (TAC) by colorimetric assay.

Results: 12 CKD and 12 HTN patients were recruited with a mean age of 56 (SD 12) and a mean blood pressure (BP) 142/88mmHg (SD 15.1). There were no significant differences between the groups in gender, age or BP. The CKD group had an eGFR of 28.3 ml/min (SD 10.5) compared with 98.2 ml/min (SD 10.9) in the HTN group (p<0.05). VitC led to a significant reduction in Aixs in both groups: from 26% (SD 8%) after NaCl to 16% (SD 11%) after VitC (t=0.05) in CKD patients and 24% (SD 12%) to 19% (SD 11%) (p<0.05) in HTN. There was no significant difference between the groups. Rate of ROS production was transiently increased in both CKD (43% p<0.05) and HTN (37% p<0.05) at 10 minutes, before falling to a baseline level at 60 minutes. TAC was initially increased in both CKD (57%, p<0.05) and HTN (50%, p<0.05) before falling to baseline at 60 minutes.

Conclusions: Ascorbic acid ameliorates arterial stiffness and paradoxically increases ROS production in both CKD and HTN. Whilst the pro oxidant effect of ascorbic acid is acknowledged, this is the first in vivo evidence of increased ROS production and further research is required to elucidate the mechanisms of this.

Funding: Private Foundation Support

FR-PO816

Fruits and Vegetables or Oral NaHCO3 Prevent Progression of Kidney Injury in Stage 1 CKD due to Hypertensive Nephropathy
Ninomi Goraya,1,2 Chanhee Jo,1 Jan Simoni,1 Donald E. Wesson.1 Internal Medicine, College of Medicine, Texas A and M, Temple, TX; 2Internal Medicine, Scott and White Healthcare, Temple, TX; 3Surgery, Texas Tech Univ Health Sciences Center, Lubbock, TX; 4Biostatistics, Scott and White Healthcare, Temple, TX.

Background: Dietary alkali reduces kidney injury and slows GFR decline in patients with reduced GFR due to hypertensive nephropathy (HN). Reduced GFR further increases cardiovascular risk of HN and kidney injury typically precedes GFR reduction. Consequently, preventing further kidney injury appears to benefit hypertensives with
FR-PO187
Epoeitin Beta Pegol (C.E.R.A.) Augmented Dietary Iron Absorption by Decrease in Serum Hepcidin Levels and Increase in Expression of Duodenal Iron Transporters

Background: Epoeitin beta pegol (C.E.R.A.) is a novel long-acting erythropoietis stimulating agent. We previously reported C.E.R.A. promotes mobilization of iron storage from reticuloendothelial cells through intensive suppression of serum hepcidin levels. The aim of this study is to evaluate the contribution of dietary iron utilization for erythropoiesis after C.E.R.A. treatment in mice.

Methods: Hematological and iron parameters including serum hepcidin levels were analyzed in C57BL/6N (B6) mice intravenously treated with 10 µg/kg of C.E.R.A. or vehicle. The expression of duodenal iron transporters, ferroportin (FPN) which is internalized by hepcidin binding and divalent metal transporter (DMT)-1, was assessed by immunohistochemical staining. B6 mice intravenously treated with 10 µg/kg of C.E.R.A. or vehicle were fed iron deficiency diet to inhibit dietary iron absorption or control diet, and transitions of hematological parameters were analyzed.

Results: C.E.R.A.-treated mice showed significantly higher hemoglobin (Hb) levels than vehicle-treated mice for 14 days after treatment, while serum hepcidin levels were continuously suppressed and serum iron levels were markedly decreased on the fifth day in C.E.R.A.-treated mice. FPN expression on the basolateral membrane of intestinal enterocytes and DMT-1 expression on luminal surface of them were increased after C.E.R.A. treatment. The inhibition of dietary iron absorption resulted in impaired Hb elevation and decrease in mean corpuscular volume (MCV) after C.E.R.A. injection.

Conclusions: C.E.R.A. augmented dietary iron absorption by the suppression of serum hepcidin levels and thereby increasing duodenal expression of FPN and DMT-1, and absorbed iron was beneficially utilized for erythropoiesis. C.E.R.A. has a strong power to promote utilization for erythropoiesis through enhancement of dietary iron absorption as well as mobilization of iron storage from reticuloendothelial cells.

FR-PO188
Calcitriol Regulates Monocyte Hepcidin and Ferritin: A Role for Vitamin D in Iron Homeostasis
Anjali B. Nayak,1 Justine Bacchetta,1 Joshua Zaritsky,1 Isidro B. Salusky,1 Martin Hewison.2 1Dept of Pediatric Nephrology, Univ of California Los Angeles, Los Angeles, CA; 2Dept of Orthopaedic Surgery, Univ of California Los Angeles, Los Angeles, CA.

Background: Calcitriol (1,25(OH)2D3) is an important component of chronic kidney disease (CKD) therapy, and its effects on immune function may have additional benefits for CKD patients. We have shown that hepatocytes and monocytes treated with calcitriol showed increased expression of hepcidin, a key iron homeostasis gene. Calcitriol also may inhibit cell proliferation and may be the only known exporter of intracellular iron. To investigate further the iron regulatory function of calcitriol, we carried out studies using human monocytes exposed to vehicle or calcitriol in the presence and absence of calcitriol.

Methods: THP-1 human monocytes were cultured in regular medium with or without added ferric nitrate (FeNO3) at (5-45 µM) FeNO3. 10 nM calcitriol in the absence of FeNO3 at 5(5-45 µM) and 1.25OH2D3 for 24 hrs. Cells were then lysed to generate RNA and the expression of various target genes analyzed using qRT-PCR.

Results: THP-1 cultured with 5, 15 or 45 µM FeNO3 in the absence of calcitriol showed increased mRNA for hepcidin (4.35, 2.81 and 4.26-fold respectively) relative to cells in regular medium. Conversely, mRNA for ferritin was decreased with increasing FeNO3 (0.27, 0.07, 0.17-fold respectively. In the absence of FeNO3, THP-1 treated with 1.25OH2D3(10 and 100 nM) showed decreased expression of hepcidin (0.25, 0.14, and 0.21-fold), and ferritin (0.17, 0.15, and 0.11-fold). This effect was also observed in THP-1 cultured with 10nM calcitriol in the presence of low dose (5µM) FeNO3, 10nM calcitriol in 5 µM FeNO3 decreased expression of hepcidin (0.26-fold) and ferritin (0.25-fold) relative to vehicle. However, 10 nM calcitriol had no effect on expression of mRNA for hepcidin or ferritin (0.75 or 0.90 µM) FeNO3 concentration.

Conclusions: These data indicate that active vitamin D, calcitriol, is a potent suppressor of hepcidin and also suppresses ferritin, a surrogate marker for intracellular iron concentrations. These effects are lost under conditions of enhanced hepcidin expression following exposure to high dose exogenous iron, suggesting a selective role for vitamin D in regulating intracellular iron concentrations.

FR-PO189
Direct Thrombin Inhibitor Dabigatran Induces Glomerular Hemorrhage with Acute Kidney Injury Similar to Warfarin Related Nephropathy
Kyle M. Ware, Zahida Qamri, Anjali A. Satoskar, Omar Sameer Hassanain, Lee A. Hebert, Brad H. Rovin, Tibor Nadasy, Sergey V. Brodsky. The Ohio State Univ, Columbus, OH.

Background: Excessive anticoagulation with warfarin can result in acute kidney injury (AKI) by causing glomerular hemorrhage and renal tubular obstruction by red blood cell (RBC) casts in some patients, especially in those with chronic kidney disease (CKD). Dabigatran was described earlier for warfarin related nephropathy (WRN). An animal model of WRN is developed. Recent evidence suggests that WRN-like syndromes are not confined to anticoagulation with warfarin, but may be seen with novel anticoagulants, such as dabigatran. The aim of this study was to investigate dabigatran effects on kidney function in an animal model of CKD.

Methods: Sham-operated (control) and 5/6 nephrectomy rats (5/6NE) were treated with different doses of dabigatran for 1 week. Changes in serum creatinine (Scr), hematuria and renal pathology were studied.

Results: Dabigatran resulted in 2-fold increase in aPTT in rats at 50 mg/kg/day (MKD). Dabigatran in a dose-dependent manner increased Scr and hematuria in both control and 5/6NE (Figure 1, A). Increase in Scr were noted in both groups when >100 MKD dabigatran were used. Hematuria increase and numerous RBC tubular casts in the kidney were seen in 5/6NE treated with ~25 MKD dabigatran (Figure 1, B) and in control with >100 MKD dabigatran.

Conclusions: Our data indicate that WRN represents part of a broader syndrome, which is anticoagulant related nephropathy. Dabigatran resulted in AKI not only in CKD, but in control rats as well, which was not the case in WRN. Our findings suggest that not only CKD patients, but other patients as well are at high risk of developing AKI if the therapeutic range of anticoagulation with dabigatran is exceeded. Close monitoring of kidney function in patients on dabigatran therapy is warranted.

FR-PO280
Intravital Multiphoton Microscopy Can Visualize Oxidative Damage and Tubulointerstitial Fibrosis after Kidney Ischemia-Reperfusion Injury
David M. Small,1 Washington Yamanida Sanchez,2 Glenda C. Gobe,1 Sandrine F. Roy.1 1Centre for Kidney Disease Research; 2Therapeutics Research Centre, Sch Medicine, Univ Queensland; 3Diamantina Institute, Brisbane, Australia.

Background: Acute kidney ischemia-reperfusion (IR) injury is common, serious, and may progress to chronic kidney disease (CKD). Mediators of oxidative stress exacerbate acute injury but their role in CKD is unclear. The aim of this project was to use in vivo multiphoton microscopy (MPM) to visualize IR-induced tubulointerstitial damage in real time, and correlate these with histology.

Methods: Bilateral IR (20min) was performed in male 4-6 week old C57BL6 mice followed by reperfusion. Groups compared with MPM were: control kidneys; 10min ischemia immediately at reperfusion; 20min ischemia and 2h post ischemia. 25mM dibucaine Biotec MPM, was used to excite NAD(P)H fluorescence (740nm) and collagen (900nm) in kidney microstructure. Z-stack images were acquired from three separate areas of cortex in each kidney and the average weighted lifetime (τ2) of NAD(P)H was determined. H&E staining was performed on fixed kidney post- MPM. Oxidative stress markers were determined by Western blots and immunohistochemistry.

Results: NAD(P)H and collagen fluorescence in control kidneys clearly showed structure of proximal and distal tubules, and sparse interstitial space with little collagen. With ischemia and immediately after reperfusion, tubules were swollen and NAD(P)H fluorescence increased, indicating oxidative stress. At 21 days post-IR, there was focal tubular atrophy, interstitial space expansion, intense endogenous fluorescence in remaining normal-looking tubules, and the τ2 of NAD(P)H increased significantly. Intense cytoplasmic autofluorescent "hot spots" in atrophic tubules were seen, and histology indicated these may be evidence of apoptosis. Histology confirmed other in vivo changes identified with MPM. Markers of mitochondrial destabilisation, apoptosis and autophagy were increased.

Conclusions: Oxidative stress mediates acute injury and CKD after renal IR. MPM is a powerful tool to visualize the cellular, subcellular, and molecular profile of the kidney in vivo.

Funding: Government Support - Non-U.S.
Targeting Connexin 43 Protects against Chronic Kidney Disease in Experimental Nephropathy in Mice

**Methods:** We generated RenTg mice, a genetic model of hypertension-induced CKD, with Cx43+/− mice. RenTgCx43+/− and littermates were sacrificed at 5 months (n=10/mice/group). Moreover, 11 month-old RenTg mice received during 1 month a Cx43 antisense (AS) or scrambled sequence (SCR) via minipump infusion (n=8 per group). After sacrifice kidneys were assessed for morphometry, inflammation and interstitial fibrosis.

**Results:** Renal cortex of RenTgCx43+/− mice presented lesser upregulation of VCAM-1 (2.1 fold) mRNAs (p<0.05), leading to reduced monocytic infiltration compared to RenTgCx43+/+ mice (quantification of F4-80 immunostainings showed 4.3±1% and 1.8±0.2% of cortex surface respectively, p<0.05). In addition, Sirius Red colorations showed limited renal fibrosis in RenTgCx43+/− mice (0.8% versus 1.3% of cortex surface for RenTgCx43+/+, p<0.05). Furthermore, functional and histological parameters such as albuminuria (p<0.05) and glomerulosclerosis (p<0.05) were both reduced by half in RenTgCx43+/+ mice (quantification of albuminuria and glomerulosclerosis showed 1.8±0.2% of cortex surface respectively, p<0.05). In addition, Sirius Red colorations were increased in RenTg mice with Cx43+/- mice. RenTgCx43+/- and littermates were sacrificed at 5 months (n=10/mice/group). Moreover, 11 month-old RenTg mice received during 1 month a Cx43 antisense (AS) or scrambled sequence (SCR) via minipump infusion (n=8 per group). After sacrifice kidneys were assessed for morphometry, inflammation and interstitial fibrosis.

**Conclusions:** Our results show for the first time the importance of Cx in renal diseases and may open towards new therapeutic strategies targeting Cx43 to protect against the progression of CKD.

**FR-P0821**

miR-205 Expression Correlates with Severity of Renal Involvement in a Mouse Model of Congenital Obstructive Nephropathy

**Background:** Congenital obstructive nephropathy (CON) is the leading cause of CKD in children. CON is a complex disease process involving pathological changes in kidney development and function resulting from obstructed urine flow beginning in utero. The megabladder (mgb/-) mouse is an animal model of CON that develops kidney disease secondary to a bladder-specific defect in smooth muscle development.

**Methods:** Expression levels of specific microRNAs were compared by microarray analysis on the Agilent platform and by qPCR of kidney samples from wild type and mgb-/- mice in situ hybridization and immunohistochemistry demonstrated the sublocalization of mir-205 and tubular markers within the nephron.

**Results:** There is increased expression of miR-205 across a panel of mgb/-/ kidneys compared to wild-type controls (2.94-fold, P<0.01). Furthermore, upon stratification of the mgb-/- mice according to severity of laterality, relative miR-205 expression levels rise with increasing severity of hydroureteronephrosis (Mild: 1.35-fold, P<0.02; Moderate: 2.30-fold, P<0.001; Severe: 5.32-fold, P<0.001; all values are relative to wild-type control). Thus, miR-205 expression correlates with the severity of CON in this animal model. In situ hybridization experiments show miR-205 localizes to the renal pelvis in wild-type and mgb/-/ kidneys, and to dilated collecting ducts in mgb-/-/ kidneys. In collecting ducts, miR-205 expression shows an inverse relationship with the presence of aquaporin-2 (Aqp2), suggesting a possible role for miR-205 in the physiological response to obstruction via Aqp2 expression or trafficking.

**Conclusions:** MiR-205 in the kidney increases proportionally to the degree of hydroureteronephrosis in the megabladder mouse kidney. An inverse pattern of collecting duct expression relative to Aqp2 indicates a possible role for miR-205 in regulation of water transport. Future studies will explore the target molecules and pathways affected by miR-205 in the pathogenesis and physiology of CON, as well as the potential of miR-205 as a noninvasive biomarker of renal maldevelopment or injury in congenital urolithogenic obstruction.

**FR-P0822**

Renal Epithelial Toxicity Is an Important Mechanism of Shigatoxin 2-Mediated Kidney Failure. Clinical and Experimental Evidence

**Methods:** Long-term outcome was investigated in patients with Stx-associated hemolytic uremic syndrome at the University Hospital in Frankfurt/Main, Germany. Patients with end stage kidney failure and uremia were treated with supportive therapy (without complement inhibiting antibodies). To corroborate clinical and histological data in vivo, murine models with global and tissue specific (renal tubular cells, endothelial cells and platelets) deficiencies for the Stx-receptor Gb3 were analyzed.

**Results:** Despite a severe affection [LDH 1944 U/L (753-2972), platelets 33/ld (19-124) and hemoglobin 6.2 g/dl (5.2-7.8); median (range)], all patients were discharged after 33 days (19-43) with no neurological symptoms and no dialysis requirement [creatinin 1.39 mg/dl (0.84-2.86)]. After a 12 month follow-up, the creatinine decreased to 0.90mg/dl (0.82-1.52). Analysis of kidney biopsies revealed a dominant acute tubular damage, but not thrombotic microangiopathy as the leading cause of the renal failure. To identify the tubular compartment as the determinant of the acute renal damage, mouse models were implemented. In wild-type mice, which -like humans- express Gb3 in renal epithelial tubules, Stx-mediated tubular damage led to lethal electrolyte disturbance. Tubule specific deletion of Gb3 protected mice from acute renal failure, but favored development of cerebral purpura.

**Conclusions:** Acute tubular damage is a clinically important and currently underestimated mechanism of Stx-mediated acute kidney failure. An excellent renal outcome can be achieved by supportive therapy only.

**FR-P0824**

RAGE Deletion Enhances Lupus Nephritis and Lymphoproliferative Syndrome in B6-MRL-lpr-J-Fas-/- Mice

**Background:** The RAGE receptor for Advanced Glycation End products is a multiligand receptor able to interact not only, with AGEs, but also with S100 proteins, Amyloid fibrils and nuclear proteins such as HMGB1. Following engagement RAGE induces a pro-inflammatory signal involved in a number of disease characterized by vascular pathology. Systemic Lupus Erythematosus is associated with increased expression of HMGB1 and RAGE. The exact role of RAGE in this disease is unknown.

**Methods:** To analyze the potential role of RAGE in SLE we generated mice invalidated for RAGE in the lupus prone genetic background B6-MRL-Fas-lpr/lpr. We compared these mice to littermates B6-MRL-lpr/lpr and WT mice.

**Results:** Mice invalidated for RAGE and carrying the Fas mutation (n=18) had a greater lupus nephritis and survival of the splenome (n=21). RAGE deletion in the B6-MRL-lpr/J-Fas-/- background was associated with more severe lupus nephritis (III and IV) and more frequent cutaneous lesions (75%) compared to the B6-MRL-J-Fas-lpr (25%) and WT (0%). INFγ levels were higher in the serum of the 2 groups of lupus prone mice compared to WT. In peripheral blood and in the spleen we found a significantly higher proportion of abnormal CD3+CD4+ lymphocytes and activated T cells in B6-MRL-lpr/J-Fas-/- compared to WT. These subpopulations were further increased in B6-MRL-lpr/J-Fas-/-RAGE-/- mice. Lastly we found an increased expression of TLR9 in the B6-MRL-lpr/J-Fas-/-RAGE-/- splenocytes.

**Conclusions:** Our results suggest a critical role for RAGE in regulation of lymphoproliferative syndrome in the B6-MRL-lpr/J-Fas-/- background. Deletion of RAGE in this genetic strain exacerbates lupus nephritis, lupus nephritis and cutaneous lesions. Mechanisms involved could be related to a dysregulation of apoptosis and a greater involvement of TLRs.

**FR-P0825**

An Antithrombotic Role of Hypoxia-Inducible Factor 3 in Renal Tubular Cells

**Background:** Chronic hypoxia in the tubulointerstitium is a final common pathway in CKD. Chronic hypoxia is present in different disease conditions and in different parts of the kidney in a family of hypoxia-inducible transcription factors (HIF), mainly HIF-1 and HIF-2. However, the function of a third member, HIF-3, remains elusive. In this study, we characterized the expression of HIF-3α in the ischemic kidney and investigated its functional role in tubular epithelial cells.

**Methods:** The expression of HIF-3α protein was characterized in models of renal fibrosis by immunohistochemistry. In vitro, the effect of HIF-3 on the induction of HIF-1 target genes was examined by luciferase reporter assays and real-time PCR. Hypoxia-responsive cells were identified by the bzlil oxide (LOX) promoter by luciferase reporter assays and site-directed mutagenesis. Migration of tubular epithelial cells in hypoxia was evaluated by scratch assays, using human proximal tubular cells (HK-2) transduced with HIF-3α or MOCK, or in CaK-1 renal cancer cells transfected with HIF-3α siRNA or its control. The effect of HIF-3α on E-cadherin and fibronectin expression was examined by promoter assays and immunoblotting, respectively.

**Results:** In immunohistochemistry of renal fibrosis models, HIF-3α protein was observed in the nuclei of ischemic tubules located in the outer medulla. In vitro, overexpression of HIF-3α suppressed the hypoxic induction of LOX most consistently and strongly among other HIF-1 target genes. Promoter analysis of the human LOX gene revealed multiple hypoxia-responsive enhancers, against each of which HIF-3α had
an inhibitory effect. Functionally, overexpression of HIF-3α in human proximal tubular cells (HK-2) suppressed cell migration under hypoxia, which was phenocopied by pharmacological inhibition of LOX and was offset by LOX overexpression. Furthermore, HIF-3 decreased the expression of fibrotenectin and counteracted the loss of E-cadherin in hypoxic renal carcinoma cells (RCC).

Conclusions: Results of these studies identify HIF-3α as a novel antiangiogenic gene which potentially plays a role in ischemic renal diseases. Funding: Government Support - Non-U.S.

FR-PO826

P2Y1 Receptor Deficiency Aggravates Progression in a Model of Chronic Renal Failure

Sebastian Alexander Pothoff, Johannes Stegbauer, Lars C. Rump, Oliver Vonend. Dept of Nephrology, Medical Faculty, Univ Düsseldorf, Düsseldorf, Germany.

Background: In chronic kidney disease, sympathetic overactivity, endothelial dysfunction and increase in shear stress contribute to a higher extracellular abundance of ATP. P2Y1 receptors play an important role in renal tubule function, inflammation and proliferation. Knockout mice (P2Y1-R KO) were used in order to investigate the impact of P2Y1 receptors in a model of chronic kidney failure.

Methods: Wildtype (WT) and P2Y1-R KO mice underwent subtotal nephrectomy (SNX) with a follow up of 56±2 days. Sham surgery mice served as controls. Survival, kidney function, kidney size, blood pressure (BP), glomerulosclerosis index were assessed.

Results: During the observation period, survival was inferior in P2Y1-R KO SNX mice. After 56 days, SNX caused an increase in serum creatine and serum urea with a significant decrease in creatinine clearance. The decline in creatinine clearance was significantly more pronounced in P2Y1-R KO than in WT mice (day 56, P2Y1-R KO vs. WT: 53.9±7.7 vs. 84.3±8.7 μmol/min, p<0.05). BP increased after SNX to a higher extent in P2Y1-R KO mice compared to WT mice (day 56, P2Y1-R KO vs. WT: 177±2 vs. 156±7 mmHg). After SNX, P2Y1-R KO showed a 2.5-fold higher urinary albumin-creatinine ratio compared to WT (day 56, p<0.05). 56 days after SNX, in contrast to P2Y1-R KO mice, WT remnant kidneys showed significant hypertrophy (increase of kidney weight compared to day 0: P2Y1-R vs. WT: 113±6 vs.150±9 g). Markers for tissue damage (TGF-β1, PAI-1) and profibrotic target genes (MCP-1) were significantly upregulated in P2Y1-R KO compared to WT SNX mice. In cultured glomerular epithelial cells, ATP induced a significantly dose-dependent increase in DNA synthesis up to 180±1.20%.

Conclusions: P2Y1-R KO has a detrimental impact on outcome after SNX compared to WT mice. Increased UAAR and absence of compensatory hypertrophy are likely the cause for the observed findings. The P2Y1 receptor is crucial for blood pressure regulation and tissue adaptation after induction of chronic kidney disease. Funding: Government Support - Non-U.S.

FR-PO827

Dickkopf Related Protein-1 Attenuates Connective Tissue Growth Factor Induced Fibrogenic Responses in Pericytes by Binding to LRP-6


Background: Pericytes are mesenchymal cells that are found in the periarteriolar capillaries. Recent genetic fate-mapping studies have identified pericytes and closely related fibroblasts as the major progenitors of scar-forming myofibroblasts. Understanding mechanisms by which pericytes become myofibroblasts is critical in development of therapeutics to treat kidney disease. We have recently reported a central role for WNT signaling pathways in this process. CTGF has been shown to be an important regulator of kidney disease. We have recently reported a central role for WNT signaling pathways in this process. Here we investigate the role of CTGF in pericyte functions and its capacity to signal via the WNT pathway.

Methods: Coll1a1-GFP, TCF-LEF1:ZEB1-GFP, LRPF6fox/LRPF6fox mice were used to generate primary cell cultures. Synthesis and purification of recombinant DKK-1.

Results: CTGF induces myofibroblast gene activation, migration, morphological changes and stress fiber formation in pericytes and these effects are abolished by DKK-1. LRPF6 gene silencing, blockade of WNT0 blockade. CTGF rapidly phosphorylates the WNT co-receptor, LRPR. Although CTGF activates WNT/betacatenin signaling in kidney pericyte cultures and this is inhibited by recombinant DKK-1, the functional changes in response to CTGF are predominantly independent of β-catenin translocation. CTGF rapidly induces JNK and MAP kinase activity, that are critical in CTGF responses in pericytes. DKK-1 blocks these responses.

Conclusions: DKK-1 is a candidate therapeutic protein that potentially inhibits fibrogenesis by mechanisms including blockade of CTGF induced fibrotic responses.

FR-PO828

Deletion of Extrarenal NADPH-Cytochrome P450 Reductase Causes Vascularization in Renal Proximal Tubular Epithelial Cells

Senyan Liu,1 2 Changlin Mei,1 Jun Gu.2 1Div of Nephrology, Shanghai Changzheng Hospital, China; 2Wadhurst Center.

Background: Vascularization is a nonspecific histologic change for cells. It can be observed in many conditions. The NADPH P450 reductase (CPR) is needed for activity of microsomal cytochrome P450 (P450) monooxygenases. Cpr-low mouse model was generated to study the function of P450s. In previous study we found the vascularization in renal proximal tubular epithelial cells (PTECs) of 6-month-old male Cpr-low mice.

Methods: Oil red O staining and transmission electron microscopy (TEM) were performed to figure out the origin of vacuoles. Serum creatinine levels were determined. Quantitative PCR and immunohistochemistry from proximal tubule (Cpr-null mice) and Cpr-low mice (XPT-CL), liver-Cpr-null mice (LCN) and extraprotontubular-Cpr-low mice (XH-CL) mice were examined. Immunofluorescence double staining was done to study the relationship between CPR expression and vacuoles in proximal tubules.

Results: Our results showed these vacuoles were Oil red O and PAS negative. TEM examination showed these vacuoles were lysosome origin. The mice with proximal vascularization had normal serum creatinine levels. Beside Cpr-null mice, the vacuolization was seen in kidney of XPT-CL mice and XH-CL mice, not in LCN mice and LCN mice. Double knockout showed vacuoles had no relation to CPR expression in proximal tubules.

Conclusions: These results suggested that vascularization in proximal tubular tubules of Cpr-low mice was caused by deletion of extra-proximal tubular or extra-hepatic >cr gene. The significance of this vascularization need further study. Funding: Government Support - Non-U.S.

FR-PO829

Feedback Loops between the Kidney and Peripheral Organs Link Proteinuria and Hypertiglyceridemia in Nephrotic Syndrome

Camille E. Mace,1 Lionel C. Clement, 1 C. Avila-Casado,2 Sumant S. Chugh. 1Medicine / Nephrology, Univ of Alabama at Birmingham; 2Pathology, UHN-Toronto General Hospital.

Background: Circulating levels of Angiopoietin-like-4, a PPAR target gene, are increased in patients with nephrotic syndrome when proteinuria reaches nephrotic levels. Unlike podocyte secreted hyposialylated Angptl4, circulating Angptl4 is fully sialylated and does not induce proteinuria.

Methods: We conducted Angptl4 mRNA expression studies in animal models of nephrotic syndrome, and noted Angptl4 upregulation in heart, skeletal muscle, liver and adipose tissue.

Results: Circulating Angptl4 had 2 major effects (a) Inhibiting lipoprotein lipase (LPL), reducing hydrolysis of triglycerides to free fatty acids (FFA), reducing FFA uptake into heart, skeletal muscle and adipose tissue, and causing hypertriglyceridemia. We found significantly elevated plasma FFA/albumin ratio in nephrotic patients and in animal models of MCD and FSGS. Loss of urinary albumin with low fatty acid levels in nephrotic syndrome and progressive hypoalbuminemia were the principal determinants of increased plasma FFA/albumin ratio. (b) Circulating Angptl4 binds to the glomerular endothelium and reduces proteinuria. Using recombinant Angptl4, transgenic rats and beta 5 integrin -/- mice, we showed that reduction in proteinuria was mediated by binding to alphav beta5 integrin. Injection of four human Angptl4 mutants with reduced LPL interaction reduced proteinuria without inducing hypertriglyceridemia in Buffalo Mna rats (FSGS) and Zucker Diabetic Fatty rats.

Conclusions: In summary, there are two feedback loops in nephrotic syndrome mediated by FFA and Angptl4. First, proteinuria results in selective loss of albumin with low FFA levels, raising plasma FFA/albumin ratio, increasing FFA entry in peripheral organs, which activates PPARs, increases Angptl4 expression and secretion, that inhibits hydrolysis of triglycerides, thereby reducing FFA uptake, but inducing hypertriglyceridemia. Second, the increased circulating Angptl4 reduces proteinuria by binding to glomerular endothelial alphav beta5 integrin, which, reduces urinary loss of low FFA bound albumin, and decreases the plasma FFA/albumin ratio. Funding: NIDDK Support

FR-PO830

The Effect of GSK-3β in the Glomerular Injury of db/db Mouse Diabetic-Nephropathy Mice

Zhangsuo Liu.1,2 Nephrology, The First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China; 1Key-Disciplines Laboratory Clinical-Medicine Henan, Zhengzhou, Henan, China.

Background: To observe the effect of BIO and diabetic nephropathy on EMT, GSK-3β expression and glomerular injury in the kidney of db/db mice, and to explore the possible mechanism of proteinuria and glomerular injury in DM, by determining whether EMT is caused by high glucose.

Methods: Male db/db mice were served as normal control. The age-matched db/db mice were randomly divided into BIO treated group and untreated group. Each group were sacrificed 8 mice every 3 weeks. On the day before sacrifice, mice were individually housed in metabolic cages for urine collection over 24 hours. Sections of renal tissues were used to observe structural changes with electron and light microscope. Expression of nephrin, α-SMA, GSK-3β, β-catenin, VDR, etc. were quantified by Western blot, RT-PCR or immunofluorescence. And the activities of GSK-3β were assayed by TRAPEZE enzyme detection kit.

Results: 1. Diabetic db/db mice had high albuminuria and remained hyperglycemic. BIO administration attenuated albuminuria, but had no significant effect to blood glucose. 2. Compared with NC group, the expressions of epithelial phenotype markers and VDR were downregulated time-dependently. And the expressions of β-catenin, snail and mesenchymal phenotype markers did the opposite. 3. The expression and activity of GSK-3β in cortex of db/db mice were time-dependently upregulated, compared with db/+m mice. 4. BIO administration to db/db mice suppressed the trends mentioned in result 2 and 3, and alleviated the pathologic changes caused by diabetic nephropathy.
Conclusions: 1. DM could lead renal cortex of db/db mice undergo EMT, BIO could partially inhibit it. 2. In high glucose conditions, GSK-3β could probably regulate EMT through VDR and other factors, besides Wnt11/beta-catenin signaling. 3. In diabetic kidney, BIO could protect renal function through reducing the urine albumin excretion, but not regulating the blood sugar.

Funding: Government Support - Non-U.S.

FR-PO831
Extracellular Sulfatases Regulate PDGF Signaling and Promote Nephropathy in Diabetes Yasutoshi Takashima, Hiroshi Yashiro, Kumi Ohashi, Hanako Yamashita, Satoshi Haru, Namiko Kobayashi, Toshiharu Ueno, Masayuki Masu, Kazuko Keino-masu, Michio Nagata. 1Renal Pathology, Univ of Tsukuba, Tsukuba, Ibaraki, Japan; 2Molecular Neurobiology, Univ of Tsukuba, Tsukuba, Ibaraki, Japan.

Background: Growth factors have important roles to regulate glomerular homeostasis. Extracellular sulfatase (Sulf) 1 and 2 are known to regulate growth factors by controlling growth factor binding with intrinsic 6-O sulfation in HSPGs. Last ASN, we demonstrated Extracellular sulfatase (Sulf) 1 and 2 are known to regulate growth factors by controlling growth factor binding with intrinsic 6-O sulfation in HSPGs. In addition, we also showed that Sulf1 knockout mice exhibit impaired glomerular hyperfiltration, that Sulf1 deficiency partially inhibits it. 2. In high glucose conditions, GSK-3β activity is increased and GSK-3β partly inhibits it. 3. In diabetic kidney, BIO could protect renal function and tubulointerstitial nephritis induced by an adenine-containing diet through reducing the urine albumin excretion, but not reducing the urine albumin excretion.

Methods: STZ-induced diabetes in Sulf DKO and Wild type(WT) was examined (100 mg/Kg BW, n=6 each). Glomerulopathy was estimated by morphometric counting of mesangial lesion as previously shown. mRNA expressions for PDGF-B, PDGF-D and its receptor and mesangial phenotype change’s marker (α-SMA) were done by real time PCR. Protein expression localization of growth factors, their receptor and protein phospho-sulfated by PDGF signaling were estimated by western blotting, and immunohistochemistry.

Results: STZ-treated Sulf DKO mice showed significantly milder mesangial changes compared to those of STZ treated WT mice at 12 weeks. STZ-treated WT mice revealed significant increase in PDGF-B, PDGF-D and its receptor and mesangial phenotype change’s marker (α-SMA) were done by real time PCR. Protein expression localization of growth factors, their receptor and protein phospho-sulfated by PDGF signaling were estimated by western blotting, and immunohistochemistry.

Conclusions: Sulf1 may modulate PDGF signaling in glomeruli and promote mesangial lesions under diabetic mellitus.

Funding: Government Support - Non-U.S.

FR-PO832
Pharmacological Stabilization of Hypoxia Inducible Factors Ameliorates Adenine-Induced Tubulointerstitial Nephritis Gunmar Schles, Bernd Klänke, Kerstin U. Amann, Kai-Uwe Eckardt, Carsten Willam. 1Nephrology and Hypertension, Univ Hospital Erlangen, Erlangen, Germany; 2Nephropathology, Univ Hospital Erlangen, Erlangen, Germany.

Background: Chronic inflammation, vascular rarefaction and extensive fibrosis of the tubulointerstitium are common hallmarks of progressive chronic kidney diseases (CKD). All three processes impair the oxygen supply to the renal tissue and can thus lead to a vicious circle. The Hypoxia Inducible Factors (HIF) are transcription factors which have a key position in regulating gene transcription under hypoxia and ischemia in order to adapt cells and organs to low oxygen tensions. In experimental models of acute kidney injury, genetic or pharmacological stabilization of HIF led to better preserved kidney structure and function. We therefore aimed to investigate the effects of HIF stabilization in an experimental CKD model.

Methods: Male C57Bl/6 mice were fed with an adenine-supplemented diet for 3 weeks to induce chronic tubulointerstitial nephritis. Mice were treated with either two HIF stabilizers (pyridine-2,4-dicarboxylate, PDA; 2-(1-Chloro-4-hydroxyisquinoline-3-carboxamido) acetic acid, ICA) or vehicle for 3 weeks starting concomitantly with the adenine-containing diet.

Results: In control animals creatinine levels rose from 0.09±0.01 mg/dl to 0.39±0.11 after 3 weeks and kidneys showed extensive tubulointerstitial fibrosis. Pharmacological HIF stabilization reduced serum creatinine by 21% (PDA) and 36% (ICA) as well as proteinuria (115% and 37%, respectively). Interstitial fibrosis (assessed by Sirius Red, fibronectin and collagen IV immunohistochemistry, tissue collagen content, and real-time PCR for fibrosis-related genes) and peri-tubular capillary rarefaction (MECA-32 immunohistochemistry, real-time PCRs for endothelial markers) were not significantly improved by both substances. But both HIF stabilizers markedly reduced tissue inflammation and fibrosis-related gene expression in the macrophages suggesting a reduced inflammatory reaction due to HIF stabilizer treatment.

Conclusions: HIF stabilizers ameliorated kidney function in a model of chronic tubulointerstitial nephritis induced by an adenine-containing diet by reducing inflammatory cell infiltration.

Funding: Government Support - Non-U.S.

FR-PO833
Preconditioning Activation of Hypoxia-Induced Factors Improves the Impaired Angiogenic Response to Ischemia in Chronic Kidney Disease in Rats Karl F. Hilgers, Isabel Schellinger, Nada Cordasic, Bernd Klänke, Johannes Jacobi, Rafael Heiss, Christoph Daniel, Andrea Hartner, Kai-Uwe Eckardt, Carsten Willam, Kerstin U. Amann. Univ of Erlangen-Nuremberg.

Background: Improving capillary supply in response to ischemia is an important mechanism for adaptation to macrovascular disease. This mechanism is impaired in chronic kidney disease (CKD). We tested the hypothesis that preconditional activation of hypoxia-inducible factors (HIF) improves the impaired capillary angiogenesis in response to ischemia.

Methods: CKD was induced in male rats by 5/6 nephrectomy; control rats were sham operated. Eight weeks later, ischemia of the right limb was induced by ligation and resection of the femoral artery. Preconditional activation of HIF target genes was performed by adding 0.1% CO to the rats’ breathing air for 6 h, beginning 24 h before the onset of ischemia. Rats were sacrificed 24 h or two weeks after the onset of ischemia to analyze gene expression or capillary density, respectively. Capillary area was assessed after immunostaining for CD31 of the gastrocnemius muscle.

Results: In control rats, capillary area increased in the ischemic hindlimb by 44±3 % 2 weeks after ischemia compared to the non-ischemic limb (p< 0.001, N=10). In contrast, there was no significant increase in the ischemic over the opposite limb in CKD rats (N=10). Pretreatment with CO did not affect the capillary density in non-ischemic limbs of CKD and control rats, nor in ischemic limbs of control rats. However, CO significantly augmented the increase of capillary area after ischemia in CKD rats (80±22% over the opposite limb, p<0.001, N=6). RT-PCR analysis showed a 2.4fold increase of VEGF after 24 h in non-CKD rats and was blunted in CKD animals (1.76fold, p<0.05). CO treatment increased VEGF expression 4.2fold in the non-ischemic and 7.2fold in the ischemic limb in CKD rats (p<0.001). The expression of other known HIF target genes, including VEGFR1, IGFBP-3, PAI-1 and HIF-2, was also induced by CO.

Conclusions: Our data provide proof of principle that HIF activation can correct the impaired angiogenic response to ischemia in rats with chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-PO834
Podocyte-Specific VEGF Overexpression Stimulates Glomerular Angiogenesis but Is Insufficient Alone to Prevent Progression of Existing Sclerosis Shaqjun Liu,1,2 Anne P. Wilson,1 Jia Ma,2 Haichun Yang,1 Agnes B. Fogo. 1Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN; 2Pediatric Nephrology, Vanderbilt University Medical Center, Nashville, TN.

Background: Glomerulosclerosis is characterized by increased matrix, obliteration of capillary lumens and loss of podocytes. VEGF is a secreted by podocytes and induces endothelial tip cell formation and new vessel branches. VEGF is decreased in sclerotic glomeruli. In this study, we investigated whether up-regulation of human VEGF in podocytes after development of glomerulosclerosis could induce angiogenesis and interrupt progression of sclerosis.

Methods: Subtotal nephrectomy (5/6Nx) was performed in 129sv Teto-podocin-Cre/human VEGF Iox (RV, n=9) and Teto-podocin-Cre mice (R, n=11). At 8 weeks after 5/6 nephrectomy, ischemia was done and sclerosis assessed (0-4 scale). VEGF was induced by doxycycline in drinking water. Mice were sacrificed four weeks later. Change in blood pressure, proteinuria, and glomerular morphology from biopsy to autopsy were assessed. DLL4, a marker of endothelial tip cells, was detected by immunostaining. VEGF was quantitated in isolated glomeruli.

Results: Human VEGF expression in RV glomeruli was significantly induced after doxycycline (44.9 ± 14.6 pg/mg), and mouse VEGF was also increased. Total glomerular VEGF in RV mice was 3.2 folds higher than R mice (276.0 ± 88.1 vs. 85.9 ± 83.6pg/mg , P<0.05). RV mice had significantly reduced blood pressure, but there were no effects on proteinuria and glomerulosclerosis. Glomerular volume was not affected by VEGF induction. However, there were more DLL4 positive endothelial cells (double staining of DLL4 and CD31 in glomeruli of RV induced mice than R control (RV 0.7±0.3 vs. R 0.2±0.2, p<0.05).

Conclusions: Our data indicate that overexpression of VEGF in podocytes stimulates angiogenesis, but is not sufficient alone to prevent glomerulosclerosis progression. Thus, we speculate that coordinated interventions to augment angiogenesis and decrease matrix are necessary to optimize effects on progressive glomerulosclerosis.

Funding: NIDDK Support

FR-PO835
Klotho Reduces Kidney Injury and Fibrosis by Targeting Renin-Angiotensin System Li Li Zhou, Dong Zhou, Roderick J. Tan, Youhua Liu. 1Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; 2Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Activation of the renin-angiotensin system (RAS) plays a pivotal role in the pathogenesis of kidney disorders in both animal models and human subjects. We recently demonstrated that Klotho, an anti-aging hormone and an endogenous antagonist of Wnt/beta-catenin signaling, is lost in renal tubular epithelia in multiple CKD models. As Wnt/beta-catenin controls the expression of multiple RAS genes, we hypothesized that Klotho may protect kidneys by targeted inhibition of RAS activation in diseased kidneys.

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

554A
Methods: To test this, a remnant kidney model after 5/6 nephrectomy was utilized in adult CD-1 male mice. Groups of mice were intravenously administered the expression vector encoding the secreted form of Klotho (pV5-sKlotho) through hydrodynamic-based gene delivery. At 5 weeks after 5/6 nephrectomy, mice were killed and kidneys collected for renal pathology and various analyses.

Results: We found that kidney injury was evident, characterized by elevated albuminuria and serum creatinine, and excessive deposition of interstitial matrix proteins. These lesions were accompanied by loss of kidney Klotho, and upregulated expression of RAS components including angiotensinogen (AGT), renin, angiotensin-converting enzyme (ACE) and angiotensin II receptor type 1 (AT1). In vivo expression of exogenous Klotho inhibited renal fibrogenic activity, abolished the induction of multiple RAS components including AGT, ACE, renin and AT1, and ameliorated morphological lesions and fibrosis. In cultured human proximal tubular epithelial cells (HKC-8), ectopic expression of Wnt1 or Wnt4 induced the expression of all major components of RAS, and co-transfection of Klotho expression vector dose-dependently blocked Wnt-triggered RAS activation.

Conclusions: Taken together, these results suggest that Klotho exerts its renal protection by targeted inhibition of RAS, a key pathogenic pathway in the evolution and progression of kidney and cardiovascular diseases.

Funding: NIDDK Support

FR-PO836

Exploring the Mechanistic Pathways in Developing Renal Injury Using the Rat UUO Model and Next Generation Sequencing (NGS) Steven M. Weldon, Thomas B. Freeman, William Logging, Peng Sun, Glenn Gibson, Xiaojun Ren, Hu Sheng Qian, Glenn A. Reinhardt. Cardiometabolic Diseases and Scientific Knowledge Discovery, Boehringer Ingelheim Pharm Inc; Ridgefield, CT.

Background: Unilateral ureteral obstruction (UUO) is a well established model used to mimic the pathophysiology involved in tubulointerstitial fibrosis (TIF). Key pathological features of UOO include oxidative stress, inflammation, apoptosis, vascular/tubular loss and TIF. NGS can generate large, reproducible data sets in a timely manner and is now becoming standard of care.

Methods: We used UOO+NGS to further explore the transcriptional regulation of molecular pathways and biological processes (BP) associated with developing TIF in rats. Rats received sham or UOO/enalapril (ENA;30 mg/kg) for up to 10d post-UOO. mRNA from cortical tissue was subjected to NGS and computational analysis to explore BP and correlated with expression of NADPH oxidases.

Results: Obstruction FR-PO837

Renoprotective Effect of Metformin in Mice with Unilateral Ureteral Obstruction Rita de Cassia Cavagneri, Denis Feliu, Hanna E. Abboud. Dept of Medicine, Univ of Texas Health Science Center, San Antonio, TX.

Background: Metformin, an indirect activator of adenosine monophosphate-activated kinase (AMPK) is widely used in patients with type 2 diabetes. Metformin has been shown to have renoprotective effects in early diabetic nephropathy. We studied the effect of metformin on inflammation and fibrosis in obstructive nephropathy.

Methods: Adult male mice were subjected to unilateral ureteral obstruction (UUO) or sham operated and subdivided into 6 groups: S (n=6), sham-operated mice, UUO (n=6), mice subjected to unilateral ureteral obstruction model; and UUO+Met (n=6), UUO mice receiving metformin by gavage (200mg/kg/day). Animals were followed for 7 days and injury of the kidney was studied. Markers for inflammation (F4/80-positive macrophages; VCAM-1; TNF-alpha), tubular injury (E-cadherin, myofibroblasts (alpha; SMA) and fibrosis (Fibronectin, Collagen and TGF-beta) were analyzed. AMPK activity was measured by in vitro kinase assay. Reactive oxygen species production was measured and correlated with expression of NADPH oxidases.

Results: Metformin significantly reduced inflammation (macrophage infiltration, TNF-alpha and VCAM-1 expression), tubular injury, interstitial fibroblast activation and tubulointerstitial fibrosis (collagen and fibronectin expression and deposition) in obstructed kidney compared to sham kidneys. When compared to obstructed kidneys and increased by metformin suggesting that metformin acts through activation of AMPK. Superoxide anion production and Nox4 and Nox2 expression were significantly increased in obstructed kidneys and were inhibited by metformin.

Funding: NIDDK Support

FR-PO839

The Macula Densa Controls Glomerular Cell Remodeling James L. Burford,1 Karie G. Villanueva,2 Anne Riquier-brison,1 Sanjeev Kumar,3 Jing Liu,4 Andrew P. McMahon,5 Janos Peti-Peterdi.1, 2Physiology and Biophysics, Univ of Southern California, Los Angeles, CA; 3Stem Cell Biology and Regenerative Medicine, Univ of Southern California, Los Angeles, CA.

Background: Macula densa (MD) cells are strategically positioned at the vascular entrance of the glomerulus and control renal hemodynamics and renin. Here we addressed if MD cells play non-traditional roles in glomerular cell plasticity/remodeling.

Methods: Serial multiphoton microscopy of the intact kidney in vivo was performed in NG2-DeRed mice to track chondroitin sulfate proteoglycan (NG2, an established progenitor cell marker) expressing pericytes over several days. In established conditions of strong MD stimulation (low salt diet/ACE inhibition) and unilateral ureteral ligation (UUO), MD cells were FACs sorted from freshly digested kidneys of mice with MD-specific expression of GFP and their RNA isolated.

Results: In established conditions of strong MD stimulation (low salt diet/ACE inhibition) and unilateral ureteral ligation (UUO), increased renal interstitial density and migration of NG2+ cells to the MD area and then into the glomerular parietal layer and mesangium were observed. NG2, Kif6, and renin immunofluorescence showed a significantly increased number of NG2+ proliferating cells in the MD area with partial co-localization with renin in response to low salt diet/ACEI for one week. The increased density of NG2+ cells was 70% inhibited by the administration of the selective COX-2 inhibitor SC58236. GUDMAP-based microarrays confirmed high expression of known MD-specific genes and identified new MD-enriched genes including Car15, Emb, Klk1b2, Wnt10a, Bmp3, Tnfrsf9, Cx3cr1, Slc7a6 that play roles in cell growth, development, guidance, and extracellular matrix interactions.

Conclusions: Our results suggest that NG2+ pericytes maybe an important progenitor cell population in the kidney. Also, via MD-derived paracrine factors MD cells play new important roles in the maintenance and remodeling of the glomerulus and the renal interstitium in health and disease.

Funding: NIDDK Support

FR-PO840


Background: Both renin angiotensin system (RAS) and mTOR pathways have been reported to play a critical role in the development and progression of HIVAN. However the role of the RAS pathway in the activation of mTOR pathway has not been investigated so far. We hypothesize that the RAS activates mTOR pathway in HIVAN.

Methods: Renal cortical sections and tissues of age and sex matched control and HIV transgenic mice (Vpr) were evaluated for the expression of renin, angiotensinogen (Agt), phospho-mTOR and phospho-p70S6K. To determine the role of renin, control and Vpr mice were administered either normal saline or amlirkine (50 mg/kg/d) by miniosmotic pump, an inhibitor or renin for 4 weeks followed by renal tissue probing for the expression of phospho-mTOR, phospho-p70S6K, and actin. To determine the effect of HIV on kidney cell renin expression, mouse proximal tubular cells (MTC) were transduced with either empty vector (EV/MTC) or NL4-3(HIV/MTC) and evaluated for renin expression. To determine the effect of renin and Ang II, MTCs were treated with renin and then evaluated for phospho-p70S6K.

Results: Renal tissues of Vpr mice displayed enhanced expression of renin, phospho-mTOR and phospho-p70S6K. Vpr mice receiving amlirkine displayed attenuated expression of phospho-mTOR and phospho-p70S6K when compared to saline receiving Vpr mice. HIV+EV expressed enhanced expression of renin, phospho-mTOR and phospho-p70S6K. However, this effect of HIV was inhibited by amlirkine. Both renin and Ang II enhanced tubular cell expression of phospho-p70S6K in a dose dependent manner. Since MTC silenced for PRR displayed attenuated expression of phospho-mTOR in response to renin, it appears that the RAS contributes to the activation of mTOR pathway both by renin as well as by Ang II.

Conclusions: HIV enhances activation of mTOR pathway in HIVAN via generation of both renin and Ang II.

Funding: NIDDK Support
FR-P0840
Sclerotic Glomerular Phenotype in HIV-Associated Nephropathy Is Dependent on the Activation of the Renin Angiotensin System

Background: HIV-associated nephropathy (HIVAN) is a common complication of HIV-1 infection in patients with African ancestry in general and with APOL1 gene risk variants in particular. Although collapsing glomerulopathy is considered a hallmark of HIVAN, significant numbers of glomeruli in patients with HIVAN also display other variants of FSFG. We proposed that collapsed glomeruli as well as glomeruli with other variants of FSFG are manifestations of HIVAN and their prevalence depends on associated host factors. We explored whether renin-angiotensin system (RAS) contributes to sclerotic, collapsing or both variants of HIVAN. We hypothesized that activation of the RAS will contribute predominantly to sclerotic lesions rather than to collapsing ones.

Methods: To evaluate the role of the RAS we have used a genetically engineered mouse model of HIVAN (Tg26) with two and four copies of angiotensinogen (Agt) gene (Tg26/Agt2 and Tg26/Agt4). Severity of renal lesions was scored in 8 weeks old control and Tg26 mice with 2 and 4 copies. To confirm the role of the RAS on the development of glomerular phenotype, Tg26 mice in groups of 4, were administered either normal saline, aliskiren (50 mg/Kg, a renin inhibitor), aliskiren + captopril (20 mg/Kg, an angiotensin blocker) for 4 weeks followed by scoring of severity of renal lesions.

Results: In Tg26/Agt2, 1 out of 6 glomeruli exhibited sclerosed phenotype, whereas 1 out of 25 glomeruli displayed collapsed phenotype; on the other hand, in Tg26/Agt4, 1 out of 3 glomeruli exhibited sclerotic phenotype and only 1 out of 7 glomeruli showed collapsed phenotype. In all experimental groups there was significant reduction of percentage of sclerosed glomeruli and only minimal reduction in collapsed glomeruli comparing to normal saline receiving Tg26/Agt2.

Conclusions: These findings suggest that manifestation of sclerotic phenotype in HIVAN is predominantly dependent on the activation of the RAS.

Funding: NIDDK Support

FR-P0841
HIV Induces Podocyte Vitamin D Receptor Downregulation through Epigenetic Factors

Background: Recent reports indicate that HIV induces podocyte injury through down regulation of vitamin D receptor (VDR) and associated activation of renin angiotensin system (Am J Physiol, 2013). However, the involved mechanism of HIV-induced down regulation of VDR is not clear. Conditionally immortalized human podocytes (CIHP) were transduced with either empty vector (EV/CIHP) or NL4-3 construct (HIV/CIHP). Protein blots of EV/CIHP and HIV/CIHP were probed for Dmnt, 1 and 3 and 3 reboxed for actin. Conditionally immortalized human podocytes (CHPI) were transduced with either empty vector (EV/CIHP) or NL4-3 construct (HIV/CIHP). Protein blots of EV/CIHP and HIV/CIHP were probed for Dmnt, 1 and 3, and additionally, cpg methylation status of EV/CIHP and HIV/CIHP was evaluated by Epipicket mRNA assay and bisulphite pyrosequencing. To determine the potential of VDR agonist on normalization of VDR in HIV/CIHPs, EV/CIHPs and HIV/CIHPs were incubated in medium containing EB1089 (1nM, a VDR agonist) for 24h (n=3) followed by protein blots preparation and subsequent their probing for VDR and actin expression. To confirm the role of hypermethylation in VDR expression, effect of 5-azacytidine (AZAC), a demethylating agent was evaluated on VDR expression in HIV/CIHP in the presence/absence of a VDR agonist.

Results: Renal tissues of age and sex matched control Tg26 (n=4) were assayed for expression of Dnmt. Epstein assay displayed more than 70% VDR cpg methylation in HIV/CHPs. Bisulphite pyrosequencing studies in HIV/CHPs confirmed enhanced methylation of cpg islands when compared to EV/CHPs. Both AZAC alone and EB1089 alone increased VDR expression in HIV/CHPs but only sub-optimally. However, AZAC exhibited an additive effect on EB1089 in enhancing VDR expression by HIV/CHPs.

Conclusions: HIV induced podocyte VDR expression through hypermethylation of VDR. Optimal expression of VDR could be achieved only by combining VDR agonist with a demethylating agent.

Funding: NIDDK Support

FR-P0842
Nicorandil Protects Podocyte from Purumycin Aminonucleoside-Induced Injury in the Rats
Takahisa Kawakami,1,2 Shuyu Ren,2 Kelly L. Hudkins,2 Ivan G. Gomez,2 Allie M. Roach,2 Charles E. Alpers,2 Jeremy Stuart Dufield,2 1Univ of Tokyo; 2Univ of Washington, Seattle.

Background: Nicorandil is a K channel opener, reduces proteinuria and ameliorates podocyte injury seen in PAN nephrosis rats. Nicorandil may serve as a novel strategy for kidney diseases involving podocyte injury.

Methods: Nicorandil induced podocytopathy was employed in mice and in conditionally immortalized mouse podocytes and podocyte dysfunction evaluated.

Results: In cultured podocytes, nicorandil elicited immediate cellular shrinkage and actin cytoskeleton disorganization as evidenced by increased cortical F-actin and diminished actin serving filaments that accounts for the loss of long bundled F-actin. Lithium counteracted adriamycin-induced collagen hyperphosphorylation by suppressing the activity of a collagen phosphatase, phosphogluconase (SSH2). In addition, adriamycin-induced hyperphosphorylation of paxillin, a focal adhesion-associated adaptor protein, was abrogated by lithium. Inhibitory phosphorylation of GSK3β seems to be essential and sufficient for lithium’s effects because ectopic expression of an uninhibitable mutant of GSK3β abrogated, whereas overexpression of a kinase dead GSK3β mimicked lithium’s activities in podocytes. Of note, both paxillin and SSH2 interacted with GSK3δ in podocytes and served as putative substrates for GSK3δ. In adriamycin injured mice, a single low dose of lithium attenuated proteinuria by more than 70%, associated with an early prevention of foot process effacement. Consistently, lithium therapy inhibited GSK3β activity in injured glomerul and blunted collagen and paxillin activities in podocytes.

Conclusions: Inhibition of GSK3β by lithium protected against podocyte injury and proteinuria by reinstating podocyte actin cytoskeleton stability via SSH2/collN pathway and regulating focal adhesion associated paxillin.

Funding: NIDDK Support

FR-P0843
A Single Low Dose of Lithium Protects against Proteinuria by Improving Podocyte Focal Adhesion and Actin Cytoskeleton Integrity
Wetwei Xu,1 Yan Ge,2 Zhi-hong Liu,2 Rujian Gong.1 1Nephrology, Brown Univ, Providence, RI; 2Research Institute of Nephrology, Nanjing, China.

Background: Evidence suggests that glycogen synthase kinase (GSK) 3β plays a determinant role in acute and chronic renal diseases. This study examined the effect of lithium, a selective inhibitor of GSK3β, on podocytopathy.

Methods: Adriamycin induced podocytopathy was employed in mice and in conditionally immortalized mouse podocytes and podocyte dysfunction evaluated.

Results: Adriamycin induced immediate cellular shrinkage and actin cytoskeleton disorganization as evidenced by increased cortical F-actin and diminished actin serving filaments that accounts for the loss of long bundled F-actin. Lithium counteracted adriamycin-induced collagen hyperphosphorylation by suppressing the activity of a collagen phosphatase, phosphogluconase (SSH2). In addition, adriamycin-induced hyperphosphorylation of paxillin, a focal adhesion-associated adaptor protein, was abrogated by lithium. Inhibitory phosphorylation of GSK3β seems to be essential and sufficient for lithium’s effects because ectopic expression of an uninhibitable mutant of GSK3β abrogated, whereas overexpression of a kinase dead GSK3β mimicked lithium’s activities in podocytes. Of note, both paxillin and SSH2 interacted with GSK3δ in podocytes and served as putative substrates for GSK3δ. In adriamycin injured mice, a single low dose of lithium attenuated proteinuria by more than 70%, associated with an early prevention of foot process effacement. Consistently, lithium therapy inhibited GSK3β activity in injured glomerul and blunted collagen and paxillin activities in podocytes.

Conclusions: Inhibition of GSK3β by lithium protected against podocyte injury and proteinuria by reinstating podocyte actin cytoskeleton stability via SSH2/collN pathway and regulating focal adhesion associated paxillin.

Funding: NIDDK Support

FR-P0844
Deficient Autophagy Results in Mitochondrial Dysfunction and the Development of Focal and Segmental Glomerulosclerosis of the Kidney
Takashia Kawakami,1,2 Shuyu Ren,2 Kelly L. Hudkins,2 Ivan G. Gomez,2 Allie M. Roach,2 Charles E. Alpers,2 Jeremy Stuart Dufield,2 1Univ of Tokyo; 2Univ of Washington, Seattle.

Background: Defocal and Segmental Glomerulosclerosis (FSGS) is a heterogeneous fibrosing disease whose etiology remains poorly understood, and for many, lacks an effective therapy. It is also recognized as a component of other kidney diseases. Autophagy is the pathway that cells degrade damaged organelles, cell membranes and proteins. The failure of autophagy may be one reason for the accumulation of cell damage and disturbance to cell homeostasis. Our Lab has recently implicated mitochondrial dysfunction, abnormal b-oxidation of triglycerides, and the aberrant production of reactive oxygen species (ROS) in the pathogenesis of tubulointerstitial kidney disease. Because of the central role of autophagy in cell homeostasis processes related to metabolism, mitochondrial and endoplasmic reticulum turnover, we explored autophagy deficiency in the kidney epithelium.

Methods: We mutated critical autophagy genes ATG5 or ATG7 during nephrogenesis, using Cre recombinase-expressing in the progenitors of kidney epithelium, under regulation of the transcription factor SIX2.

Results: Mice with ATG5 or ATG7 mutations develop effacement of podocyte foot processes and albuminuria with minimal histological changes by 2 months of age. By 4 months they exhibit profound glomerular and tubular changes, which bear remarkable similarity to human FSGS, developing severe albuminuria, advanced renal failure and death by six months. Ultra-structurally, in addition to the characteristic features of FSGS, podocytes and tubular cells show vacuolization, smaller damaged mitochondria, and...
changes to the endoplasmic reticulum. At these early time points, ATG5 and ATG7 decreased to cause all the manifestations of FSGS.

Conclusions: Mitochondrial dysfunction and ER stress are the result of impaired autophagy organelle turnover in podocytes and kidney tubular epithelium. The impairment in autophagy is sufficient to cause all the manifestations of FSGS.

FR-PO487

Mitochondrial Dysfunction in Podocyte Induces Proteinuria via Decrease of Alpha Actinin-4 and Synaptophysin

Dae Eun Choi,1 Jin Young Jeong,1 Sarah Chung,1 Yoon-Kyung Chang,2 Ki Ryang Na,2 Kang Wook Lee,2 Young Tai Shin.1
1Internal Medicine, Chungnam National Unv Hospital, Daejeon, Republic of Korea; 2Internal Medicine, Daejeon Saint Mary Hospital, Daejeon, Republic of Korea.

Background: Our previous report showed that Cri1 deletion induce severe mitochondrial destruction in mice podocyte. There are few studies about relation of mitochondria and proteinuria in podocytes of glomerulus. We evaluated the changes of acute cytoskeletal and architecture in mitochondrial injured podocyte.

Methods: We used immobilized mouse podocyte cell line. Cri1 silencing(siRNA) RNA treatment was used for inducing mitochondrial damage. We divided 3 groups; control podocytes, scramble(sc) RNA treated podocytes, Cri1 siRNA treated podocytes. We checked the expression of mitochondrial respiratory complex I-V, WT-1, and Cri1 for mitochondrial dysfunction in immortalized podocyte. We evaluated the expression of alpha actinin 4, synaptophysin, nephrin, ZO-1, and collagen using western blot. Using confocal microscopy, we examined actin cytoskeleton architecture and mitochondria of podocyte.

Results: Cri1 siRNA treatment reduced the expressions of mitochondrial respiratory complex IV and O2 consumption in cultured podocytes. Alpha actinin-4 and synaptophysin were decreased in Cri1 siRNA treated podocyte compared to control and Cri1 siRNA treated podocytes. There were no differences in nephrin and ZO-1. Cri1 siRNA treated podocyte showed an enhanced formation of dot-like alpha actinin-4 and an increase of fragment mitochondria in confocal microscopy compared to scRNA treated podocyte. Podocyte migration was increased in Cri1 siRNA treated podocyte.

Conclusions: With the above results, it is speculated that mitochondrial dysfunction induced by cri1 inhibition reduces alpha actinin-4 and synaptophysin in podocyte.

Funding: Government Support - Non-U.S.

FR-PO488

Apol1 Protein in Non-Diseased Human Podocytes: Endogenous Synthesis versus Uptake?

Jijun Ma,1 James A. Snipes,1 Mariana Murea,2 Peter A. Antinozzi,3 Gregory S. Shelness,2 Simon C. Satchell,2 Bernhard Banas,1 Peter W. Mathieson,1 Matthias Kretzler,2 Snerzana Petrovic,2 Michael D. Ross,1 Martin R. Pollak,1 Lawrence Rudel,1 John S. Parks,1 Barry I. Freedman,1 Wake Forest School of Medicine; 1Univ of Bristol, United Kingdom; 2Univ of Regensburg, GA; 3Univ of Michigan at Ann Arbor; 4Harvard Medical School.

Background: Based on heat-induced epitope retrieval on paraflin-embedded kidney sections, Apol1 protein is found localized to human proximal tubule cells (PTCs) and podocytes; however, it is unknown the extent to which this reflects local synthesis versus uptake.

Methods: Immunofluorescence microscopy (IF) was performed on non-diseased nephrology cryo-sections from subjects with normal kidney function and in various cell lines using an antibody specific for native human Apol1. RNA in situ hybridization (ISH), Western blot (WB), and RT-PCR studies were also performed.

Results: IF revealed that Apol1 co-localized with synaptopodin and Wilm’s tumor suppressor in podocytes and was present in renal tubule cell cytoplasm, albeit with lower signal intensity than podocytes. ISH detected Apol1 mRNA in both glomeruli and tubules, consistent with endogenous synthesis in these cell types. Based on RT-PCR, Apol1 mRNA was absent in mesangial or HEK293 cells; however, comparable expression was observed in all other cell types analyzed, including: immortalized human podocytes, glomerular endothelial cells (GEC) and PTC; primary GECs and podocytes; and HepG2 cells. Based on IF and WB, Apol1 protein was also detected in these cell lines but not in mesangial or HEK293 cells. Based on IF, Apol1 signal intensity was lower in both the immortalized and primary podocytes, as compared to the kidney cryo-sections. To explore the basis for this apparent discrepancy, we observed that Apol1 protein (reference sequence) was readily taken up by human podocyte and PTC lines in vitro, but not by mesangial or GEC lines.

Conclusions: We speculate that the higher in vivo levels of Apol1 observed in human podocytes on cryo-section may reflect endogenous protein synthesis as well as uptake of additional Apol1 from the circulation or glomerular filtrate.

Funding: NIDDK Support

FR-PO489

Rituximab Ameliorates Proteinuria in Rat Adriamycin Nephropathy Independently With Its Action to B Lymphocyte

Yuichi Takahashi, Hishashi Kamada, Asami Takasaki, Ayako Wakamatsu, Yoshiyasu Fukusumi, Masayuki Tomita, Hiroshi Kawachi.
Dept of Cell Biology, Insutitute of Nephrology, Niigata, Japan.

Background: Rituximab, a monoclonal antibody against CD20 on B lymphocytes, is reported to reduce proteinuria in some kidney diseases. It is postulated that Rituximab has cross-reactivity to sphinomyelin phosphodiesterase acid-like 3b (SMPLD3b), and plays a protective role for podocyte by preserving the SMPLD3b function. However, the direct action of Rituximab in podocyte is not proved yet, and the pharmacological mechanism of rituximab and the function of SMPLD3b in podocyte are still uncertain.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author/disclosure.
Methods: Because it is reported that rituximab has no reactivity to rat CD20, we analyzed the effect of rituximab on proteinuria in rat experimental model. Adriamycin (ADR) induced nephropathy was induced in rats by the single injection of 6 mg/kg BW of ADR, and the rats were intravenously injected with rituximab (10 mg/kg BW/week) from day 0. The kinetics of proteinuria were analyzed, and the kidney materials were removed on day 28 after disease induction. To elucidate the pharmacological mechanism of rituximab, the expressions of nephrin and podocin, the functional molecules of the slit diaphragm, and SMPDL3b were analyzed.

Results: The rituximab treatment clearly reduced the amount of proteinuria in ADR nephropathy (day 18, 25.62±5.66 vs. 18.35±3.97 μg/mg protein, p<0.001). These results demonstrated that rituximab most likely rescues the decreased expression of nephrin and podocin on day 28. The binding of the injected rituximab to glomeruli was confirmed in rat kidney sample removed 1 h after the rituximab injection. The injected rituximab is observed at the discontinuous linear pattern along the capillary loop of glomeruli, and the staining pattern is very similar to that of SMPDL3b detected by the same specific antibody against SMPDL3b. SMPDL3b staining clearly decreased at very early phase of ADR nephropathy.

Conclusions: The findings suggested that the decreased expression of SMPDL3b was involved in the initiation event of ADR nephropathy. It is conceivable that the injected rituximab bound SMPDL3b in podocyte and ameliorated proteinuria independently with its action to B lymphocyte.

Funding: Government Support - Non-U.S.

FR-PO850

Repopulation of Denuded GBM by Visceralized Parietal Epithelial Cells (vPECs) Is a Transient Mechanism to Limit Proteinuria

Samy Hakroush,1,2 Angelika Cebulla,1 Thomas Schaldecker,2 Peter H. Mundel,1 Astrid Weins.2

Methods: Mice on a mixed C57Bl6/Balb/c background were analyzed at baseline and at several timepoints after i.v. injection of various concentrations of adriamycin (ADR) or vehicle, using clinical parameters, light and electron microscopy as well as immunohistostchemistry.

Results: We found that ADR induces podocyte lysis through DNA damage. In contrast to other models, autophagy, ER stress and necrosis are not involved in the pathogenesis of ADR nephropathy. Following podocyte loss, vPECs are activated in two pathways: In the majority of glomeruli, PECs undergo striking vacuolization to attach to denuded glomerular basement membrane (GBM), which is followed by detachment of PECs from the parietal basement membrane (PBM). This results in repopulation of denuded GBM by PECs, ultimately leading to glomerulosclerosis. Less frequently, PECs do not undergo vacuolization, but cover the denuded GBM via formation of proliferative pseudocapses. Of note, all “visceralized” PECs (vPECs) covering the GBM do not express VEGF, but instead show high expression of HIF1. The clinical relevance of our findings was underscored by detection of v-PECs in biopsies of human glomerulopathies.

Conclusions: In conclusion, we propose that repopulation of the glomerular tuft by vPECs represents a compensatory response following podocyte loss in senescence and proliferative glomerular lesions, which is triggered by denuded GBM and is aimed at diminishing urinary protein loss. However, as vPECs do not express VEGF, they fail to induce revascularization of the hyalinized tuft, which results in hypoxic cell death.

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

FR-PO851

Rac1 in Podocytes Protects Glomeruli against the Formation of Sclerosis

Kim Asano,1 Katsuhiko Asanuma,1 Fumiko Kodama,1 Miyuki Takagi,1 Yoshiko Hirota2, Eiko Tanaka,1 Takuto Seki,1,2 Kanae Nomaka,1,2 Yu Sasaki,1 Teruo Hidaka,1 Lawrence B. Holzman,1 Yasuhiko Tomino.1

Results: In the model system, sequential kidney biopsies at 1, 2, and 4 weeks revealed that glomerular podocytes continued to decrease over time until global podocyte depletion (ESKD) by estimations using these three different methods. Urine protein and TGF-β1 mRNAs were excrated persistently at high levels throughout the time course of progression in experimental but not in control rats. In addition, methylprednisolone (MP) therapy slowed podocyte depletion and progression process, and also decreased urine TGF-β1 mRNA excretion. Furthermore, in patients with crescentic glomerulonephritis, urine podocyte and TGF-β1 mRNA excretion were significantly increased compared with healthy control.

Conclusions: These results emphasize the podocyte depletion hypothesis, and show that urine podocyte and TGF-β1 mRNA could serve to identify and monitor the progression process in crescentic glomerulonephritis.

Funding: Private Foundation Support

FR-PO852

Urine Podocyte and TGF-β1 mRNAs as Progression Markers in Crescentic Glomerulonephritis

Akihiro Fukuda,1 Yuji Sato,1 Takashi Iwakiri,1 Masao Kikuchi,1 Kazuo Kitamura,2 Roger C. Wiggins,2 Shouichi Fujimoto.1

Methods: To determine whether the same principles apply to crescentic glomerulonephritis we used the crescentic anti-GM1 glomerulonephritis rat model and in parallel experiments we examined urine samples of patients with crescentic glomerulonephritis.

Conclusions: In conclusion, we propose that repopulation of denuded GBM by vPECs represents a compensatory response following podocyte loss in sclerotic and pseudocrescents. Of note, all “visceralized” PECs (vPECs) covering the GBM do not express VEGF, but instead show high expression of HIF1. The clinical relevance of our findings was underscored by detection of v-PECs in biopsies of human glomerulopathies.

Funding: C2 Grant, JSPS, Japan

FR-PO853

A Protective Role of Indoleamine 2, 3-Dioxygenase (IDO)-General Control Non-Repressed-2 (GCN2) Kinase Axis in Glomerulonephritis

Kapil Chaudhary,1 Lei Huang,1 Maggie McMenamin,2 Michael P. Madaio,2 Tracy L. McGaha.1

Background: Indoleamine 2, 3-dioxygenase (IDO), a tryptophan (Trp) catabolizing enzyme rapidly induced in dendritic cells and macrophages by interferons (type I and II), depletes Trp at the site of inflammation. General Control Non-repressed (GCN2) kinase senses amino acid depletion (uncharged t-RNAs) and activates cellular stress response by affecting global as well as specific mRNAs translation. Including in kidney much is unknown about the functional role of IDO during inflammation in stromal cells.

Methods: Nephrotoxic serum nephritis (NTN) was induced in IDO-KO, GCN2-KO and WT (C57Bl6) mice by passive administration (i.p.) of low and high dose sheep nephrotoxic serum (NTS). Multiple i.v. injections of Cpg free DNA coated nano-particles (DNPs) were used to induce IDO expression in vivo. Enzymatic activity of IDO (kynurenines production) was measured by HPLC. Autophagy response in differentiated podocytes was measured by staining for LC3B.

Results: Compared to WT, IDO-KO and GCN2-KO mice developed more severe kidney damage by 3rd week of NTN as evident by significantly higher BUN, proteinuria levels and histopathological scores. IDO1 expression was induced at mRNA and protein levels by podocytes by day 10 of NTN. Interferons (IFN-γ and IFN-β)-1 induced IDO activity in podocytes in vitro. Systemic administration of DNOPs induced IDO activity in kidneys and significantly reduced BUN and proteinuria levels, and NGAL expression by day 21 of NTN, while IDO-KO mice did not show any protection. Expression of CHOP, a marker of endoplasmic reticulum (ER) stress and apoptosis, was significantly higher in IDO-KO and GCN2-KO mice than in WT mice.


Funding: Private Foundation Support

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

Underline represents presenting author/disclosure.

558A

Pathobiology: Basic/Experimental Pathology - I
Role of miRNA let-7b in the Deregulation Process of IgA1 Glycosylation in IgA Nephropathy

Grazia Serino,1,2 Fabio Sallustio,1,2 Claudia Curci,3 Sharon N. Cox,1 Francesco Pesce,1 Giuseppe De Palma,1 Francesco Paolo Schena.1,2

1Dept of Emergency and Organ Transplantation, Univ of Bari, Bari, Italy; 2C.A.R.S.O. Consortium, Valenzano, Bari, Italy; 3Dept of Genomics of Common Disease, Imperial College, London, United Kingdom; 4Schenia Foundation, Research Center for Kidney Diseases, Valenzano, Bari, Italy.

Background: IgA Nephropathy (IgAN) is characterized by aberrant O-glycosylation in the region of IgA1. The initiation step in O-glycan formation is attachment of N-acetylgalactosamine (GalNAc) to the IgA1 hinge region, catalyzed by GalNAc-transferase 2 (GALNT2). In our previous work (JASN 23: 814-24,2012) we found that let-7b is one of the miRNAs, significantly upregulated in IgAN patients.

Methods: To investigate the molecular mechanisms in which let-7b is involved, we performed a bioinformatic analysis to predict targets genes which were biologically validated by transient transfection experiments ex vivo using peripheral blood mononuclear cells (PBMCs) of 3 IgAN patients and 4 HBD. Then, we measured by Real-time PCR the content of let-7b in PBMCs of 60 Caucasian IgAN patients and 60 healthy blood donors (HBD).

Results: We identified let-7b gene targets using the overlapping results of at least two different algorithms (miRBase 19.0, TargetScan 5.2, PicTar and RNA22 1.0). Bioinformatic analysis revealed that GALNT2, the enzyme initiating O-Glycosylation of IgA1, was the potential target of let-7b. Then, we demonstrated that let-7b decreased GALNT2 levels validated by transient transfection experiments ex vivo using peripheral blood mononuclear cells (PBMCs) of 3 IgAN patients and 4 HBD. Then, we measured by Real-time PCR the content of let-7b in PBMCs of 60 Caucasian IgAN patients and 60 healthy blood donors (HBD).

Conclusions: let-7b is one of the miRNAs, significantly upregulated in IgAN patients. Further studies are needed to investigate the potential role of let-7b in the progression of IgA1 nephropathy.

Funding: Government Support - Non-U.S.

Recombinant Pentraxin-2 Therapy Attenuates the Progression of Alport Nephropathy in Col4a3 Deficient Mice

Naoki Nakagawa,1 Allie M. Roach,2 Bryce Gordon Johnson,1 Ivan G. Gomez,3 Mark L. Lusher,2 Jeremy Stuart Duffield.1 Renal Div, Kidney Research Institute, Univ of Washington, Seattle, WA; 2Promedior Inc, Boston, MA.

Background: Alport syndrome is an inherited form of kidney disease caused by a mutation in the gene coding the capillary basement membrane collagen IV. The disorder is characterized by progressive glomerulonephritis, leading to glomerulosclerosis, tubulointerstitial disease and organ failure. Col4a3 mouse with spontaneously develop severe kidney disease highly similar to human disease. Pentraxin-2 is a naturally produced protein released by mesangial cells and the reduction of serum Gal-de cient IgA1 (r=0.3, p<0.0001) positively correlated with high serum levels of the galactose-deficient (Gal-deficient) IgA1 (r=0.3, p=0.007) supporting that abnormal increase of serum Gal-de cient is consequent to high let-7b content in PBMCs of IgAN patients.

Methods: We speculate that the deregulation of let-7b causes GALNT2 reduction that could lead to aberrant O-glycosylation of IgA1 in IgAN patients. Our results give novel additional information on the abnormal O-glycosylation process of IgA1 in IgAN patients.

Funding: Government Support - Non-U.S.

Epigallocatechin-3-Gallate (EGCG) Inhibits Amyloid Formation in Amyloidogenic Light Chain Purified Kidney

Jianmin Teng,1 Etbara Turbat-herrera,1 Takahito Moriyama,2 Guillermo A. Herrera.1

1Pathology, LSU Health, Shreveport, LA; 2Medicine, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: In our previous studies, we have shown amyloid formation after treatment with glomerulopathic amyloidogenic light chains (AL-GLC) purified from the urine of patients with renal biopsy-proven AL-amyloidosis. C-fos plays an important role in the generation of signals resulting in amyloidogenesis. Other studies have shown that EGCG, found in green tea and red wine, is able to ameliorate amyloid-beta protein –associated amyloidosis in Alzheimer’s disease.

Methods: Human mesangial cells (HMC) were grown until confluence, made quiescent for 2 days, and then incubated with AL-GLC and EGCG for 4 hours. Western Blots and immunofluorescence staining were used to assess the effect on c-fos. Rat kidneys were isolated and mounted on an ex-vivo kidney perfusion platform. AL-GLC and EGCG were perfused through the renal artery for 24 hours, then the kidneys were fixed and examined using light, immunofluorescence, and electron microscopy (transmission and scanning). Proprietary panels were used to compare with experimental data.

Results: After incubation with AL-GLC, amyloidogenic light chains were noted in mesangial areas and c-fos translocated from HMC cytoplasm into nuclei. In EGCG treated group, cytoplasmic to nuclear translocation of c-fos was inhibited and amyloid formation was significantly decreased.

Conclusions: EGCG down-regulates translocation of c-fos into MC nuclei when MCs are incubated with AL-GLC. In MCs co-incubated with EGCG, nuclear c-fos translocation is significantly decreased and amyloid formation is decreased. The inhibitory effect of EGCG on amyloid fibril formation is more effective compared with control group.

Funding: NIDDK, NIH, Bethesda.

CD36 Receptor Blockade Protects against Chronic Kidney Disease Progression in a Remnant Kidney Model

Bocharov,2 Alejandro Alvarez-Prats, 1 Yuning George Huang, 1 Xuzhen Hu, Yuning George Huang, Robert A. Star, Peter S.T. Yuen.

1NIDDK, NIH; 2CC, NIH, Bethesda.

Background: CD36 blockade protects against chronic kidney disease (CKD) progression. CD36 fatty acid receptor is a pattern-recognition receptor expressed by various cell types involved in innate immune response.

Methods: CD36 blockade was performed in 5/6 nephrectomized (5/6Nx) rats treated with Angiotensin II (AngII) by continuous infusion for 4 weeks. Another group of WT rats received the same AngII infusion but were treated with control saline. Results: CD36 inhibition did not progress to CKD and were used as controls (N=8/group). BUN was measured by colorimetry, creatinine by HPLC, albumin and serum HMG1 by ELISA. ACR was analyzed weekly. Histological analyses of kidney sections were performed.

Results: CD36 inhibition was measured by anti-caspase-3 immunohistochemistry. Statistical analysis was performed by ANOVA.

Conclusions: CD36 receptor blockade protects against chronic kidney disease progression in a remnant kidney model.

Funding: NIDDK Support

CD36 Receptor Blockade Protects against Chronic Kidney Disease Progression in a Remnant Kidney Model

Ana C. Souza, Takayuki Tsuji, Alejandro Alvarez-Prats, Xuzhen Hu, Yuning George Huang, Robert A. Star, Peter S.T. Yuen.

1Pathology, LSU Health, Shreveport, LA; 2C.A.R.S.O. Consortium, Valenzano, Bari, Italy.

Background: In our previous studies, we have shown amyloid formation after treatment with glomerulopathic amyloidogenic light chains (AL-GLC) purified from the urine of patients with renal biopsy-proven AL-amyloidosis. C-fos plays an important role in the generation of signals resulting in amyloidogenesis. Other studies have shown that EGCG, found in green tea and red wine, is able to ameliorate amyloid-beta protein –associated amyloidosis in Alzheimer’s disease.

Methods: Human mesangial cells (HMC) were grown until confluence, made quiescent for 2 days, and then incubated with AL-GLC and EGCG for 4 hours. Western Blots and immunofluorescence staining were used to assess the effect on c-fos. Rat kidneys were isolated and mounted on an ex-vivo kidney perfusion platform. AL-GLC and EGCG were perfused through the renal artery for 24 hours, then the kidneys were fixed and examined using light, immunofluorescence, and electron microscopy (transmission and scanning). Proprietary panels were used to compare with experimental data.

Results: After incubation with AL-GLC, amyloidogenic light chains were noted in mesangial areas and c-fos translocated from HMC cytoplasm into nuclei. In EGCG treated group, cytoplasmic to nuclear translocation of c-fos was inhibited and amyloid formation was significantly decreased.

Conclusions: EGCG down-regulates translocation of c-fos into MC nuclei when MCs are incubated with AL-GLC. In MCs co-incubated with EGCG, nuclear c-fos translocation is significantly decreased and amyloid formation is decreased. The inhibitory effect of EGCG on amyloid fibril formation is more effective compared with control group.

Funding: NIDDK, NIH, Bethesda.

Background: CD36 blockade protects against chronic kidney disease (CKD) progression. CD36 fatty acid receptor is a pattern-recognition receptor expressed by various cell types involved in innate immune response.

Methods: CD36 blockade was performed in 5/6 nephrectomized (5/6Nx) rats treated with Angiotensin II (AngII) by continuous infusion for 4 weeks. Another group of WT rats received the same AngII infusion but were treated with control saline. BUN was measured by colorimetry, creatinine by HPLC, albumin and serum HMG1 by ELISA. ACR was analyzed weekly. Histological analyses of kidney sections were performed.

Results: CD36 inhibition was measured by anti-caspase-3 immunohistochemistry. Statistical analysis was performed by ANOVA.

Conclusions: CD36 receptor blockade protects against chronic kidney disease progression in a remnant kidney model.

Funding: NIDDK Support
FR-PO859

The Role of the Intestinal Microbiota in the Development of Diabetes in BTBR and BTBR ob/ob Mice

Methods: Starting at age 4 weeks, BTBR and BTBR ob/ob mice were fed normal mouse chow, and either water or water with an antibiotic cocktail (Ampicillin, Vancomycin, Metronidazole and Neomycin). Mice were analyzed for weight, blood glucose, glucose tolerance, urine protein, and histopathology. Fecal bacteria were analyzed by culture and 16S rDNA sequencing.

Results: Antibiotic treatment suppressed intestinal microbiota in BTBR mice, which was associated with a significant improvement in fasting glucose levels and glucose tolerance. In contrast, antibiotic treatment altered but did not suppress microbiota in BTBR ob/ob mice, which developed clinical and morphological features that closely mimicked diabetic nephropathy in humans (J Am Soc Nephrol. 2010;21(9):1533-42). In this study we analyzed the role of the microbiome in modulating the BTBR and BTBR ob/ob mouse models of diabetes.

Conclusions: Antibiotic treatment suppressed intestinal microbiota in BTBR mice, which was associated with a significant improvement in fasting glucose levels and glucose tolerance. In contrast, antibiotic treatment altered but did not suppress microbiota in BTBR ob/ob mice, which developed clinical and morphological features that closely mimicked diabetic nephropathy in humans (J Am Soc Nephrol. 2010;21(9):1533-42).

FR-PO860

Timing Is Critical in Determining Intervention Effectiveness. Moderate Calorie Restriction Enhances Angiotensin II Blockade Effectiveness in Preventing Progression

Methods: Transgenic AA-4EBP1 Fischer 344 rat podocytes express a dominant negative AA-4EBP1 transgene driven by the human podocin promoter. Homozygous 4EBP1 rats reached ESKD by 12 weeks. (% glomerulosclerosis = 26.2±7.0 at week 12).

Results: 40% calorie restriction (CR) prevented FSGS, proteinuria, podocyte loss, glomerulosclerosis and progression to ESKD in the AA-4EBP1 rat model system. We previously demonstrated that 40% calorie restriction (CR) prevented FSGS, proteinuria, podocyte loss, glomerulosclerosis and progression to ESKD in the AA-4EBP1 rat model system (Fukuda et al, JASN, 2013).

Conclusions: The impact of moderate calorie reduction is an under-recognized variable in clinical trials. New evidence from our lab showing the impact of calorie restriction on renal damage and progression to ESKD in the AA-4EBP1 rat model system is discussed.

FR-PO861

Dipeptidyl Peptidase 4 Deficiency Reduces Renal Injury in the Remnant Kidney Model in the Rat

Methods: Dipeptidyl peptide 4 (DPP4) is an exopeptidase inactivating incretins that promote insulin secretion and were therefore used in the treatment of type II diabetes. Beside its ability to cleave incretins, several chemokines like RANTES and CCL2 were also regulated by DPP4. In lung as well as in renal ischemia/repairfusion injury (IRI) and in acute heart rejection, treatment with DPP4 inhibitors were protective, but the effect of DPP4 inhibition in chronic kidney disease is unknown.

Conclusions: CD36KO protection is not due to a developmental abnormality, since adult WT mice treated with L37pa are also protected from CKD progression. At this dose and route of administration, L37pa did not cause any detectable side effects.

Funding: NIDDK Support

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

Underline represents presenting author/disclosure.

S60A
(p<0.05) total heart lesions. Furthermore, there was a marked increase in hydroxyproline level (collagen) observed in catheterized-NX rat hearts which was significantly reduced by both IV and PO treatments with PBI-4050. This reduction in hydroxyproline level correlated with the histological heart sections (Masson’s trichrome stain). Moreover, GFR was increased and inflammation of the kidney (as measured by urinary MCP-1 level) was decreased in PBI-4050-treated catheterized-NX rats.

Conclusions: Together, our results suggest that implantation of a catheter may induce heart fibrosis, and PBI-4050 offers the potential as a novel therapy for the treatment of kidney and heart fibrosis.

FR-PO864
Galacto-Oligosaccharides Modified Gut Microbiota and Attenuated Renal Injury
Satoshi Unuma,1 Takamoto Ohse,2 Airi Jo,1 Akira Shigehisa,2 Koji Kawakami,2 Takahiro Matsuki,2 Osamu Chonan,3 Masami Nangaku,1 1Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; 2Yakult Central Institute,Kentachhi,Japan.

Background: Tubulointerstitial injury is a final common pathway to end stage renal disease. We have previously reported that uremic toxins cause tubulointerstitial injury through oxidative stress and endoplasmic reticulum (ER) stress. Galacto-oligosaccharides (GOS) are utilized by beneficial microbes. Since the precursor of indoxyl sulfate, indole, is synthesized by gut microbiota, we focused on the effects of GOS on indoxyl sulfate synthesis by gut microbiota and renal function in kidney disease.

Methods: Two weeks after induction of the 5/6 nephrectomized (Nx) model, the rats were divided into two groups, control diet group (ConNx) and GOS-fed group (GOSNx). After two weeks administration of GOS, we measured serum indoxyl sulfate and examined the gut microbiota with pyrosequencing method, theecal contents, and the renal injury.

Results: A comprehensive analysis of gut microbiota revealed a significant increase in Bifidobacteriaceae and decrease in Ruminococcaceae by GOS. While no significant changes were detected in blood pressure, body weight and food consumption of the rats, cecal indole and serum indoxyl sulfate were significantly reduced in GOSNx. Renal injury was improved and infiltrating macrophages were significantly decreased in GOSNx. We next examined ER stress as a pathway of renal injury caused by indoxyl sulfate. Immunohistochemistry and quantitative PCR revealed that GRP78, CHOP, and ORP150 were significantly increased in ConNx and significantly decreased in GOSNx compared with ConNx. TUNEL positive cells were also significantly increased in ConNx and significantly decreased in GOSNx compared with ConNx.

Conclusions: GOS administration to 5/6 nephrectomized rats modified gut microbiota, reduced serum indoxyl sulfate, and attenuated renal injury. ER stress was reduced by GOS administration and amelioration of ER stress was implicated in a mechanism of kidney protection. GOS can be a novel therapeutic agent against kidney injury. Funding: Pharmaceutical Company Support – Yakult Honsha Co., Ltd.

FR-PO865
Integrin β6 in Macula Densa Cells Modulates Potential Tubuloglomerular Feedback
Beom Jin Lim, Haichun Yang, Agnes B. Fogo. Pathology,Microbiology and Immunology, Vanderbilt Univ Medical Center; Nashville, TN.

Background: The heterodimeric integrin αvβ6 is expressed in tubular epithelial cells and the juxtaglomerular apparatuses (JGA) in the kidney. It binds and activates latent transforming growth factor-β (TGF-β), and thus has profibrotic effect. We previously observed that β6-/- mice showed increased glomerulosclerosis vs. wild type (WT) mice with disproportionately milder interstitial fibrosis after 5/6 nephrectomy (Nx). The development of glomerulosclerosis was TGF-β-dependent, but was related to increased renin activity in JGA. These results suggested that β6-/- mice may have dysregulated tubuloglomerular feedback mechanisms. We therefore evaluated the effect of integrin β6 knock down in isolated mouse macula densa cells (MMD1).

Methods: 5/6 Nx kidneys of β6-/- vs. WT mice were analyzed for nNOS and COX-2. Integrin β6-specific gene knock down was performed by shRNA transduction in MMD1 cells, and assessed by real time RT-PCR and immunofluorescence microscopy. Cells were then treated with isosomolar normal salt or low salt solution for 8 hours. nNOS and COX-2 were measured by western blot.

Results: Kidneys from β6-/- mice showed decreased nNOS expression and similar COX-2 expression vs. WT mice, but immunohistochemistry showed decreased nNOS and increased COX-2 intensity in β6-/- mice which was assessed by real time RT-PCR in shRNA-transfected MMD1 cells was decreased to 41.5% of WT cells. Control scrambled shRNA had no effect. Integrin β6 knock down cells showed higher baseline expression vs. WT cells of both COX-2 (COX-2-a/α: 1.15±0.02 vs. 0.01±0.00, p<0.05) and nNOS (nNOS/α: 0.10±0.01 vs. 0.02±0.01, p<0.05). After stimulating with low salt, COX-2 expression was similarly increased in β6 knock down and WT cells (0.83±0.01 vs. 0.78±0.01, pNOS), but nNOS expression was increased only in β6 knock down cells (0.26±0.02 vs. 0.06±0.01, p<0.05).

Conclusions: We conclude that the absence of integrin β6 in macula densa cells results in altered expression of tubuloglomerular feedback-related molecules. The findings support our hypothesis that the absence of integrin β6 may affect progression of glomerulosclerosis by dysregulated tubuloglomerular feedback mechanisms. Funding: NIDDK Support

FR-PO867
SNF472 Inhibits Vitamin D Induced Cardiovascular Calcification in Rats
Rats Marketer,1 Miquel D. Ferrer,2 Fernando Tur,3 Bernat Isern,2 Carolina Salcedo,2 Joan S. Perelló,1,2 1Div of Nephrology, Klinikum Coburg GmbH, Coburg, Germany; 2Research and Development Dept, Laboratoris Sanitafi SL, Palma de Mallorca, Spain; 3Laboratory of Renal Lithiasis Research, Institute of Health Sciences Research (UINC3), Univ of the Balearic Islands, Palma de Mallorca, Spain.

Background: Cardiovascular calcification has been shown to be an independent predictor of cardiovascular events in CKD patients. This study investigated the effects of SNF472, an intravenous formulation of mites-ino-soluble hexaphosphate, on vitamin D induced vascular calcification, and compare its effects with cinacalcet and sodium thiosulfate (STS).

Methods: The study was done in 40 male Sprague Dawley rats divided into 3 groups of 10–16 animals. Group 1 received daily intravenous vehicle or 1 mg/kg SNF472. Group 2 received vehicle or 15 mg/kg of cinacalcet p.o. Group 3 received vehicle or 400 mg/kg of sodium thiosulfate i.p. Calcification was induced by 5 daily oral administrations of 75000 IU/kg of vitamin D starting on day 3 of treatment. Five sham treated animals served as control. Serum samples for the determination of calcium and phosphorous concentrations were collected on days 8 and 14. Rats were sacrificed on day 14 and aortas and hearts removed for calcium analyses.

Results: The administration of vitamin D induced a marked increase in aortic and bony calcium levels. Calcium and phosphorous from control sera increased significantly compared to the sham group, and were not affected by any of the treatments. The intravenous administration of SNF472 at 1 mg/kg resulted in reductions by 60% in aortic and 68% in heart tissues. Animals treated with Cinacalcet and STS showed small reductions. The only significant reduction occurred with cinacalcet in aorta (24%).

Conclusions: SNF472 might be an alternative therapeutic principle for cardiovascular calcification treatment.

Funding: Pharmaceutical Company Support - Sanifit, Government Support - Non-U.S.
Coagulation Protease-Activated Protein C Selectively Trans Activates XBP1 via p85α and p85β to Restore Endoplasmic Reticulum Homeostasis in Diabetic Nephropathy


Background: A growing body of recent work suggests that endoplasmic reticulum (ER) stress response is causally linked to diabetes complications. However the specific physiological stimuli and molecular mechanism through which hyperglycemia modulates ER stress are not known.

Methods: In an attempt to determine the role of hyperglycemia in regulating ER-stress we have employed mouse models of both type-1 (streptozotocin) and type-2 (db/db) diabetes-induced nephropathy (DN).

Results: In DN hyperglycemia selectively impairs nuclear translocation of the highly conserved transcription factor spliced X-box binding protein-1 (sXBP1). This result in severe ER-stress associated with increased nuclear levels of the active form of activating transcription factor-6 (ATF6) and ATF6 mediated transcriptional activation of CHOP. In addition inducible expression of ATF6 specifically in podocytes aggravates ER-stress and DN. We next show that treatment with activated protein C, a coagulation protease with well-established nephroprotective properties, selectively trans activates XBP1 via PI3K regulatory subunits p85α and p85β and restores ER-homeostasis in DN. In a mice model with impaired thiamopromodulin (TM)-dependent PC activation (TM<sup>lox/lox</sup>-ER-stress and DN is aggravated. Conversely in a mouse model with constitutively higher plasma levels of aPC (A<sup>PC<sup>α</sup></sup>) ER-stress is inhibited, highlighting the physiological role of aPC in regulating ER-stress in DN. While deletion of Chop or inhibition of ER-stress with tauroursodeoxycholic acid protected against DN in TM<sup>lox/lox</sup> and wild type mice, Conditional deletion of XBP1 (XBP1<sup>flox/flox</sup>x Pod<sup>cre</sup>) abolished the protective effect in A<sup>PC<sup>α</sup></sup> mice. In podocytes and endothelial cells XBP1 is selectively, but independently of IRE1, activated by aPC in transgenic models and which is required to inhibit hyperglycemia induced ER-stress.

Conclusions: These studies revise our understanding of regulation of ER-stress in DN and might have major implications for treatment of DN in humans.

Glycogen Synthase Kinase 3 and the Podocyte: A Tale of Two Isoforms

Joseph Hurcombe,1 Abigail Charlotte Lay,1 Gavin Iain Welsh,1 C. Avila-Casado,3 Peter Baldwin,1 Indra R. Gupta,2 Tomoko Takano.1 1Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom; 2Cardiovascular Research Institute, Div of Nephrology, North Western Univ, Chicago, IL; 3Dept Veterinary Biosciences, Univ Helsinki, Finland.

Background: Glycogen synthase kinase 3 (GSK3) is a multi-functional serine/threonine kinase existing as two distinct but related isoforms (α and β) with an established role in the modulation of insulin signaling. There is evidence that the GSK3 isoforms have different functions: GSK3β null mice die during late embryogenesis due to hepatocyte apoptosis whereas total GSK3 or knockout mice are viable and interestingly, exhibit enhanced insulin sensitivity. A number of cell-specific GSK3 knockout mouse models have been described and indicate that the functions of the GSK3 isoforms are cell-type dependent.

Methods: In order to investigate the role of the GSK3 isoforms in podocyte development, we have used Cre/LoxP technology to generate mice with podocyte-specific ablation of GSK3α or GSK3β.

Results: Using an in vitro and in vivo approach we have shown that in the glomerulus, GSK3α is preferentially expressed in the podocyte and that both of its isoforms are phosphorylated and thus deactivated in response to insulin. Mice lacking either GSK3α or GSK3β specifically in the podocyte are viable with normal life span (up to 2 years) with no evidence of proteinuria and normal renal histology indicating a degree of redundancy between the isoforms in the podocyte. In contrast, mice null for both GSK3 isoforms (13 of 107 mice studied), although born at normal Mendelian frequency, die predictably at 12-14 days at which time they are proteinuric, with grossly abnormal vacuolated glomeruli. Both Cre<sup>flox/</sup>α<sup>fl</sup> and Cre<sup>flox/</sup>β<sup>fl</sup> GSK3 isoforms were detected in podocytes after the late capillary stage. When CA-Rac1 was induced in podocytes in adult mice, 3/7 double transgenic mice (Gα<sub>α</sub>-Rac1, Gβ<sub>β</sub>-Rac1) were rescued by wild-type but not by the mutant GDI<sub>α</sub> and GDI<sub>β</sub>. Therefore GDI<sub>β</sub> is a negative regulator of Rac1 activity.

Conclusions: This work reveals a fundamental role of GSK3 in the podocyte and its importance in glomerular development and survival.

APOL1 Encodes a Novel miRNA That Induces PKR, and miRNA Levels Are Increased in Plasma Exosomes from G1 Homozygous Individuals

Anita A. Wasik,1 Susanna Koskelainen,1 Mervi E. Hyvonen,1,2 Luca Musante,1 1Harurman Institute, Univ Helsinki, Finland; 2Children’s Hospital, Univ Helsinki, Finland.

Background: Coding variants in APOL1 are strongly associated with FSGS among African Americans. We hypothesized that APOL1 variants might harbor an miRNA and reported that a single amino acid deletion, D185Del, is a loss-of-function mutation of GDI<sub>α</sub> that causes congenital nephrotic syndrome. We hypothesize that the loss of the inhibitory action of GDI on PKR leads to hyper-activation of Rac1 in podocytes and nephrotic syndrome.

Results: When CA-Rac1 was induced in podocytes in adult mice, Rac1 activity was rescued by wild-type but not by the mutant GDI<sub>α</sub> and GDI<sub>β</sub>. PKR activity was measured in podocytes in vivo by treating double transgenic mice (carrying a tetracycline-inducible CA-Rac1 and a reverse tetracycline transactivator driven by the podocin promoter) with doxycycline.

Conclusions: These studies revise our understanding of regulation of ER-stress in DN and might have major implications for treatment of DN in humans.

Ezrin Is Downregulated in Diabetic Kidney Glomeruli and Regulates Cortical Actin Dynamics and Glucose Transport in Cultured Podocytes

Anita A. Wasik,1 Susanna Koskelainen,1 Mervi E. Hyvonen,1,2 Luca Musante,1 1Harurman Institute, Univ Helsinki, Finland; 2Children’s Hospital, Univ Helsinki, Finland.

Background: Diabetic nephropathy (DN) is a major cause of end-stage renal disease but the pathophysiological mechanisms associated with its development are poorly characterized.

Methods: To characterize the early pathophysiological mechanisms leading to podocyte injury in DN we performed quantitative proteomic profiling of glomeruli isolated from rats with streptozotocin-induced diabetes and controls using fluorescence-based two-dimensional difference gel electrophoresis coupled with mass spectrometry.

Results: We identified 29 differentially expressed spots, including ezrin and its interaction partner NHERF2 that were downregulated in the streptozotocin group. Ezrin and NHERF2 link plasma membrane proteins to the actin cytoskeleton. Quantitative Western blot and immunofluorescence analyses confirmed downregulation of ezrin and NHERF2 in the glomeruli of streptozotocin-treated rats. Knockdown of ezrin by siRNA in cultured podocytes induced cortical actin remodeling and glucose uptake at basal conditions, but reduced insulin-stimulated actin remodeling and glucose uptake as compared to

APOL1 cDNA and APOL1 miRNA induced PKR phosphorylation; these effects were seen with G1 but not G0. Human podocyte-like urine-derived epithelial cells (G1/G2 genotype, compared to G0/G0 genotype) manifested proliferation defects and downstream effects including increased type I collagen production, phosphorylation of eIF2α and inhibition of protein translation, all of which were reduced following APOL1 knock down.

Conclusions: We report that APOL1 miRNA generates a miRNA whose expression is higher in G1 genotype cells. APOL1 G1 cells exhibit an activated PKR-related host defense pathway compared to G0 cells. Up-regulation of APOL1 derived miRNA provides a new pathogenic mechanism for APOL1 nephropathy associated with the G1 variant and suggests that possible therapeutic targets include APOL1 miRNA and PKR.

Funding: NIDDK Support
control siRNA-transfected cells. The ezrin-dependent actin remodeling involved an actin depolymerizing protein coflin that is essential for actin filament turnover. Furthermore, immunohistochemical analysis revealed reduced expression of ezrin in the podocytes of human patients with diabetes.

**Conclusions:** Our findings suggest that ezrin may play a role in the development of the renal complication in diabetes by regulating actin cytoskeleton organization and glucose transport in podocytes.

**Funding:** Private Foundation Support

---

**FR-PO873**

Nck1 but Not Nck2 Regulates Podocyte Actin Dynamics through Activation of RhoA

Lisa Maria Buvall,1 Priyanka Rashmi,1 Astrid Weins,2 Anna Greka,1 Peter H. Mundel.1 2Nephrology, Harvard Medical School and Massachusetts General Hospital, Boston, MA; 3Pathology, Harvard Medical School and Brigham and Women’s Hospital, Boston, MA.

**Background:** Podocyte dysfunction, represented by foot process effacement, disruption of the slit diaphragm and proteinuria, is often the initial insult leading to progressive kidney disease. Nck1/2 are widely expressed adapter proteins that recruit proline rich proteins via their SH3 domains. Ncks are essential for the development and maintenance of the glomerular filtration barrier and stabilize the podocyte actin cytoskeleton by phosphorylating the slit diaphragm protein nephrin.

**Methods:** To study Nck actin-regulatory pathways in cultured podocytes we use cell biological and biochemistry assays in combination with lentiviral gene silencing and overexpression approaches.

**Results:** Here we identify Nck1 but not Nck2 as regulators of RhoA signaling in podocytes. We show that Nck1, but not Nck2, is a substrate of the ubiquitin ligase c-Cbl, which mediates ubiquitination and proteasomal degradation of Nck1. We uncover lysine 176 in Nck1 as the ubiquitin acceptor site, which is conserved from Xenopus to human. We have previously reported that synaptotagmin, a proline rich actin binding protein, promotes stress fiber formation by blocking the Smurf1 mediated ubiquitination of RhoA. Now we find that synaptotagmin competes with c-Cbl for binding to Nck1, thereby blocking the ubiquitination of Nck1 by c-Cbl. Gene silencing of c-Cbl in synaptotagmin depleted podocytes restores Nck1 abundance, confirming c-Cbl as the specific ubiquitin ligase responsible for ubiquitination of Nck1. Expression of c-Cbl resistant Nck (K176R), but not Nck2, restores stress fibres in synaptotagmin depleted podocytes through activation of RhoA signaling.

**Conclusions:** These findings highlight the functional difference between Nck1 and Nck2 and reveal a proteasomal regulation as a key to distinct and non-redundant Nck effects on RhoA signaling.

**Funding:** NIDDK Support

---

**FR-PO874**

Synaptic Vesicle Protein 2B Is Essential for Maintaining the Integrity of the Podocyte Slt Diaphragm; SV2B KO Mice Are Vulnerable to the Podocyte Injury Yoshiyasu Fukumori, Asami Takasaki, Ayako Wakamatsu, Yuichi Takashashi, Naoko Miyauchi, Masayuki Tomita, Hiroshi Kawachi. Dept of Cell Biology, Institute of Nephrology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

**Background:** We have previously reported synaptic vesicle protein 2B (SV2B) was expressed in podocyte, and the cultured podocyte of which SV2B was knock-downed with siRNA failed to arrange the proper localization of CD2AP, which is one of the component of slit diaphragm (SD) (JASN, 2006). SV2B is expressed on vesicle surface and plays a role in vesicle trafficking. However, synaptic vesicle like trafficking system in podocyte, and the role of SV2B are not well understood.

**Methods:** To elucidate the function of SV2B in vivo, we generated SV2B knockout (KO) mice. The expression of CD2AP and other critical molecules of the SD (nephrin, NEPH1, podocin and ZO-1) in SV2B KO mice, and their sensitivity to podocyte injury were analyzed.

**Results:** In SV2B KO mice without any treatment, a slight increase in the amount of proteinuria (KO 19.88 mg/24h vs. WT 2.39). The staining of CD2AP, nephrin, NEPH1, podocin and ZO-1 was clearly decreased in KO mice overloaded with BSA (nephrin: KO 1.39 mg/24 h vs. wild type (WT) 0.64, p<0.02), and the alteration in the expression of vesicular glutamate transporter, a molecule expressed on synaptic vesicle associated proteins were analyzed in SV2B KO mice. mRNA expression after uninephrectomy, whereas about 50% of SV2B KO mice died after the treatment. The staining of CD2AP, nephrin, NEPH1, podocin and ZO-1 were analyzed.

**Conclusions:** We have previously reported synaptic vesicle protein 2B (SV2B) was expressed in podocyte, and the cultured podocyte of which SV2B was knock-downed with siRNA failed to arrange the proper localization of CD2AP, which is one of the component of slit diaphragm (SD) (JASN, 2006). SV2B is expressed on vesicle surface and plays a role in vesicle trafficking. However, synaptic vesicle like trafficking system in podocyte, and the role of SV2B are not well understood.

**Funding:** NIDDK Support

---

**FR-PO875**

CD2AP Phosphorylation on Tyrosines Y10 and Y273 Has a Physiological Relevance for Slt Diaphragm Stability

Irina Schaefer, Beina Teng, Kirstin Worthmann, Hermann G. Haller, Mario Schiffer. Nephrology, Medical School Hannover, Hannover, Germany.

**Background:** CD2AP is an adaptor protein that can transmit intracellular signals involved in survival and cytoskeletal regulation of the cell. We have shown that CD2AP tyrosine phosphorylation determines binding to nephrin. Until now it is unknown if phosphorylation of CD2AP has a physiological relevance for slit diaphragm stability. The aim of these studies was to analyze the involvement of CD2AP phosphorylation for slit diaphragm stability in vivo.

**Methods:** Evolutionarily highly conserved tyrosine residues were identified in every SH3 domain of CD2AP on positions Y4/10, Y119 and Y273/280. By site directed mutagenesis we established for every tyrosine a single mutant or for close-by tyrosines double or triple mutants. We furthermore generated mRNA from WT- and mutated CD2AP DNA. By cross-species rescue experiments in CD2AP-knockdown zebrafish we analyzed the physiological relevance of every single tyrosine for slit diaphragm stability. Analysis was performed by morphology, mortality rate and filtration of GFP-labeled fatty acid-binding protein.

**Results:** Knockdown of CD2AP by morpholin injection in zebrafish leads to edema and foot process effacement. Most of the larval fishes died after 5 days. Cross-species rescue experiments by injection of CD2AP mRNA after morpholin injection showed a rescue of the CD2AP-knockdown phenotype. To analyze the importance of the tyrosines we injected mRNA of the single tyrosine mutants. The absence of tyrosines Y10 or Y273 showed no rescue of the CD2AP-knockdown phenotype. These zebrafish larvae developed big edema, showed a high mortality rate and GFP-labelled fatty acid-binding protein was filtrated through the damaged glomerular filtration barrier. Larvals with rescued phenotypes remain healthy with intact filtration barrier.

**Conclusions:** These results suggest that CD2AP phosphorylation on tyrosines Y10 and Y273 have a physiological importance for stability of the slit diaphragm in vivo.

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

---

**FR-PO876**

Role of Podocytes in Endocytosis and Glomerular Filter Integrity

Madhusudan M. Venkatadri, Rakesh Verma, Puncet Garg. Div of Nephrology, Univ of Michigan, Ann Arbor, MI.

**Background:** Vesicular trafficking and autophagy is vital part of cell development and growth and to maintain a balance between synthesis, degradation and recycling of cellular components. We generated a Podocyte specific deletion of vps34, a phosphoinositide kinase that plays a critical role in both vesicular trafficking as well as autophagy. Careful characterization of the vesicles showed differences from what was reported in recently published podocyte specific deletion of vps34. Furthermore, using this model we examined the role of podocyte in preventing filter clogging as endocytosed protein processing is altered in the absence of vps34.

**Methods:** Kidneys from Hpc and Immunogold EM (IEM) were harvested from wild type and podocyte specific vps34 deleted mice (vps34KO). Cell culture studies used stable podocyte cell line generated from the vps34KO mouse infected with adenovirus carrying cre (Podvps34-cre). Results: As previously reported, vps34KO mice are normal at birth, develop massive proteinuria and accumulation of vesicles by 3 weeks of age. IHC and IEM studies from kidney section and Podvps34-cre Cells reveal two distinct populations of vesicles, early and late endosomes that are Rab5 and Lampl positive and syntaxin 6 positive vesicles that are in flux with the trans-golgi network (TGN). Autophagic vesicles were not seen. Immunogold EM shows Nephrin in vesicles suggesting either endocytosis of Nephrin or aberrant trafficking of newly synthesized Nephrin from the TGN. To study the role of podocytes in endocytosis of filtered proteins we perfused mice with FITC-human albumin (FITC-:ha) as well as FITC-labeled exogenous IgG and albumin in wild type and vps34KO mice. There was no leak of mouse IgG, albumin or infused FITC-:ha in normal wild type mouse using IF and IEM studies. There was accumulation of mouse IgG and albumin in Podocyte vesicles of non-proteinicre 2 weeks old vps34KO mice.

**Conclusions:** Perturbation of the endocytic machinery suggests the improper targeting of slit diaphragm proteins is in part due to failure of trafficking of vesicles to and from the golgi network. This model also provides evidence for the role of podocytes in maintaining a healthy filter and prevent clogging.

**Funding:** NIDDK Support

---

**FR-PO877**

AMPK Activation by AICAR Is Protective against Podocyte Damage and Glomerulosclerosis

Stephen O’Brien, John N. Vassiladiadis, Mandy M. Smith, Hong Ling, Steven R. Ledbetter, Cynthia M. Arbeezy, Stefan Waversik. Tissue Protection and Repair Unit, Genzyme/Sanofi R&D Center, Framingham, MA.

**Background:** Podocyte injury is a key step in the onset and progression of glomerulosclerosis. Cellular functions that counteract cell stress, such as autophagy and mitochondrial biogenesis, are critical for podocyte damage resistance. AMP-activated Protein Kinase (AMPK) regulates multiple stress-protective responses, and we therefore hypothesized that AMPK activation can protect podocytes from injury.

**Methods:** To functionally test the role of AMPK in podocyte health, pyruvycin aminomucoside (PAN) was used to cause oxidative stress in cultured immortalized podocytes. PAN treatment reduced AMPK[12] phosphorylation in podocytes, indicating decreased AMPK activation. Furthermore, PAN induced apoptotic markers, mitochondrial

---

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

Underline represents presenting author/disclosure.

---

563A
membrane depolarization, and expression of the ER stress marker CHOP. Co-treatment with 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), an AMP analog capable of stimulating AMPK, increased phospho-AMPK, reduced albuminuria, CHOP induction, and apoptosis. To test whether in vivo AMPK activation can reduce glomerular injury, we examined the effects of AICAR treatment in adenovirus-induced nephropathy (AN), a mouse model of glomerulosclerosis. Vehicle-treated AN mice were heavily albuminuric. An adenovirus that expresses Bmp7 is controlled kidney injury. Immunostaining with the proliferation marker Ki67 revealed an increase in dividing cells in the tubular, mural, and interstitial compartments. In contrast, AN mice treated with 500 /mg/kg/day AICAR showed a marked reduction in albuminuria (p < 0.05 vs. AN).16 Scoring of glomerular pathology (p < 0.001 vs. AN + Ve) and of the Ki67 + cells/glomeruli (p < 0.001 vs. AN + Ve) also indicate reduced glomerular injury in AICAR-treated AN mice.

**Conclusions:** Taken together, these data suggest that AICAR treatment prevents glomerular injury by reducing podocyte injury, and that the mechanism of this protection is through AMPK activation.

**Funding:** Pharmaceutical Company Support - Genzyme/Sanoﬁ

---

**FR-PO878**

**Expression of Cleavage Resistant CD2AP in a Model of Inflammatory Glomerular Disease**

**Mehtem M. Altnias**, 1 Changli Wei, 1 Jing Li, 2 Phillip Ruiz, 2 Jochen Reiser. 1 Medicine, Rush Univ, Chicago, IL; 2 Surgery, Univ of Miami, FL.

**Background:** We recently showed that a cytosolic variant of the cysteine protease cathespin L (CatL) is a common downstream effector in many glomerular diseases. The GTPass1 dynamin, synaptopodin and CD2AP were shown to be key targets of this enzyme. These findings emphasized the need for the integrity of these target proteins and thus podocyte foot process (FP) structure and function.

**Methods:** We utilized the serum nephritis (SN) mouse model in which injection of an antibody that reacts with the glomerular basement membrane (GBM) causes glomerular disease. We deleted CatL cleavage site from CD2AP aminoacid sequence by site directed mutagenesis. We analyzed proteinuria, podocyte apoptosis, crescent formation, glomerular sclerosis and glomerular hypercellularity.

**Results:** SN is associated with cytosolic CatL induction in podocytes that leads to proteolytic cleavage of CD2AP N-terminal but a stable C-terminal fragment (pS2) and the release of denisin to podocyte nucleus, a response that was largely absent in CatL KO mice. Both, wild type (WT) and CatL KO mice developed strong and comparable levels of proteinuria in response to anti-GBM antibody. Interestingly, the expression of the CD2AP cleavage resistance synaptopodin and dynamin remained the same in WT mice suggesting that development of proteinuria is independent of CatL during SN. In contrast, kidney histology after SN revealed that only WT animals developed features of disease progression.

To further analyze the effects of stable CD2AP on progressive kidney disease, we expressed WT CD2AP and CD2AP that is cleavage resistant against CatL. Mice received WT CD2AP showed a significant reduction of N-terminal CD2AP but not the mice expressed cleavage resistant CD2AP after SN. The expression of cleavage resistant CD2AP directly impacted on the severity of disease progression.

**Conclusions:** The stabilization of CD2AP by removing CatL or protecting CD2AP alters the course of a glomerular disease shifting progression into a more benign phenotype. This finding will allow us to develop additional strategies for renal protection that are in addition to anti-proteinuric modalities focusing on podocyte survival.

**Funding:** NIDDK Support

---

**FR-PO879**

**Akt Recruits Dab2 to Albumin Endocytosis**

**Eli Erkan,** Hui Li, Kenneth R. Hallowes. 1 Univ of Pennsylvania.

**Background:** Proximal tubule epithelial cells encompass a highly sophisticated endocytic machinery to retrieve albumin in the glomerular filtrate. Megalin-cubilin complex and the endocytic adapter disabled 2 (Dab2) play a pivotal role in albumin endocytosis. We demonstrated that protein kinase B (Akt) mediates albumin endocytosis in the proximal tubule through an interaction with Dab2. Our goal was to examine the nature of Akt-Dab2 interaction. We proposed that Akt phosphorylates Dab2.

**Methods:** We utilized GST-pulldown and yeast two hybrid experiments to examine the interaction sites between Akt and Dab2. Phosphorylation of Dab2 and the phosphorylation sites by Akt were examined by in-vitro phosphorylation experiments and site-directed mutagenesis. Physiological relevance of this phosphorylation event was investigated by ablation studies. The effect of Akt on membrane expression of megalin-cubilin was demonstrated that protein kinase B (Akt) mediates albumin endocytosis in the proximal tubule and phosphorylation of Dab2 by Akt is essential in recruitment of Dab2 to the endocytic pathway and trafficking of megalin-cubilin. We propose that understanding the link between cell signaling events and albumin endocytosis may decipher the mechanism of tubulointerstitial injury that is inflicted by proteinuria. Further research is warranted to investigate other potential Akt targets in the endocytic machinery.

**Funding:** NIDDK Support

---

**FR-PO880**

**Cyclic AMP Signaling Prevented against Podocyte Apoptosis via Activation of Protein Kinase A and Mitochondrial Fusion**

**Zhaohui Ni,** Xiaoying Li, Kenneth R. Hallowes.

**Background:** Our previous in vitro studies suggest that cyclic AMP (cAMP) signaling protects against doxorubicin (ADR) and puromycin aminonucleoside (PAN) induced apoptosis in podocytes. Since cAMP is an important second messenger and plays a key role in cell survival and differentiation via protein kinases (PKA) or exchange protein directly activated by cAMP (Epac) pathways, we sought to determine the mechanism in cAMP-mediated protection of podocytes.

**Methods:** Doxorubicin was used to induce nephrosis in mice. Conditional immortalized mouse podocytes were used in vitro studies.

**Results:** In the doxorubicin nephrosis model, we found that forskolin—a selective activator of adenylate cyclases—attenuated albuminuria and improved the expression of WT-1. We failed to find 8-pCPT-2-O-Me-cAMP, a selective cAMP/Epac activator, improved PAN-induced apoptosis of cultured podocytes. When podocytes were treated with 8-pCPT-cAMP (a selective cAMP/PKA activator), PKA activation were increased in a time-dependent manner and prevented against PAN-induced podocytes loss and caspase 3 activation, as well as mitochondrial membrane potential reduction. We found that PAN and ADR resulted in a decrease of Mfn1 expression and mitochondrial fission in podocytes. Both PAN and ADR had no effect on Drp1 phosphorylation and Fis and Opa expression. 8-pCPT-cAMP restored the Mfn1 expression in puromycin or ADR-treated podocytes and induced Drp1 phosphorylation, as well as mitochondrial fusion. Treatment podocytes with an activator of PKA resulted in mitochondrial fission, podocytes loss and cleaved caspase 3 expression. Arachidonic acid abolished 8-pCPT-cAMP protective effects on PAN-treated podocytes. Mdivi, a mitochondrial division inhibitor, prevented PAN-induced cleaved caspase 3 expression in podocytes.

**Conclusions:** We concluded that activation of cAMP alleviated doxorubicin mouse podocyte injury. PKA signaling resulted in mitochondrial fusion in podocytes, at least partially mediated the effects of cAMP.

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

---

**FR-PO881**

**Twisted Gastroulation, a BMP Antagonist, Exacerbates Podocyte Injury**

**Motoko Yamagita,** 1 Sachiko Yamada, 1 Jin Nakamura, 1 Misako Asada, 1 Masayuki Takase, 2 Taiji Matsusaka, 2 Takiguchi, 2 Ryo Yamada, 1 Hiroshi Kawachi, 1 Eri Muso, 1 Aris N. Economides. 1 Nephrology, Graduate School of Medicine, Kyoto Univ, Kyoto, Japan; 2 Internal Medicine, Tokai Univ School of Medicine, Kanagawa, Japan. 1 Cell Biology, Nephrology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan; 2 Nephrology and Dialysis, Kitano Hospital, Osaka, Japan; 3 Regeneron Pharmaceuticals, Inc., NY.

**Background:** Podocyte injury is the first step in the progression of glomerulosclerosis. Previous studies have demonstrated the beneficial effect of bone morphogenetic protein 7 (Bmp7) in podocyte injury and the existence of native Bmp signaling in podocytes. Bmp7 encodes the activity of Bmp7 that is controlled by cell-type specific Bmp antagonists that inhibit the binding of Bmp7 to its receptors, we screened for Bmp antagonist expressed by podocytes, and analyzed the function.

**Methods:** We utilized conditionally immortalized murine podocytes, and Twsg1-lacZ reporter mice.

**Results:** The product of Twisted gastroulation (Twsg1), a Bmp antagonist, was the most abundant Bmp antagonist in murine cultured podocytes. The administration of Bmp induced podocyte differentiation through Smad signaling, whereas the simultaneous administration of Tws1 antagonized the effect. Tws1 was expressed in the glomerular parietal cells (PECs) and distal nephron of the healthy kidney, and additionally in damaged glomerular cells in a murine model of podocyte injury. Tws1 null mice exhibited milder hypoaalbuminemia and hyperlipidemia, and milder histological changes while maintaining the expression of podocyte markers during podocyte injury model.

**Conclusions:** Tws1 plays a critical role in the modulation of protective action of Bmp7 on podocytes, and inhibition of Tws1 is a promising means of development of novel treatment for podocyte injury.

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

---

**FR-PO882**

**Nephrin Activation Induces Endosomal Signaling Necessary for Coordinated Focal Adhesion and Lamellipodial Dynamics**

**Qingfeng Fan,** Lawrence B. Holzman. 1 Renal Div, Univ of Pennsylvania, Phila., PA.

**Background:** Nephrin ligation induces Nephrin tyrosine phosphorylation-dependent nephrosis. Nephrin endocytosis might be a mechanism by which podocyte junctions are disassembled and by which Nephrin protein and signaling is degraded in disease

---

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

**Underline represents presenting author/disclosure.**

**564A**
states. Alternatively, receptor-mediated endocytic trafficking can have signal-propagating functions, wherein “signaling endosome” complexes signal to distinct subcellular compartments. We hypothesized that Nephrin signaling ensures proper stress induction responses in podocytes.

**Methods:** We evaluated the dynamics of Nephrin endosomal trafficking, focal adhesion (FA) turnover, and lamellipodial activity in cultured podocytes following chimeric CD16-CD16NCD expression. We hypothesized that increased SA exposure induces podocyte pro-inflammatory responses.

**Results:** CD16NCD expressing podocytes exhibited augmented SA-stimulated COX-2 induction (~30 fold) compared to control cells, suggesting this as a novel potential therapeutic target.

**Conclusions:** Derlin-2 loss of function reduces podocyte injury in injury models, including diabetes and podocytopathy.

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

**Key Phrases:** Serum Albumin and Associated Factors Induce Inflammatory and Stress Responses in Podocytes and Glomeruli

**Author:** Shripa Agrawal, Adam J. Guess, Melinda A. Chanley, Rainer Bennsford, William E. Smoyer

**Methods:** Male Wistar rats received low endotoxin BSA (5 mg/g BSA) daily for 5 days and proteinuria and glomerular mRNA analyzed. Also, mRNA and protein were analyzed from mouse podocytes exposed to 40 mg/ml BSA, human SA (HSA), reconstituent HSA (rHSA), charcoal-treated BSA (C-TB), and globulin-, endotoxins, glycoproteins or fatty acids. Podocyte and alveolar macrophages were treated with 1 μg/ml LPS.

**Results:** BSA-injected rats developed marked albuminuria and enhanced glomerular gene expression of COX-2, MCP-1, CXCL1 and HSP25. In podocytes, physiological BSA levels increased basal COX-2, MCP-1 and CXCL1 expression by 1.8-fold, 1.4-fold, and 1.5-fold respectively, compared to basal expression. HSP25 expression was induced (~30 fold) by SA in podocytes. While BSA, HSA and globulin-, endotoxins-, glycoprotein- and fatty acid-free SA only moderately induced COX-2, MCP-1 and CXCL1 expression, and TNF-α, IL-1β, IL-6 and MIP-2 expression was markedly induced (~30 fold) by SA in podocytes. While BSA, HSA and HSA-glomerular mRNA also analyzed. Also, mRNA and protein were analyzed from mouse podocytes exposed to 40 mg/ml BSA, human SA (HSA), reconstituent HSA (rHSA), charcoal-treated BSA (C-TB), and globulin-, endotoxins, glycoproteins or fatty acids. Podocyte and alveolar macrophages were treated with 1 μg/ml LPS.

**Results:** BSA-injected rats developed marked albuminuria and enhanced glomerular gene expression of COX-2, MCP-1, CXCL1 and HSP25. In podocytes, physiological BSA levels increased basal COX-2, MCP-1 and CXCL1 expression by 1.8-fold, 1.4-fold, and 1.5-fold respectively, compared to basal expression. HSP25 expression was induced (~30 fold) by SA in podocytes. While BSA, HSA and globulin-, endotoxins-, glycoprotein- and fatty acid-free SA only moderately induced COX-2, MCP-1 and CXCL1 expression, and TNF-α, IL-1β, IL-6 and MIP-2 expression was markedly induced (~30 fold) by SA in podocytes. While BSA, HSA and HSA-glomerular mRNA also analyzed. Also, mRNA and protein were analyzed from mouse podocytes exposed to 40 mg/ml BSA, human SA (HSA), reconstituent HSA (rHSA), charcoal-treated BSA (C-TB), and globulin-, endotoxins, glycoproteins or fatty acids. Podocyte and alveolar macrophages were treated with 1 μg/ml LPS.

**Results:** BSA-injected rats developed marked albuminuria and enhanced glomerular gene expression of COX-2, MCP-1, CXCL1 and HSP25. In podocytes, physiological BSA levels increased basal COX-2, MCP-1 and CXCL1 expression by 1.8-fold, 1.4-fold, and 1.5-fold respectively, compared to basal expression. HSP25 expression was induced (~30 fold) by SA in podocytes. While BSA, HSA and globulin-, endotoxins-, glycoprotein- and fatty acid-free SA only moderately induced COX-2, MCP-1 and CXCL1 expression, and TNF-α, IL-1β, IL-6 and MIP-2 expression was markedly induced (~30 fold) by SA in podocytes. While BSA, HSA and HSA-glomerular mRNA also analyzed. Also, mRNA and protein were analyzed from mouse podocytes exposed to 40 mg/ml BSA, human SA (HSA), reconstituent HSA (rHSA), charcoal-treated BSA (C-TB), and globulin-, endotoxins, glycoproteins or fatty acids. Podocyte and alveolar macrophages were treated with 1 μg/ml LPS.

**Results:** BSA-injected rats developed marked albuminuria and enhanced glomerular gene expression of COX-2, MCP-1, CXCL1 and HSP25. In podocytes, physiological BSA levels increased basal COX-2, MCP-1 and CXCL1 expression by 1.8-fold, 1.4-fold, and 1.5-fold respectively, compared to basal expression. HSP25 expression was induced (~30 fold) by SA in podocytes. While BSA, HSA and globulin-, endotoxins-, glycoprotein- and fatty acid-free SA only moderately induced COX-2, MCP-1 and CXCL1 expression, and TNF-α, IL-1β, IL-6 and MIP-2 expression was markedly induced (~30 fold) by SA in podocytes. While BSA, HSA and HSA-glomerular mRNA also analyzed. Also, mRNA and protein were analyzed from mouse podocytes exposed to 40 mg/ml BSA, human SA (HSA), reconstituent HSA (rHSA), charcoal-treated BSA (C-TB), and globulin-, endotoxins, glycoproteins or fatty acids. Podocyte and alveolar macrophages were treated with 1 μg/ml LPS.

**Results:** BSA-injected rats developed marked albuminuria and enhanced glomerular gene expression of COX-2, MCP-1, CXCL1 and HSP25. In podocytes, physiological BSA levels increased basal COX-2, MCP-1 and CXCL1 expression by 1.8-fold, 1.4-fold, and 1.5-fold respectively, compared to basal expression. HSP25 expression was induced (~30 fold) by SA in podocytes. While BSA, HSA and globulin-, endotoxins-, glycoprotein- and fatty acid-free SA only moderately induced COX-2, MCP-1 and CXCL1 expression, and TNF-α, IL-1β, IL-6 and MIP-2 expression was markedly induced (~30 fold) by SA in podocytes. While BSA, HSA and HSA-glomerular mRNA also analyzed. Also, mRNA and protein were analyzed from mouse podocytes exposed to 40 mg/ml BSA, human SA (HSA), reconstituent HSA (rHSA), charcoal-treated BSA (C-TB), and globulin-, endotoxins, glycoproteins or fatty acids. Podocyte and alveolar macrophages were treated with 1 μg/ml LPS.

**Results:** BSA-injected rats developed marked albuminuria and enhanced glomerular gene expression of COX-2, MCP-1, CXCL1 and HSP25. In podocytes, physiological BSA levels increased basal COX-2, MCP-1 and CXCL1 expression by 1.8-fold, 1.4-fold, and 1.5-fold respectively, compared to basal expression. HSP25 expression was induced (~30 fold) by SA in podocytes. While BSA, HSA and globulin-, endotoxins-, glycoprotein- and fatty acid-free SA only moderately induced COX-2, MCP-1 and CXCL1 expression, and TNF-α, IL-1β, IL-6 and MIP-2 expression was markedly induced (~30 fold) by SA in podocytes. While BSA, HSA and HSA-glomerular mRNA also analyzed. Also, mRNA and protein were analyzed from mouse podocytes exposed to 40 mg/ml BSA, human SA (HSA), reconstituent HSA (rHSA), charcoal-treated BSA (C-TB), and globulin-, endotoxins, glycoproteins or fatty acids. Podocyte and alveolar macrophages were treated with 1 μg/ml LPS.
FR-PO887

Exploring the Role of Annexin A2 in the Glomerulus
Biao Li1, Tuncer Onay,2 Chengjin Li3, Susan E. Quaggin.4
1Dept of Nephrology, Feinberg Cardiovascular Research Institute, Chicago, IL; 2Dept of Nephrology, Feinberg Cardiovascular Research Institute, Chicago, IL; 3Dept of Nephrology, Feinberg Cardiovascular Research Institute, Chicago, IL; 4Dept of Nephrology, Feinberg Cardiovascular Research Institute, Chicago, IL.

Background: Annexin A2 (Annexin A2) is a phospholipid binding protein, which participates in a number of critical cellular processes that include specific binding to plasmalemma, formation of filopodia and lamellipodia through interaction with actin and acting as a capping protein for actin. Our previous studies identified Annexa2 to be involved in podocyte attachment and foot process (FP) formation triggered by soluble Flt1 (sFlt1) binding to the podocyte surface. We hypothesize that Annexa2 cooperates with sFlt1 to guide cytoskeletal changes for FP formation and maintenance.

Methods: We generated an Annexa2 foxed mouse line and used it to develop a whole body and podocyte specific knockout (KO) mice. The stability of the FP cytoskeleton was tested by protamine sulfate perfusion of KO and WT mice followed by heparin recovery. In vitro, cell cycle and motility of human podocytes was examined, following knockdown (KD) of Annexa2 by siRNA.

Results: Histologic analysis did not demonstrate any major differences between Annexa2 global or podocyte -KO and control kidneys at 4 weeks of age; however, diffuse fibron deposition was observed in glomerular capillaries of KO kidneys. Following perfusion with protamine sulfate, KO mice showed a trend towards protection. In vitro, KD of Annexa2 in human podocytes resulted in a dramatic increase in podocyte cell size, development of cytosolic stress fibers, and formation of focal adhesions. Furthermore, Annexa2 KD podocytes demonstrated a marked decrease in proliferation (Day 5, 1.3±0.12 X 10^5 vs. 2.5±0.29 X10^5; p=0.029). Cell cycle was arrested at G1 determined by FACS (0.79±0.14% vs. 0.709±0.04%; p=0.001). Cell motility was also decreased.

Conclusions: Loss of Annexa2 appears to confer stability to podocyte FPs when acutely challenged. Further studies are ongoing to determine how Annexa2 regulates podocyte adhesion, FP formation and function.

Funding: Government Support - Non-U.S.

FR-PO888

Mutual Antagonism of WT1 and β-catenin Dictates Podocyte Health and Disease
Li Li Zhou,1 Roderick J. Tan,2 Dong Zhou,1 Youhua Liu.1 1Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; 2Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Activation of β-catenin, the principal mediator of canonical Wnt signaling, plays a critical role in mediating podocyte de-differentiation and dysfunction in the evolution of proteinuric kidney diseases. However, the mechanism by which β-catenin induces podocyte injury remains poorly understood. Here, we demonstrate that β-catenin directly antagonizes Wilms tumor 1 (WT1), a key transcription factor exclusively expressed in podocytes and required for the maintenance of podocyte differentiation and glomerular filtration barrier function.

Methods: BALB/c and cultured podocytes were used. Expression of various genes was analyzed by qRT-PCR, Western blot and immunostaining, respectively.

Results: In BALB/c mice injected with adriamycin, WT1 protein was gradually lost in glomerular podocytes at 1, 3 and 5 weeks. Interestingly, loss of WT1 was apparently not due to podocyte depletion in this model, as other podocyte-specific markers including synaptopodin and α-actinin-4 were preserved. Loss of WT1 was closely associated with loss of nephron and acquisition of Smad2/3, Snail1, PAI-1, Fsp1 and MMP-7. In vitro, over-expression of β-catenin suppressed WT1-mediated podocytin expression. Conversely, over-expression of WT1 in podocytes inhibited β-catenin-mediated Smad2 and PAI-1 expression, suggesting that WT1 and β-catenin mutually antagonize each other. We found that β-catenin-induced WT1 protein degradation through the ubiquitin-proteasomal pathway, and incubation with MG-132 preserved WT1. In vivo, either inhibition of β-catenin signaling by small molecule inhibitor IC5G-001 or administration of WT antagonist Klotho restored WT1 protein and attenuated podocyte injury and proteinuria in adriamycin nephropathy.

Conclusions: These findings suggest that β-catenin signaling targets WT1 degradation, leading to podocyte dedifferentiation and dysfunction. Our results also indicate that WT1 and β-catenin play an opposing role in podocyte biology and their ratio dictates podocyte health and disease in vivo.

Funding: NIDDK Support

FR-PO889

CLIC5A Deficiency Accentuates Glomerular Damage in DOCA/Salt Hypertensive Mice
Mhattab Tavaassoli, Laiji Li, Lin-Fu Zhu, Benjamin Alexander Adam, Barbara J. Ballermann. Medicine, Univ of Alberta, Edmonton, Canada.

Background: Glomerular capillary (GC) hypertension is a risk factor for glomerular injury, including diabetic nephropathy. Podocytes extend inter-digitating actin-based foot processes around the exterior of glomerular capillaries, buttressing the vessel wall against the prevailing high intra-capillary pressure. CLIC5A is highly and uniquely expressed at the apical plasma membrane (PM) of podocyte foot processes, where it is part of the Ezrin-NHERF2 complex that links podocalyxin to cortical actin, and deletion of CLIC5A in mice leads to ezrin dephosphorylation and disorganization of podocyte foot processes (Am. J Physiol 298:F1492, 2010). This study explored the hypothesis that lack of CLIC5A is detrimental to glomerular integrity under conditions of increased mechanical strain.

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

Poster/Friday

FR-PO890

Lysosomal Processing of Albumin in Podocytes
John M. Carson,1 Kayo Okamura,1 Hidefumi Wakashiu,2 Evgenia Dobrinskikh,1 Jeffrey B. Kopp,2 Judith Blaine.1 1Univ of Colorado Denver, Aurora, CO; 2NIDDK, NIH, Bethesda, MD.

Background: Albuminuria is a strong, independent predictor of CKD progression. The mechanism by which albuminuria on its own provokes kidney injury is unknown. In collapsing FSGS, where albumin vacuoles in podocytes are a prominent feature, podocyte loss and glomerulosclerosis occur rapidly. In minimal change disease, albumin accumulation in podocytes is nominal and decline in renal function is gradual. We hypothesize that podocyte processing of albumin, via cathepsin B, may be an important determinant of podocyte injury and loss.

Methods: Human urine was isolated from subjects with polycystic kidney disease (PKD) and type 2 diabetes mellitus (DM). Urine samples were processed on HUPECs treated with albumin (400 µg/mL). Albumin degradation was measured by quantifying FITC-albumin HUPECs with FITC-albumin. Co-localization of albumin with lysosomes was determined by confocal microscopy. Albumin degradation was measured by Western blot. Lysosomal acidification was measured by Western blot. Degradation degradation experiments were repeated in HUPECs treated with chloroquine, a lysosome inhibitor, or MG-132, a proteasome inhibitor. Lysosomal activity was measured by fluorescence recovery after photobleaching. Cytokine production was measured by ELISA. Cell death was determined by Trypan blue staining. In vivo, staining with albumin and LAMP-1, a lysosome marker, was performed on tissue from a Denys-Drash mouse model of albuminuria.

Results: HUPECs endocytosed albumin which co-localized with LAMP-1. Co-localization was not MG-132 or chloroquine sensitive. Albumin degradation was measured by Western blot. Albumin abundance in HUPEC lysates by Western blot. Degradation experiments were repeated in HUPECs treated with chloroquine, a lysosome inhibitor, or MG-132, a proteasome inhibitor. Lysosomal activity was measured by fluorescence recovery after photobleaching. Cytokine production was measured by ELISA. Cell death was determined by Trypan blue staining. In vivo, staining with albumin and LAMP-1, a lysosome marker, was performed on tissue from a Denys-Drash mouse model of albuminuria.

Conclusions: These data suggest lysosomal dysfunction may contribute to podocyte injury and glomerulosclerosis in diabetes mellitus.

Funding: NIDDK Support

FR-PO891

Molecular Characterization of Podocyte-Endothelial Cell Signaling Crosstalk Identifies New Endothelial Cell Targets for Prevention of Glomerular Diseases
Ilse S. Daehn,1 Gabriella Casalena,1 Liping Yu,1 Kerstin Ebefors,2 Detlef O. Schloendorf,1 Borje Haraldsson,2 Erwin P. Bottinger.1 1Dept of Medicine - Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY; 2Molecular and Clinical Medicine - Nephrology, Institute of Medicine, Univ of Gothenburg, Gothenburg, Sweden.

Background: Crosstalk between endothelial cells and podocytes in glomeruli is essential for maintaining structural and functional integrity. Crosstalk is involved in the onset and progression of proteinuric kidney disease. Interactions between podocytes and endothelial cells mediate podocyte survival and proliferation via paracrine mechanisms. Crosstalk is involved in the onset and progression of proteinuric kidney disease. Interactions between podocytes and endothelial cells mediate podocyte survival and proliferation via paracrine mechanisms. Previous studies have shown that endothelial cells can activate podocytes via Ednra activation, which precedes subsequent podocyte loss and proteinuria [Daehn et al., ASN 2011]. We have further characterized endothelial-podocyte interactions in glomerular diseases.

Materials and Methods: In vitro, cells were cultured on HUVEC monolayers in the presence or absence of different factors and analyzed using Western blotting, immunofluorescence, and quantitative real-time PCR. In vivo, adriamycin-induced glomerulosclerosis was induced in mice (n=10 per group) and the expression of target genes was analyzed using qPCR. Results: In vitro, the expression of target genes was significantly increased in glomerular endothelial cells treated with endothelial cell activator molecule (ECAM). In vivo, adriamycin-induced glomerulosclerosis was significantly reduced in mice treated with ECAM (p<0.05). Conclusion: These findings suggest that ECAM is a novel target for the prevention of proteinuric kidney disease.

Funding: National Institutes of Health (NIH) grant T32DK007258 (to I.S.D.)
Conclusions: Podocyte injury induces Edn1 as an essential mediator of endothelial mitochondrial stress and dysfunction that underlies proteinuric podocyte-initiated segmental glomerulosclerosis. Prevention of endothelial damage may be considered a new therapeutic approach for FSGS.

Funding: NIDDK Support

FR-PO892
PLA2R Tightly Associates with Integrin αβ1, in the Podocyte Membrane: A New Insight into IMN Pathogenesis Qiansheng Zhu, Liyo Kao. Medicine, Univ of California, Los Angeles, Los Angeles, CA.

Background: PLA2R has been firmly established to serve as the major antigen on the podocyte surface targeted by circulating autoantibodies in patients with idiopathic membranous nephropathy (IMN), however, the pathobiology of how the antibodies binding to the extracellular domain of PLA2R then cause IMN remains largely unclear. Other than serving as a scavenger receptor for inactivation and removal of the secreted integrin intracellular cytoskeleton organization. We hypothesize that PLA2R may interact with that is highly expressed on the basal surface of podocytes along the glomerular basement membrane (GBM), where it is critically involved in GBM matrix arrangement and podocyte intracellular cytoskeleton organization. We hypothesize that PLA2R may interact with integrin αβ1, in the human podocytes and that autoimmune antibodies binding to PLA2R perturbs the downstream signaling pathways of both PLA2R and integrin αβ1, resulting in the altered GBM and altered podocyte cytoskeleton organization in IMN.

Methods: In the present study, we tested PLA2R and integrin αβ1, interaction in the differentiated human podocytes, the human kidney cortex and HEK 293 cells co-expressing PLA2R and integrin αβ1, by using immunocytochemistry, co-immunoprecipitation and biochemical analysis.

Results: We discovered that two populations of PLA2R exist in the human podocytes, one co-localizes with integrin αβ1, in both the endoplasmic reticulum and the plasma membranes, and the other is free. Immunoprecipitation study using an anti-integrin αβ1, antibody revealed that PLA2R associates with integrin αβ1, not only in the differentiated human podocytes, but also in the human kidney cortex and the HEK 293 cells co-expressing PLA2R and integrin αβ1, heterologously. Further analysis showed this interaction occurs in the extracellular domains between the two receptors.

Conclusions: Our findings demonstrated for the first time that PLA2R associates tightly with integrin αβ1, on the podocyte surface, which may provide new insights into the pathogenic mechanism of IMN mediated by auto-antibodies binding to PLA2R.

Funding: Private Foundation Support

FR-PO893
Glepp1 Deficiency Promotes GBM Humps Eva Koenigshausen, Laura Lennartz, Ivo Quack, Thorsten Wiech, Lars C. Rump, Lorenz Sellin, Nephrology, Heinrich Heine Univ, Duesseldorf, Germany; Pathology, Univ Hospital Eppendorf, Hamburg, Germany.

Background: Proteinuria is one of the symptoms of inherited and acquired glomerular kidney diseases. Proteinuria evolves out of the damage of the glomerular filter. One major components of the glomerular slit diaphragm is nephrin, which is phosphorylated by src kinases. A loss of nephrin out of the glomerular slit, for example by endocytosis, results in proteinuria. GLEPP1 is a receptor tyrosine phosphatase in the podocyte foot process. Mutations in the GLEPP1 gene were shown to be associated with FSGS in childhood. The precise function of GLEPP1 is not fully understood.

Methods: Perfused kidneys from mice were fixed in 4% paraformaldehyde or in RNA stabilization reagent. For light microscopy kidneys were embedded in paraffin, stained with PAS, or were embedded in Epon and processed for electron microscopy. RNA was isolated and qPCR for Col4 alpha1 and alpha2 was performed. Mouse urine further PAS staining, or were embedded in Epon and processed for electron microscopy.

Results: In the present study, we tested Glepp1 deletion in the extracellular domains between the two receptors.

Conclusions: Our findings demonstrated for the first time that PLA2R associates tightly with integrin αβ1, on the podocyte surface, which may provide new insights into the pathogenic mechanism of IMN mediated by auto-antibodies binding to PLA2R.

Funding: Private Foundation Support

FR-PO894
Patterns of Circulating Autoantibodies in Patients with Lupus Nephritis Dawn J. Casteg, Daniel J. Birmingham, Ami S. Joglekar, Jon B. Klein, John Barker Harley, Erik Korte, Brad H. Rovin, Kenneth R. Meleish, David W. Powell. Medicine, Univ of Louisville, Louisville, KY; Medicine, The Ohio State Univ, Columbus, OH; VAMC, Louisville, KY; Pediatrics, Cincinnati Children’s Hospital, Cincinnati, OH.

Background: Lupus nephritis (LN) occurs in at least 50% of SLE patients, but the nephritogenic autoantibodies responsible have yet to be identified. Recently, an autoantibody to the M-type phospholipase A2 receptor on podocytes was identified as causing podocytopathy membranous nephropathy using immunoblot analysis of patient sera. This study used sera from SLE patients with and without LN to test the hypothesis that patients with different classes of LN express unique patterns of autoantibodies against native glomerular proteins.

Methods: Human glomerular extracts were IgG depleted and separated by SDS-PAGE and immunoblotted with 1:200 dilution of sera from 16 Class V LN patients, 10 Class III/IV LN patients, 10 SLE patients without nephritis, and 5 normal controls (NC).

Results: A reactive band between 43-46 kDa was present in 14/16 patients with class V LN and 5/10 patients with class III/IV LN, but was seen in only 1/10 SLE patients without nephritis and 2/5 NC. A reactive band between 36-40 kDa was present in 11/16 patients with class V LN, 3/10 patients with class III/IV LN, 2/10 SLE patients without nephritis, and 1/5 NC. A reactive band between 23-28 kDa was present in 10/16 patients with class V LN, 8/10 patients with class III/IV LN, 4/10 SLE patients without nephritis, and 2/5 NC. A reactive band between 98-105 kDa was present in the majority of subjects in all groups, including NC. Using LC-MS/MS we identified 14 membrane-associated podocyte proteins, including AAMP and NCEH1 in the 43-46 kDa molecular weight range and ANBP1 in the 36-40 kDa range.

Conclusions: We conclude that LN patients express unique patterns of autoantibodies against native glomerular proteins that will allow identification of the targets of nephritogenic autoantibodies that cause various forms of LN.

Funding: Other NIH Support - NIAID; NIAMS

FR-PO895
Neph1 Signaling, a Novel Therapeutic Target for Protection of Podocytes against Glomerular Injury Deepak Nihalani, Eshthamm Arif, Babita Kumari, Lawrence B. Holzman. Medicine, Univ of Pennsylvania, Philadelphia, PA.

Background: Podocytes are specialized epithelial cells that are critical components of the glomerular filtration barrier and their dysfunction leads to proteinuria and renal failure. Thus preserving podocyte function in the event of a glomerular injury is therapeutically significant.

Methods: We used zebrafish as an in vivo model and poocyte cell culture as an in vitro model to demonstrate that inhibiting Neph1 signaling prevents podocyte from glomerular injury.

Results: In this study, we show that inhibiting the intracellular signaling of Neph1 by transducing the cytoplasmic domain of Neph1 (Neph1CD) in cultured podocytes protects podocytes from PAN induced injury. In addition to inhibiting the PAN induced Neph1 phosphorylation, the Neph1CD transduced cells were resistant to PAN induced cytoskeletal damage. In an in vivo assay using zebrafish model system, we demonstrated that transduction of Neph1CD in zebrafish prevented them from PAN induced injury. Further biochemical analysis using subfractionation of the transduced and control podocyte cells showed that unlike the control cells Neph1 was retained in the lipid raft fractions in the transduced cells following treatment with PAN. In accordance, the immunofluorescence analysis suggested that Neph1CD transduced cells had increased ability to retain endogenous Neph1 at the membrane in response to PAN induced injury. Consistent with these observations, maintaining high levels of Neph1 at the membrane using a podocyte cell line expressing chimeric Neph1 had a similar protective effect from PAN induced injury with increased propensity to maintain tight junctions in podocytes. The albumin filtration assay further supported these results as these cells were resistant to PAN induced leakage.

Conclusions: Collectively, these results identify Neph1 signaling as a novel therapeutic target for the prevention of podocyte damage that is commonly observed in various glomerular diseases.

Funding: NIDDK Support, Private Foundation Support

FR-PO896
Involvement of Planar Cell Polarity Pathway in Glomerular Development and Function Brittany L. Rocque, Elena Torban. Deps of Physiology and Medicine, McGill Univ, Montreal, Canada.

Background: The Planar Cell Polarity (PCP) signaling pathway is crucial for tissue development and function. Vangl2 protein is central in the PCP pathway: its loss is embryonic lethal causing neural tube defects in mice and humans. In the kidney, PCP signaling is thought to be important for the organization of glomerular epithelial cells, podocytes, along the glomerular basement membrane. Podocyte cell protrusions, foot processes (FP), are critical for kidney filtration functions; loss of FP architecture results in proteinuria and severe glomerulosclerosis. In our previous studies, we demonstrated an effect of PCP pathway on podocyte shape, actin rearrangement and cell motility (Babayeova, 2011, AJP). We, therefore, hypothesized that the PCP pathway is involved in glomerular development and function.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure. 567A

**Background:** Studies have demonstrated that NADPH oxidase-derived reactive oxygen species activates NLRP3 inflammasomes causing hyperhomocysteinemia (hhcy)-induced podocyte and glomerular injury, but the mechanism regarding how the hhcy inflammasomes changes in oxidative stress is still unknown. Thioredoxin Interacting Protein (TXNIP) mediates hhcy-induced inflammasome activation in vivo.

**Methods:** hhcy-induced oxidative stress was administered to adult mice by feeding a high hcy diet or transgenic mice expressing hcy in podocytes. TXNIP inhibition was achieved by doxycycline (DOX)-inducible and reversible knockdown of TXNIP in podocytes. Podocytes isolated from DOX-elicited mice were then treated with SIRT1 inhibitor in vitro. Podocytes were isolated from wild-type (WT) and Sirt1-deficient (Sirt1−/−) mice for analysis in vitro.

**Results:** TXNIP blockade demonstrated glomerular protective effects through reduced proteinuria and albuminuria. TXNIP knockdown upregulated the expression of proteins known to contribute to podocyte injury and inflammation. In vivo, TXNIP inhibition significantly reversed podocyte injury and preserved glomerular morphology.

**Conclusions:** TXNIP is an essential mediator of hhcy-induced podocyte injury. Blocking TXNIP may provide a new therapeutic strategy for hhcy-induced podocyte injury.
Sirt1 by adapting a novel in vivo RNA interference (RNAi) model. Sirt1 protein and mRNA levels were assessed by western blotting and quantitative realtime PCR. Urinary protein excretion was quantified by antibody and SDS gel electrophoresis followed by Coomassie Blue staining. Serum creatinine was measured by HPLC. PAS-stained kidney sections and transmission electron microscopy were used to assess renal histology and podocyte morphology.

Results: We achieved temporal and spatial control over Sirt1 expression in kidney podocytes and tubular cells. We confirmed that up to ~30% reduction of Sirt1 in podocytes is dispensable for normal kidney function. Mice with global Sirt1 knockdown developed more proteinuria compared to those without Sirt1 knockdown when both were injected with Adrurnamylin (ADR). Furthermore, ADR-treated mice with podocyte-specific Sirt1 knockdown developed more severe glomerulosclerosis, podocyte foot process effacement and proteinuria, which were partially reversed upon reversal of Sirt1 knockdown, whereas mice with tubular-specific Sirt1 knockdown were not susceptible to ADR-induced nephropathy.

Conclusions: Podocyte Sirt1 serves a protective role in ADR-induced nephropathy.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO902

PPARγ in Podocytes Promotes Resistance to Crescentic Glomerulonephritis

Carole Hénique-Grijec,1,2 Guillaume Bolles,1,2 Marine Milan,1,2 Pierre-Louis F. Tharaux,1,2 Paris Cardiovascular Research Centre - PARCC, INSERM, Paris, France;1 Univ Paris Descartes, Sorbonne Paris Cité, Paris, France.

Background: The nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) agonists have beneficial effects on renal structure and function in models of diabetes and chronic kidney diseases. In this study, we have explored the involvement of PPARγ in crescentic progressive glomerulonephritis (RPGN).

Methods: RPGN was induced by injection of anti–glomerular basement membrane anti-sense (nephrotoxic serum, NTS). We administered Pioglitazone starting in a delayed manner (4 days after NTS injection). Pod-PPARγ agonist, limited renal injury in RPGN. Pioglitazone ameliorated podocyte damage and reduced proteinuria. Pioglitazone administration was effective when performed from the first day of NTS injection or when started in a delayed manner (4 days after NTS injection). Loss-of-function approach: We generated mice with specific deletion of PPARγ alleles in podocytes (Pod-PPARγ mice). Pod-PPARγ mice developed more severe glomerular injury and RPGN upon NTS administration. Pod-PPARγ mice displayed a 2-fold increase in Albuminuria to Creatinuria ratio at day 10 (2843 +/- 329 vs. 1664 +/- 207 g/mol, p<0.001) than wild-type mice and higher crescent incidence (35.6 +/- 5.4 vs. 15.6 +/- 3.7%, p<0.01). Accordingly, PPARγ deletion in podocytes promoted worsening of blood urea nitrogen levels (199.9 +/- 11.6 vs. 56.7 +/- 9.0 mg/dl, p<0.001). Such aggravation was not due to an effect on proliferation and migration of primary podocytes.

Conclusions: In conclusion, PPARγ activity is essential for resistance to crescentic RPGN by providing protective effects on podocyte phenotype and the glomerular architecture during experimental RPGN. PPARγ is involved in mitochondrial biogenesis and function. Moreover, it is known that mitochondria are the main site of reactive oxygen species production. In cells exposed to oxidative stress, NRF2 activity is increased, further driving the transcriptional activation of genes whose expression is essential to control cellular redox homeostasis. Thus, we have also further explored the role of oxidative stress via NRF2 anti-oxidant pathway in this model.

Funding: Government Support - Non-U.S.

FR-PO906

Podocytes Lacking Cell Surface Heparan Sulfate Show Enhanced Production/Shedding of Nephrin Positive Microparticles/Exosomes

Kevin J. McCarthy, Deborah J. McCarthy. Pathology, LSU Health Sciences Center-Shreveport, Shreveport, LA.

Background: Several recent reports have shown that one cell surface proteoglycan, family, syndecans (SDCs), play a key role in the regulation of exosome production/release. Since heparan sulfate (HS) is found covalently attached to SDCs and mediate SDC interactions and clustering at the cell surface, we hypothesized that loss of HS from SDC core proteins on podocyte (podo) pedicels would affect the production of podo urinary exosomes.

Methods: Mutant mice having podo lacking the ability to assemble heparan sulfate (HS) on SDC proteins were previously described (PEXTKO mice, Kid Int 74:289-299). Kidneys from wild type (WT), unilateral nephrectomized (UNX) WT, PEXTKO, and PEXTKO UNX

FR-PO905

Self-Regulation of HO-1 in GEC

Maria Detsika,1 Pu Duann,2 Elias A. Lianos,3 Medicine, National and Kapodistrian Univ of Athens, Greece;3 Div of Nephrology, Univ of Medicine and Dentistry of New Jersey.

Background: Although Heme oxygenase (HO-1) is a renoprotective, glomerular epithelial cells (GEC) have a limited ability to upregulate HO-1 as shown in HO-1 inducing forms of GEC injury. This raises the question of whether HO-1 induction in GEC is subject to tight regulation and was addressed in normal rat glomeruli.

Methods: Glomeruli were isolated from male, wild type (WT), Sprague-Dawley rats (SD), hmox1+/-, SD, hmox1+/- SD, and SD with (GEC)-targeted HO-1 overexpression (GEC+HO-1). Hmox1+/- and Hmox1+/- SD were obtained using Zinc Finger Nuclease (ZFN) technology designed to generate a 10-bp deletion in a specific HO-1 sequence within exon 3. GEC+HO-1 SD were obtained by Sleeping Beauty Transposon mediated transgenesis using a nephrin promoter. Glomeruli from WT, Hmox1+/-, Hmox1+/- and GEC+HO-1 SD were treated with defined Heme concentrations for 18 h. Glomerular HO-1 protein and mRNA levels were assessed by western blotting and Real-time PCR amplification.

Results: A 60-70% reduction in constitutive HO-1 levels and complete HO-1 absence was observed in hmox1+/- and hmox1+/- glomeruli, respectively. In WT glomeruli, low Heme (6-200 mM) concentrations increased HO-1 synthesis (mRNA and protein) in a dose dependent manner. At higher Heme concentrations (400 mM), HO-1 synthesis (mRNA and protein) was reduced to constitutive levels while at 800 mM there was an even higher reduction to almost constitutive levels. In hmox1+/- glomeruli, Hmox1 (400 mM) failed to reduce HO-1 synthesis. In GEC+HO-1 glomeruli, there was a shift of the inhibitory effect of Heme on HO-1 synthesis to lower Heme concentrations (200 mM) capable of inducing HO-1 in WT glomeruli. This effect was blocked in WT glomeruli co-incubated with Heme and MG132, (proteasome inhibitor) at concentrations that increased endogenous HO-1 levels.

Conclusions: Heme-mediated HO-1 synthesis in GEC is negatively regulated by HO-1 protein levels achieved, pointing towards a negative feed-back regulatory mechanism. This may serve as a HO-1 switch-off mechanism, upon injury-mediated HO-1 induction, preventing HO-1 from reaching potentially cytotoxic levels.

Funding: Pharmaceutical Company Support - ELPEN Pharmaceutical Industry

FR-PO903

Angiotensin II and Diacylglycerol Cause Activation of Stat-3 in Podocytes through a Pathway That Includes TRPC6 Channels, Calcineurin, and CaM Kinase Stuart E. Dryer,1,2 Moussa Abkhezr.1 1 Dept of Biology and Biochemistry, 1Dept II of Internal Medicine

Results: Application of 100 nM angiotensin II (Ang II) for 15 min-1 hr caused a marked increase in the phosphorylation of Stat-3 on tyrosine Y705. A similar effect was seen after treatment with 100 μM of the diacylglycerol analog 1-oleoyl-2-acetyl-sn-glycerol (OAG). In confocal microscopy, we observed that both treatments led to accumulation of Stat-3 in the cell nucleus. Stat-3 phosphorylation and nuclear localization were reduced by pretreatment with the pan-TRP channel inhibitor SKF-96365, and by siRNA knockdown of TRPC6, which also reduced basal phosphorylation of Stat-3. The effects of OAG persisted in cells treated with the PKC inhibitor chelerythrine. We used several agents to examine pathways downstream of TRPC6 that could lead to Stat-3. We observed that Ang II-evoked phosphorylation of Stat-3 was blocked by pretreatment with the CaM Kinase inhibitor KN-93, by the calcium inhibitor cyclopiazonic-A, and by the JAK inhibitor AG490.

Conclusions: Stat-3 is a downstream effector of TRPC6 signaling, but Ang II may activate more than one cascade leading to tyrosine phosphorylation of this transcription factor. It remains to be determined if calcineurin, CaM kinase and JAK comprise parallel pathways feeding into Stat-3.

Funding: Pharmaceutical Company Support - Pfizer

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

Underline represents presenting author/disclosure.

569A
Akioka, Yutaka Yamaguchi, Motoshi Hattori. Unclear. To clarify the sequential events in the glomeruli after exposure of FSGS plasma reperfusion (0 hour), one hour after reperfusion, and several days after reperfusion. FSGS mitochondrial protein expression. Similar to those in vivo results, AA treatment could accompanied with marked decrease of mtDNA copy number and mtDNA-encoded ATP content, oxygen consumption rate and mitochondrial membrane potential as well as increase cellular reactive oxygen species in cultured podocytes.

Conclusions: Aristolochic acid can induce podocyte damage and dysfunction, which may be mediated by promoting mitochondrial DNA damage and dysfunction in podocytes. Funding: Government Support - Non-U.S.

FR-PO099

Background: IgA nephropathy (IgAN) is an autoimmune glomerulonephritis wherein immune complexes (IC) composed of galactose-deficient IgA1 (Gd-IgA1) and anti-glucan autoantibodies deposit in the glomeruli. We developed an animal model by using in vitro-formed IC from human Gd-IgA1 myeloma protein and recombinant Gd-IgA1-specific IgG for induction of IgAN-like disease in mice. The purpose of this study was to quantify mesangial proliferation in this model of IgAN.

Methods: Severe-combined-immunodeficiency (SCID) mice were repeatedly injected every other day (total 3 injections) with Gd-IgA1-IgG IC (IC-group) or with Gd-IgA1 only (control group). Kidneys from IC-group mice were removed 1, 4, 7, and 14 days after the last IC administration and from the control group mice 1 day after the last Gd-IgA1 administration. Kidneys were fixed in formalin, processed, and embedded in paraffin. Transverse sections, 5 μm thick, were stained with periodic-acid Schiff. Using IP Lab software, multiple glomeruli for each animal were examined and average cellularity per unit of glomerular area was calculated.

Results: Mesangial cellularity in the control group was 34.6±1.1 x 10^5 nuclei per μm² with normal histology at 1 day after the last injection of Gd-IgA1. In the IC-group, significantly increased cellularity of mesangial cells was observed at 1, 4, and 7 days after the last injection: 42.6±1.6, 39.9±0.7 and 42.8±1.8 x 10^5 nuclei per μm², respectively. At 14 days after the last injection, glomerular cellularity declined to baseline, 58.1±3.5 x 10^5 nuclei per μm². The glomerular changes were consistent with those of human IgAN as they included glomerular hypercellularity and mesangial matrix expansion.

Conclusions: Our passive mouse model of IgAN confirms the importance of circulating Gd-IgA1-IgG IC in the pathogenesis of IgAN and induction of histopathologic changes typical of human IgAN. Morphometric evaluation of the glomerular cellularity is an objective method for assessment of pathological changes in this model.

Funding: NIDDK Support

FR-PO0910
Global Analysis of Glucocorticoid Action in Human Podocytes James McCaffrey, Hellyeh Hamidi, Nicholas J. Webb, David W. Ray, Rachel Lennon. Institute of Human Development, Univ of Manchester, United Kingdom; Dept of Nephrology, Royal Manchester Children’s Hospital, United Kingdom.

Background: Children presenting with nephrotic syndrome (NS) typically receive an empiric course of glucocorticoid (Gc) therapy. Glucocorticoids activate ligand-dependent transcription factors. Those who do not respond to Gc treatment are at high risk of developing end stage renal disease. The clinically-relevant, podocyte-specific mechanisms of action of glucocorticoids in NS have not been determined. Elucidating relevant pathways will guide novel therapeutic targeting. We undertook a global analysis of Gc-regulated genes in human podocytes to generate hypotheses for Gc mechanisms of action.

Methods: The transcriptional profile of prednisolone-treated and prednisolone-naïve wild type human podocytes were compared using the Affymetrix U133 Plus 2.0 Array. Comparing whole genome expression data from the two cell groups allowed the creation of a list of Gc-regulated transcripts. This list underwent enrichment analysis for gene ontology terms with two independent software packages, and further experimental validation with live cell imaging and immunofluorescence.

Results: 606 Gc-regulated transcripts were identified (fold change with treatment ±1.5, q-value <0.05). Enriched gene ontology terms included those associated with regulation of apoptosis, cell signalling and cell motility. Live cell imaging analysis showed that Gc exposure significantly reduced podocyte motility (0.0034 μm/sec in untreated cells Vs. 0.0025 μm/sec in treated cells, p-value <0.0001), and altered sub-cellular localisation of synaptopodin, which has already been implicated in both regulation of podocyte motility and recovery of the filtration barrier from proteinuria-inducing agents.

Conclusions: Whole genome transcriptional profiling of human podocytes allowed identification of Gc-regulated transcripts. Selected follow-up validation demonstrated that glucocorticoids affect podocyte motility in vitro, and alter the localisation of synaptopodin, a key regulator of cytoskeletal dynamics. These findings may relate to the therapeutic effect of glucocorticoids in NS.

Funding: Pharmaceutical Company Support - GlaxoSmithKline, AstraZeneca, ICON, Government Support - Non-U.S.
FR-PO911
Localization of SGLT2 in Bowmann’s Capsule of Mouse Kidney
Niloofoar M. Tabatabai,1 Paula North,2 Kevin R. Regner,3 Suresh Kumar,3 Christine Duris,4 Amy B. Blodgett,5 1Medicine, Medical College of Wisconsin; 2Pathology, Medical College of Wisconsin.

Background: SGLT2 is a sodium-dependent glucose transporter. Genetic mutations in human and gene knock out studies in mouse have shown that SGLT2 is responsible for most of the glucose reabsorbed from the renal glomerular filtrate. Treatment of diabetic patients with inhibitors of SGLT2 increases the urinary excretion of glucose and lowers the serum concentration of glucose. It is known that SGLT2 is expressed in early proximal tubule. In this study, we re-examined SGLT2 localization by immunohistochemical analyses on kidneys from wild-type mice using our custom SGLT2 antibody.

Methods: Male C57Bl/6 mice at 4, 12, and 22 weeks of age were used. Western blot was performed with SGLT2 antibody (0.77 μg/ml) on proteins from whole kidney lysate (25 μg) or cortical brush border membrane (BB) (2 μg), and detection was carried out by chemiluminescence. For immunohistochemistry, formalin-fixed paraffin-embedded tissues were sectioned (4 μm) and stained with SGLT2 (1 μg/ml) or nephrin antibody, and staining was detected with horse-radish peroxidase chromogen method (IHC). Slides were counterstained with hematoxylin and then scanned to make digital images. Fluorescence detection (IF) of SGLT2 and nephrin staining was done using Cy3 and Alexa-647 coupled secondary antibodies, respectively, and nuclei were stained with 4-6-Diamidino-2-Phenylindole. Fluorescence imaging was done with a Zeiss confocal microscope. SGLT2-stained glomeruli were counted in IHC slides and expressed as percent total glomeruli.

Results: In Western blot, SGLT2 antibody hybridized to a ~60 kDa protein in whole kidney lysate and in brush border membrane. As expected, SGLT2 antibody stained cortical region and apical side of the proximal tubule cells in kidneys from three age groups. SGLT2 staining was also observed in Bowman’s capsule, and IF double staining showed that it was not co-localized with nephrin. SGLT2-positive glomeruli were 14%, 67%, and 87% in tissue sections from 4, 12, and 22 week old mice, respectively.

Conclusions: Our results suggest that SGLT2 is expressed in glomerular parietal epithelial cells and that this expression may be regulated by age.

Funding: NIDDK Support, Other NIH Support - NIEHS

FR-PO912
Shiga Toxin 1 Induces ICAM-1 Protein Expression in Human Glomerular Microvascular Endothelial Cells
Elena Volekhina,1 Thea J. Van der Velden,1 Diniec Westra,1 Nicole Van De Kar,1 1Dept of Pediatric Nephrology, Radboud Univ Nijmegen Medical Centre (RUNMC), Nijmegen, Netherlands; 2Dept of Laboratory Medicine, Radboud Univ Nijmegen Medical Centre (RUNMC), Nijmegen, Netherlands; 3Dept of Pediatrics, Univ Hospitals Leuven, Leuven, Belgium.

Background: Hemolytic uremic syndrome (HUS) is often preceded by infection with Shiga toxin (Stx) producing E. coli. Escherichia coli O157:H7, also known as STEC, is responsible for the majority of cases of HUS. Shiga toxin 1 (Stx1) binds to the A chain of the α2,3-sialylated ganglioside, GM1, on the cell membrane and subsequently triggers cell death by inducing apoptosis of podocytes and increasing sensitivity to suPAR. While this work is warranted, these data suggest that Stx1 is a potent inducer of ICAM-1 expression in podocytes.

Methods: Human umbilical vein endothelial cells (HUVEC) and human glomerular microvascular endothelial cells (GMVEC) from three donors were treated for 6, 12, 24 and 48 hours with 0, 0.1, and 1.0 nM of Stx1 with or without pretreatment with TNFα. The culture supernatant and cells were collected for ELISA and qPCR analyses to assess the expression of ICAM-1 on protein and mRNA levels.

Results: Stx1 upregulated levels of soluble ICAM-1 in culture supernatant of GMVEC when cells were preincubated with TNFα in time- and dose-dependent manner for up to 20 times (p<0.001). This upregulation on the protein level was consistent with enhanced ICAM-1 mRNA expression. Incubation of TNFα only enhanced release of soluble ICAM-1 in both cell lines for up to 10 fold (p<0.001).

Conclusions: Our results indicate that increased expression of ICAM-1 protein in GMVEC is directly triggered by Stx1. This feature might contribute to podocyte dysfunction in glomerular diseases and prevent podocyte dysfunction in glomerular diseases. Currently, a majority of therapeutics approved for proteinuric kidney diseases focus on improving systemic hemodynamics and metabolite levels but do not directly address harmful changes seen in podocytes. Therefore, new therapeutics to prevent podocyte dysfunction in glomerular diseases are urgently needed. However, current methods are inadequate for podocyte targeted drug discovery. Here we describe a high content approach for the discovery of novel podocyte targeted therapeutics.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

FR-PO913
A Common B3 Integrin Polymorphism L33P Renders Enhanced Reactivity to Soluble Urokinase Receptor: Relevance to Focal Segmental Glomerulosclerosis
Changli Wei, Jing Li, Jochen Reiser. Dept of Internal Medicine, Rush Univ Medical Center, Chicago, IL.

Background: Our recent findings suggest soluble urokinase receptor (suPAR) as a circulating focal segmental glomerulosclerosis (FSGS) factor. Induction of suPAR activates podocyte Vβ3 integrin both in vivo and in vitro, thus contributing to the development of proteinuria and an FSGS-like nephropathy. B3 integrin activation is enhanced in platelets with the β3 integrin genetic polymorphism L33P (P<0.2). We tested several well defined cohorts of native and transplanted FSGS patients and found the prevalence of L33P to be around 20%. Thus we hypothesized that L33P renders enhanced reactivity to suPAR, so that comparatively lower or normal suPAR levels might already cause increased B3 integrin activation in podocytes and glomerular injury.

Methods: B3 integrin mutation L33P was generated by QuickChange site-mutagenesis and cloned into Lenti viral system. Fully differentiated cultured human podocytes were infected with retrovirus expressing mutant β3 integrin L33P, or wild-type β3 integrin or same amount of control virus. 48 h after infection, cells were treated with different amount of recombinant suPAR protein or saline. 24 h later, the cells were harvested to test at 83 integrin activity.

Results: Compared to human podocytes infected with mock virus, cells received β3 integrin showed significantly higher baseline β3 integrin activity, with highest signal observed in β3P/β3 integrin infected cells. Simultaneous suPAR treatment even at low level further enhanced β3 integrin activity and the highest β3 integrin activation signal was again found in podocytes infected with β3P/β3 integrin.

Conclusions: In summary, β3 integrin polymorphism P31 allows for enhanced β3 integrin activity in human podocytes (lowered activation threshold), and generates increased sensitivity to suPAR. While in vivo work is warranted, these data suggest that β3 integrin polymorphism P31 may play a role in FSGS where suPAR level is not significantly increased.

Funding: NIDDK Support

FR-PO914
VEGF165b Protects against Increases in Glomerular Water Permeability in the Pod-DTR Model of Glomerular Disease
Degan Stevens, Andy Salmon, David O. Bates, Steve Harper, Sebastian Oltean. Physiology and Pharmacology, Univ of Bristol, Bristol, United Kingdom.

Background: The pod-DTR transgenic mouse model (podocin promoter – diaphtheria toxin receptor) is an inducible model of glomerular disease triggered by podocyte injury after treatment with diaphtheria toxin (DT). The vascular endothelial growth factor splice isoform VEGF165b has been shown to decrease glomerular water permeability (LpA/Vi) in kidney injury. This study investigates whether VEGF165b over-expression can rescue the glomerular injury phenotype of the pod-DTR model.

Methods: WT, Pod-DTR and double-transgenics (Pod-DTR x neph-VEGF165b) mice were used. A single dose of DT (0.5, 1.5 or 100μg) was administrated to all groups. Glomerular LpA/Vi was measured on day 0 prior to DT administration (n=4, p<0.05) in comparison with WT controls. This normalized by day 14 at both doses. Glomerular LpA/Vi is significantly increased in pod-DTR mice treated with 1 and 5ng/g DT compared to WT-DT treated controls (n=4, p<0.05). When pod-DTR x neph-VEGF165b mice were treated with the same doses, LpA/Vi was significantly lowered (p<0.05). There is a reduction in neprhin staining in pod-DTR mice treated with 1ng/g DT, as well as an increase in glomerular area (n=3, p<0.05) in comparison to WT mice.

Conclusions: An increase in glomerular permeability to water is observed in pod-DTR transgenic mice after 1 or 5 ng/g DT administration. This is rescued by over-expression of VEGF165b in podocytes, suggesting a protective role in this model of glomerular injury.

Funding: Other NIH Support - Medical Research Council

FR-PO915
High Content Screening for the Discovery of Podocyte Targeted Therapeutics
Tristan Hays, Mehmet M. Altintas, Mohd Hafeez Faridi, Jochen Reiser, Vineet Gupta. Dept of Internal Medicine, Rush Univ Medical Center, Chicago, IL.

Background: Podocyte dysfunction and loss are commonly associated with proteinuric kidney diseases and adversely effect glomerular filtration. Currently, a majority of therapeutics approved for proteinuric kidney diseases focus on improving systemic hemodynamics and metabolite levels but do not directly address harmful changes seen in podocytes. Therefore, new therapeutics to prevent podocyte dysfunction in glomerular diseases are urgently needed. However, current methods are inadequate for podocyte targeted drug discovery. Here we describe a high content approach for the discovery of novel podocyte targeted therapeutics.

Methods: Automated high-throughput imaging and analysis was used as an unbiased approach to quantify phenotypic changes of podocytes. Conditionally immortalized podocytes were treated with increasing doses of the podocyte damaging agent puromycin aminonucleoside to mimic in vivo podocyte damage. Cells were stained for the nucleus, cytoplasm, F-actin, and focal adhesions to visualize podocyte changes. Cells were then treated with increasing doses of puromycin aminonucleoside to mimic in vivo podocyte damage. Cells were then used to screen an FDA approved compound library for the identification of novel podocyte protective agents. Cells were then used to screen an FDA approved compound library for the identification of novel podocyte protective agents as potential therapeutics for the treatment of proteinuric kidney diseases.

Conclusions: We have developed a novel, high-throughput assay for unbiased scoring of changes in podocyte health in vitro. Application of this method may provide a tool for the identification of novel podocyte protective agents as potential therapeutics for the treatment of proteinuric kidney diseases.
SIK1 colocalized with nephrin in human glomerular podocytes and SIK1 and nephrin protein expression were highly correlated (r=0.78, p<0.001).

Conclusions: The present findings show that SIK1 polymorphism modulate BP control together with ADD1 and EO possibly by modulation of the tubular NK activity. Direct relationship between SIK1 and nephrin expression suggests that SIK1 may be also involved in podocyte damage and kidney injury.

FR-PO917

Angiotensin II Induces Podocyte Apoptosis by the Modulation of CD2AP: Role of ROS, AMPK, and PI3-K

Tae-Sun Ha.

Background: Angiotensin II (Ang II) induces dysfunction of glomerular podocytes, which play a crucial role in establishing glomerular filtration barrier perselectivity, thereafter, proteinuria. The glomerular slit diaphragm (SD), a slit between interdigitating foot processes of podocytes, serves as a size-selective barrier and is linked to the actin-based cytoskeleton by adaptor proteins, including CD2-associated protein (CD2AP). Therefore, damages to CD2AP affect not only function of the slit diaphragm, but also directly disrupt the podocyte cytoskeleton, leading to pathological changes inducing proteinuria. In addition, CD2AP can facilitate the nephrin-induced phosphoinositide 3-kinase (PI3-K)/Akt signaling, which protects podocytes form apoptosis. We investigated the changes of CD2AP and podocyte apoptosis by Ang II. We suggest that Ang II induces the relocalization and reduction of CD2AP protein in podocytes via AT1R, which would cause podocyte apoptosis by the oxidative stress and the suppression of AMPK and PI3-K signalings.

Funding: Government Support - Non-U.S.

FR-PO918

JAK/STAT-Associated Inflammatory Markers and the Benefits of JAK/STAT Signaling Inhibition in Peritoneal Dialysis

Tiane Dai, Ying Wang, Cynthia C. Nast, Janine A. La Page, Sharon G. Adler.

Background: Peritoneal barrier (PBarrier) pathology limits long-term peritoneal dialysis (PD). Inflammation induces PBarrier failure. JAK/STAT signaling is implicated, direct evidence is sparse.

Methods: Mesothelial cells were cultured in heat-stirrled, filter-sterilized, or filter-sterilized peritoneal dialysis fluid (PDF) with glucose degradation products (GDP) added with or without the pan-JAK inhibitor (JAKI) pyridone (P6). Phospho-JAK1/2, STAT1/3, peristin, and cleared caspase-3 (CC-3) were measured by immunoblotting, and CC-3 by immunohistochemistry (IHC). Ex vivo, JAK-activators IL6 and IL15 were measured by electrochemiluminescence (ECL, Meso Scale Discovery, Gaithersburg, MD) and proteins with STAT binding sites in or near their promoter regions (IL6, MCP-1, and peristin) were measured by ECL, ELISA, and/or immunoboolting in 20 peritoneal dialysis effluent (PDE) samples from 8 new (N) and 7 long-term (LT) PD patients. PDE cell-free fluid (PCEF), phospho-JAK1/2 were measured in 4 N and 4 LT patients. In vivo, PD was performed in rats with saline (PDC, N=3), 4.25% dextrose PDF (PFD4.25%, N=3), or PFD4.25%+5mg/kg JAK1/2i (N=4) x10 days. PBarrier was stained with trichrome & anti-phospho-JAK1/2i. During 30 days, in vitro, all PDFs induced phospho-STAT1/3 and CC-3; P6 attenuated STAT1/3 phosphorylation, peristin secretion, and CC-3 activation. Ex vivo, cell pellet JAK was phosphorylated in LT but not N patients. In PDE, the STAT-regulated proteins MCP-1, IL-6, and peristin (normalized to CA125) were higher in LT vs N patients. In rats, PFD4.25%, but not saline, activated JAK, and induced mesothelial cell hyperplasia, inflammation, and fibrosis. JAK1/2i abrogated these changes.

Conclusions: JAK/STAT signaling directly mediates PBarrier pathology, which is attenuated by JAK1/2i. Therapy to preserve residual renal function is implemented in PD. Fewer therapeutic strategies target PBarrier function preservation. Studies coupling inflammatory biomarkers with PBarrier function may provide support for testing JAK/STAT inhibition to address this unmet clinical need.

Funding: Pharmaceutical Company Support - Meso Scale Discovery, Rockland, MD; DaVita Clinical Research

FR-PO919

Effect of Adipose Tissue-Derived Mesenchymal Stem Cells in Peritoneal Fibrosis

Amanda Pires, Filipe M. Silva, Irene L. Noronha.

Background: Adipose tissue-derived mesenchymal stem cells (ADMSC) display immunomodulatory effects and may represent a strategy to block peritoneal fibrosis (PF), a serious complication of long-term peritoneal dialysis. The aim of the study was to analyze the effect of ADMSC in an experimental model of PF developed in uremic rats.

Methods: CKD was induced in Wistar rats with a 0.75% adenine-containing diet, during 30 days. PF was induced with intraperitoneal injection of chlorhexidine gluconate. ADMSC were injected IV at days 15 and 21. Rats were divided into 5 groups (n=10/group): Control CKD PF CKD+PF CKD+PF+ADMSC. ADMSC were injected IV at days 15 and 21. Rats were divided into 5 groups (n=10/group): Control, normal rats; CKD, rats receiving adenine-containing diet; PF, rats receiving chlorhexidine gluconate to induce PF; CKD+PF, CKD rats with PF; CKD+PF+ADMSC, CKD rats with PF treated with ADMSC. Peritoneal membrane thickness was measured by Masson trichrome. Macrophages (MO), T-cells and α-smooth muscle actin (α-SMA) were analyzed by immunohistochemistry, and cytokine expression was analyzed by qPCR at day 30.

Results: Infusion of ADMSC significantly reduced the peritoneal membrane thickness, α-SMA expression, MO and T-cell infiltration, and mRNA cytokine expression in the peritoneal membrane.

Conclusions: ADMSC were effective in protecting the development of peritoneal fibrosis in the experimental model of PF, probably due to their immunomodulatory properties.
FR-P0920
Effect of DNA Demethylation in Experimental Encapsulating Peritoneal Sclerosis
Sung Ji-Hee Park, Hye-Myang Ryu, Eun-Joo Oh, Solyun Oh, Ji-Sun Ahn, Soon Youn Choi, Ji-Young Choi, Jang-Hee Cho, Chan-Duck Kim, Yong-Lim Kim.
Div of Nephrology and Dept of Internal Medicine, Kyungpook National Univ Hospital, Daegu, Republic of Korea.

Background: Encapsulating peritoneal sclerosis (EPS) is characterized by progressive inflammation and excessive fibrosis of peritoneum in patients on peritoneal dialysis, and eventually leads to constriction of viscera and bowel obstruction in the later stages. This study aims to evaluate the therapeutic effect of DNA demethylation in experimental EPS.

Methods: Experimental EPS was induced by intraperitoneal injection of 0.1% chlorhexidine gluconate (CG) and 15% ethanol to non-uremic male SD rats (n=19) which were divided into 3 groups: control group (C, n=5) with normal saline injection, EPS group (CG, n=7) with CG injection for 4 weeks and treatment group (CGA, n=7) with 5’-azacytidine injection for the last 2 weeks during CG injection. Morphometric analysis of peritoneum was performed with immunohistochemical staining for type 1 collagen and α-SMA. The expression of TGF-β, fibroblast-specific protein (FSP)-1 and DNA methyltransferase (DNMT)-1 were detected by enzyme digestion and RT-PCR; 2. HMrSV5 cells were divided into 3 groups: control group, ECS group (transfected with ECS plasmid) and blank plasmid group (transfected with blank plasmid).

Conclusions: DNA demethylation by 5’-azacytidine treatment improved pathologic changes of peritoneum in experimental EPS and it was associated with reversal of increased expression of DNMT1 and hypermethylation of RASAL1.

Funding: Private Foundation Support.

FR-P0921
Statin Inhibits Peritoneal Dialysis-Related Epithelial-Mesenchymal Transition
Hye-Young Kang,1 Hyung Jung Oh,2 Seung Hyoek Han,2 Shin-Wook Kang.1,2
BK21,1 Dept of Internal Medicine, College of Medicine, Yonsei Univ, Seoul, Korea.

Background: Small GTPases are demonstrated to be activated through the mevalonate pathway and to be involved in epithelial-mesenchymal transition (EMT). However, little is known about the effect of statins, which inhibit isoprenylation, on peritoneal dialysis (PD)-related EMT.

Methods: In vitro, human peritoneal mesothelial cells (HPMCs) were exposed to normal glucose (NG, 5.6 mM), NG + mannitol, or high glucose (HG, 100 mM) with or without simvastatin (SV, 10 μM). In addition, isoprenoid product (GGPP, 5 μM)-induced EMT and HG-induced small GTPases were evaluated. In vivo, PD catheters were inserted into 32 Sprague-Dawley rats, and saline (C, n=16) or 4.25% PD fluid (PDF, n=16) was infused for 4 wks. 8 rats from each group were treated with 5 mg/kg/day of SV intraperitoneally.

Results: The thickness of peritoneal peritoneum and the number of vessels in omental fat were significantly increased in PD patients compared to CG group. DNM1T1 was significantly increased in CG group, whereas it was reduced in CGA group. Hypermethylation of RASAL1 was associated with decreased expression of RASAL1 protein in CG group, whereas it was reversed in CGA group.

Conclusions: Owing to the effects of statins on isoprenylation, the expression of statins might be associated with EMT in PD.

Funding: None.

FR-P0922
The Predictive Value of Matrix Metalloproteinase-2 and Plasminogen Activator Inhibitor-1 in Peritoneal Dialysis Patients Who Develop Encapsulating Peritoneal Sclerosis
Deisra Lopes Barreto, Dirk Gjibert Struijk, Raymond T. Krediet.
Internal Medicine, Div of Nephrology, Academic Medical Center, Univ of Amsterdam, Amsterdam, Netherlands.

Background: Encapsulating peritoneal sclerosis (EPS) is the most severe morphological complication that may occur in 3% of peritoneal dialysis (PD) patients. Recently the use of effluent matrix metalloproteinase-2 (MMP-2) and plasminogen activator inhibitor-1 (PAI-1) as potential biomarkers of peritoneal fibrosis has been demonstrated during longitudinal follow-up of incident PD patients. This study focuses on effluent MMP-2 and PAI-1 as early markers in the preceding years of patients who develop EPS.

Methods: In this nested case-control study, patients who developed EPS were compared with a control population of at least 57 months. Levels of effluent MMP-2 and PAI-1 were measured by an ELISA. Area under the receiver operating characteristic curves (AUC) were calculated. The time courses of AR of MMP-2 and PAI-1 were studied by means of a linear repeated-measures model in the years prior to the diagnosis of EPS adjusted for age. Furthermore, time-specific ROC analyses were executed to assess the predictive value of the markers in the years prior to diagnosis of EPS.

Results: In total 11 patients developed EPS and 34 controls were assembled. No difference in the time course of AR of MMP-2 was present between controls and EPS patients. In contrast, higher AR of PAI-1 were found in EPS patients as compared to the controls (p<0.002). The time-specific ROC analyses indicated a discriminatory ability for PAI-1 (AUC=0.78, p=0.01), whereas this was absent for AR of MMP-2.

Conclusions: It is unlikely that MMP-2 can be used as a biomarker of EPS as no distinction between patients who develop EPS and controls can be made. The time course confirmed the persistent contribution of MMP-2 in peritoneal tissue remodeling. Throughout, elevated levels of AR of PAI-1 are present in patients who develop EPS, pointing to progressive peritoneal fibrosis and sclerosis. AR of PAI-1 has a fair discriminative capacity from 3 years prior to EPS diagnosis. Therefore, PAI-1 can be possibly be used to monitor peritoneal fibrosis and serve as biomarker of EPS.

FR-P0923
Over-Expression of E-cadherin Attenuated Epithelial-Mesenchymal-Transition Induced by TGF-β in Human Peritoneal Mesothelial Cells
Hao Zhang, Ke Zhang, Liu Yan, Bin Yi.
1BK21; 2Dept of Internal Medicine, College of Medicine, Yonsei Univ, Seoul, Korea.

Background: Uptodate the investigation shows that E-cadherin (ECAD) might not only the effector but also regulator in Epithelial-mesenchymal transition (EMT). We aimed to over express the ECAD with plasmid transfection into human peritoneal mesothelial cell lines (HMrSV5) and to investigate the effects of ECAD over-expression on the epithelial-mesenchymal transition HMrSV5 cells.

Methods: 1. Using E. coli DH5α to amplify the ECAD cDNA plasmid and blank plasmid, the plasmid was identified by enzyme digestion and RT-PCR; 2. HMrSV5 cells were divided into 3 groups: control group, ECS group (transfected with ECAD plasmid) and blank plasmid group (transfected with blank plasmid). The transfection efficiency was detected by Flow cytometry. The level of ECAD mRNA and protein in 12h, 24h, 36h, 48h and 72h were detected by RT PCR. The level of α-SMA and Vimentin protein were detected by western blot. Immunofluorescence was used to detect the ECAD and α-SMA protein level.

Results: 1. The recombinant plasmids are verified by sequencing analysis, with the sequence identified in gene bank. 2. The transfection efficiency with ECAD transfection was peaked on 36th(74.12%). Level of ECAD mRNA is increased with ECAD transfection after 12h (p<0.05), and increased on 36th (p<0.01).

In TGF-β group, the protein level of α-SMA and Vimentin are increased by TGF-β in a time-dependent manner (p<0.01, compared with control group), and ECAD mRNA level is decreased (p<0.01, compared with control group). Otherwise, the effect is attenuated in ECAD + TGF-beta group (p>0.01, compared with TGF-β group).

Conclusions: 1. ECAD cDNA can plasmid transfection does over express ECAD in HMrSV5 cells; 2. Over-expression ECAD with ECAD cDNA plasmid can attenuate the EMT induced by TGF-β in HMrSV5 cells.

Funding: Government Support - Non-U.S.

FR-P0924
Paricalcitol Ameliorate Epithelial to Mesenchymal Transition of Peritoneal Mesothelial Cells
Seokhui Kang,1 Tae woo Kim,2 Kyu-hyang Cho,1 Jong-Won Park,1 Kyung woo Yoon,1 Jun-Young Do.1
1Internal Medicine, Yeungnam Univ Hospital, Daegu, Republic of Korea; 2Internal Medicine, Soonchunhyang Univ Gumi Hospital, Gumi, Republic of Korea.

Background: Paricalcitol plays an important role not only in the establishment and maintenance of calcium metabolism but also in direct effects on renal and extra-renal tissues. The aim of this study is to evaluate the effect of paricalcitol on epithelial to mesenchymal transition (EMT) of peritoneal mesothelial cells.

Methods: The effects of paricalcitol on EMT in both human peritoneal mesothelial cells (HPMCs) and peritoneal membranes were evaluated. HPMCs were incubated with TGF-β and/or paricalcitol. EMT was assessed with α-smooth muscle actin (α-SMA) and E-cadherin. Furthermore, 36 male Sprague-Dawley rats were equally divided into three groups: C (control), PD (peritoneal dialysis), and PD + Par (peritoneal dialysis and paricalcitol). Peritoneal dialysis was performed for 24 hours twice a week for 8 weeks. The morphometric analyses performed on the peritoneal membranes of tissue specimens obtained at the end of the study.

Results: In vitro, exposure of HPMCs to TGF-β resulted in an increase of the expression of mesenchymal markers such as α-SMA and was associated with a decrease in the expression of epithelial markers, E-cadherin. Treatment of HPMCs with paricalcitol showed an amelioration of TGF-β-induced changes in markers of EMT. In addition, paricalcitol decreased the expression of phosphorylated-Smad2/3 and increased the expression of Smad4. The cobblestone-like appearance of HPMCs were converted to a fibroblast-like morphology after treatment with TGF-β. Treatment with paricalcitol blocked this morphologic transformation. In vivo, Trichrome-stained parietal peritoneum

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

573A
of abdominal wall showed a marked increase in submesothelial matrix in PD group, which is ameliorated by paricalcitol (7.42 ± 1.53 μm in C group, 49.26 ± 7.89 μm in PD group, and 22.04 ± 3.64 μm in Pari group).

Conclusions: Our results suggest that paricalcitol has a protective effect on EMT in peritoneal mesothelial cells. It was mediated by TGF-β/Smad pathway.

FR-PO925
Impact of Alanine-Glutamine on Peritoneal Health – Results from the Clinical Phase I/I of PD-protect™
Klaus K. Schröder,1 Michael Bochm,2 Rebecca Herzog,2 Katharina Gruber,1 Anton Lichtenauer,2 Lilian Kuster,3 Andreas Gleiss,1 Christoph Aufricht,1 Andreas Vychytil1.1Medical Univ of Vienna, Austria; 2Zytoprotec GmbH, Austria.

Background: Peritoneal dialysis fluids (PDF) impair peritoneal health via their bio-incompatible composition, resulting in clinical complications such as deterioration of membrane function and infections. Supplementation of parental nutrition with alanine-glutamine dimetide has been shown to improve clinical outcome e.g. in critically ill patients.

Methods: In a phase I/I trial (EudraCT 2010-022840-29) at the Medical University of Vienna 20 stable patients (6 with a history of prior peritonitis) on PD underwent a single 4h dwell of standard PDF (Dianeal® PD 3.86%, Baxter) or PD-protect™ (Dianeal® with 8 mM alanine-glutamine dimetide® (Dipeptiven®, Fresenius-Kabi)) in an open, randomized, two-period, cross-over design. Following a peritoneal equilibration test (PET) PDF effluent was tested for oxidative stress, sterile inflammation and reduced immunocompetence.

Results: Safety of PD-protect™ was demonstrated by stable laboratory and clinical data and by absence of any drug-related adverse event. PD-protect™ also demonstrated efficacy in the sub-group of "peritonitis positive" patients with attenuated peritoneal levels of advanced oxidized protein products (AOPP) and significantly reduced interleukin 8 (IL-8). In addition, highly sensitive fluorescent cyanine dyes and 2D-DIGE were used to quantify the oxidative stress proteome of cell pellets from PD effluents (5 μg) yielding 2D gels containing more than 1300 spots. Ex-vivo assay exposure of PBMC to PD effluent from the PD-protect™ group significantly improved LPS-induced cytokine release, associated with significantly increased intracellular glutathione levels.

Conclusions: The obtained data clearly show the potential of PD-protect™ for improving peritoneal health by counteracting PD related pathomechanisms at least in the clinically highly relevant risk population that has previously suffered from peritonitis. These results will form the basis for a trial investigating the effects of more extended treatment in a larger number of PD patients.

Funding: Pharmaceutical Company Support - Zytoprotec GmbH

FR-PO926
The Peritoneal Endothelial Glycocalyx in Uremic Rats – The Effect of Dialysis Solutions and Relationships with Peritoneal Transport
Carmen A. Vlahu,1 Dirk Gijsbert Struijk,1,2 Raymond T. Krediet,1 1Dept of Nephrology, Academic Medical Center, Amsterdam, Netherlands; 2Nephrology, Academic Medical Center, Amsterdam, Netherlands.

Background: Continuous peritoneal dialysis (PD) leads to continuous exposure of the peritoneal membrane to high concentrations of glucose and its degradation products, causing inflammation and angiogenesis, which may all alter the endothelial glycocalyx. We investigated the changes in peritoneal endothelial glycocalyx induced by chronic kidney failure (CKF) and by long-term PD, using a conventional or a 'biocompatible' dialysis solution. These changes were related to peritoneal transport and morphological alterations of the peritoneal membrane.

Methods: Forty-four Wistar rats were divided in 4 groups: normal kidney function (NKF); CKF (574A), CKD (574B), CKDP (574C). Peritoneal fluid was collected for each group and peritoneal transport parameters were assessed by measuring the perfused boundary region (PBR) near the vessel wall. A standard technique (SDF) imaging of the peritoneal blood vessels. The status of endothelial glycocalyx was assessed by measuring the red blood cells column width (RBCW) and the thickness of the permeable phase of the glycocalyx. Glycocalyx was measured as the ratio of the vessel wall to the capillary lumen. The vessel density was assessed by measuring the number of functional small pores in the peritoneal mesothelial cells. It was mediated by TGF-β/Smad pathway.

Conclusions: The negative correlation between the state of the systemic endothelial glycocalyx and the transport of small solutes, suggests that a thicker permeable phase of the glycocalyx delays the access of small solutes from blood to the small inter-endothelial pores, probably by decreasing their diffusion velocity. The above mentioned correlation was absent in patients with fast transport status, suggesting that in this group, the increase in the number of perfused vessels, probably induced by locally produced substances, leading to an increased number of functional small pores, prevails.

Funding: Private Foundation Support

FR-PO927
Systemic Microvascular Endothelial Glycocalyx and Peritoneal Transport in Peritoneal Dialysis Patients
Patients: Carmen A. Vlahu,1 Dirk Gijsbert Struijk,1,2 Hans Vink,3 Raymond T. Krediet,1 1Dept of Nephrology, Academic Medical Center, Amsterdam, Netherlands; 2Nephrology, Academic Medical Center, Amsterdam, Netherlands; 3Cardiovascular Research Institute Maastricht, Netherlands.

Background: During peritoneal dialysis (PD), the capillary wall, coated at the luminal side by the endothelial glycocalyx, represents the main transport barrier between blood and the peritoneal cavity, and could thereby influence peritoneal transport. However, the measurement of peritoneal solute transport is also dependent on the number of perfused peritoneal capillaries. In this study we investigated the relationship between the systemic endothelial glycocalyx and parameters of peritoneal transport in PD patients.

Methods: Investigations were performed in 17 stable PD patients. We performed SDF imaging of the peritoneal blood vessels. The state of the endothelial glycocalyx was measured by assessing the red blood cells column width (RBCW) and the perfused boundary region (PBR) near the vessel wall. All patients underwent a standard Peritoneal permeability analysis.

Results: PBR and RBCW were 3.6 ±0.4μm and 10.2±6.0μm. Fast transport status was defined as the presence of two of the following parameters: glucose absorption >75%, MTACreatinine<13 ml/min, MTATCureate<11 ml/min. In the patients with a non fast transport status, PBR positively correlated with net ultrafiltration (p=0.01, r=0.6) and negatively correlated with MTATCreatinine (p<0.04, r=0.4) MTATCurea (p=0.02, r=0.5), glucose absorption (p<0.01, r=0.7). Such relationships were absent in those with a fast transport status.

Conclusions: Our results suggest that paricalcitol has a protective effect on EMT in peritoneal mesothelial cells. It was mediated by TGF-β/Smad pathway.

FR-PO928
High Glucose Promotes TGF-β1 Production by Inducing FO5 Expression in Human Peritoneal Mesothelial Cells
Shigehiro Doi, 1 Ayumu Nakashima,2 Takao Masaki.3 1Blood Purification, Hiroshima Univ Hospital, Hiroshima, Japan; 2Regeneration and Medicine, Hiroshima Univ Hospital, Hiroshima, Japan; 3Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: Peritoneal fibrosis is a serious complication of peritoneal dialysis (PD). A high concentration of glucose in PD fluid is a major factor in the development and pathology of peritoneal fibrosis. Although it is known that high glucose induces production of transforming growth factor-beta 1 (TGF-β1), the mechanism remains elusive. The aim of this study was to determine the gene(s) involved in high glucose-induced TGF-β1 production in human peritoneal mesothelial cells (HPMCs).

Methods: Microarray analysis was performed following 3-hour preincubation of HPMC in 4% glucose medium. The transcriptional genes were selected by Gene Ontology analysis for biological processes, including regulation of transcription and DNA-dependent. In the selected genes, mRNA amplification was confirmed. Effects of the small interfering RNA (siRNA) treatments of the increased genes on the regulation of TGF-β1 mRNA were assessed by Real time PCR. Finally, enzyme-linked immunosorbent assays (ELISA) was performed to determine the gene(s) that contributes to production of TGF-β1 protein in the medium.

Results: Microarray analysis revealed that the expression of 51 genes increased by more than 3-fold. By Gene Ontology analysis, 13 were selected for further study. Real time PCR confirmed mRNA amplification for 9/13 genes. Furthermore, the high glucose-induced up-regulation of TGF-β1 mRNA was attenuated by the siRNA of 4 genes: MDS1 and EVI1 complex locus (MECOM), FBJ murine osteosarcoma viral oncogene homolog B (FO5), FBJ murine osteosarcoma viral oncogene homolog (FOS), and activating transcription factor 3 (ATF3). ELISA showed that siRNA treatment of FO5, but not MECOM, FOSB or ATF3, suppressed the increase of TGF-β1 protein in the medium.

Conclusions: FO5 is a downstream effector of high glucose stimulation in HPMC that contributes to TGF-β1 production, and suggest that blocking FO5 expression may be a therapeutic target for peritoneal fibrosis.

Funding: Private Foundation Support

FR-PO929
Peritoneal Fibrosis: A Study Comparing Histological Assessment with Abdominal Wall UltraSonography
Alfersto C. Abrahams,1 Amelie Dendooven,2 Jan Willem Van der Veer,3 Gerard Stapper,1 Paul Berger,3 Tri Q. Nguyen,3 Marianne C. Verhaar,1 Walther H. Boer.1 1Nephrology; 2Radiology; 3Surgery, UMC, Utrecht, Netherlands.

Background: Long-term peritoneal dialysis (PD) causes peritoneal thickening (fibrosis). Longitudinal measurements of the thickness of the peritoneum could be useful to screen PD patients for evolving encapsulating peritoneal sclerosis. Abdominal wall ultrasonography (US) has been used to measure peritoneal thickness. However, no studies have directly related measurement of the peritoneal thickness by US with histologic examination of peritoneal biopsies. We hypothesized that US provides a reliable non-invasive method to measure peritoneal thickness.
Methods: We obtained biopsies of the parietal peritoneum of 50 patients during kidney transplantation: 5 uremic patients, 13 HD patients, and 32 PD patients with different vintage (<2yrs n=10; 2-4yrs n=14; >4yrs n=9). The extent of peritoneal fibrosis was determined by measuring the thickness of the submesothelial compact zone on H&E-stained formalin-fixed tissue sections. In 32 of these patients the parietal peritoneum was examined by US using a high resolution 2D real-time scanner with a linear 17 MHz probe.

Results: There was no agreement between the methods used when the difference between the paired measurements was plotted against the mean value (bias=257±95µm, 95% limit of agreement 4.6-511µm) with US measuring higher results compared to biopsy assessments (37±95µm vs 113±62µm, p<0.0001). Increased peritoneal thickness as assessed in biopsies was observed in patients who had undergone PD for >4yrs (160±102µm) compared to uremic patients (94±41µm, β=83µm, p=0.011) and patients who had undergone PD for <2yrs (94±41µm, β=83µm, p=0.008). US showed no differences in thickness between groups.

Conclusions: This is the first study that directly compares measurements of peritoneal thickness by US to microscopic examination. We observed no agreement between the methods. This may be due to the possibility that US measurements include other components of the parietal peritoneum than the submesothelial compact zone. Prospective longitudinal studies are needed to determine whether US can be used for routine assessment of PD thickness.

FR-PO930
Suppressive Effects of Intraperitoneal L-carnitine on Peritoneal Fibrosis Caused by Chronic Dialysate Exposure in Rats Yoshihiro Matsumoto, Yasushi Shinada, Youichi Nojima.

Background: Conventional glucose-containing peritoneal dialysates are reportedly not biocompatible and may be associated with the development of peritoneal sclerosis. L-carnitine is a natural substance (molecular weight, 161 Da) that plays a critical role in fatty acid oxidation and mitochondrial homeostasis. In the present study, we aimed to evaluate the beneficial effects of L-carnitine on peritoneal fibrosis that develops due to chronic exposure to conventional glucose-containing dialysates.

Methods: We prepared dialysis fluids containing 188 mM glucose (GluPD) as well as dialysis fluids containing 169 mM glucose and 19 mM L-carnitine (10% of glucose replaced with L-carnitine; CarPD). Sprague-Dawley rats (n = 7 for each treatment) were intraperitoneally administered GluPD or CarPD twice a day for 6 days per week. After 13 weeks, we histologically examined the parietal peritoneum of the rats and measured peritoneal thickness. Mesothelial cells on the liver surface were enumerated using imprint technique, and the numbers of mesothelial cells were compared between the treatment groups.

Results: The peritoneal thickness in rats treated with GluPD and CarPD was significantly greater than that in non-treated rats. The thickening of the peritoneum in rats treated with CarPD was significantly suppressed by 50-70% compared to that in rats treated with GluPD. However, the number of mesothelial cells on the liver surface was greater in rats treated with GluPD and CarPD as compared to that in non-treated rats; the difference in this value between rats treated with GluPD and CarPD was not significant.

Conclusions: Considering the suppression of peritoneal thickening in rats treated with CarPD, the use of the L-carnitine-containing dialysates might be effective in improving or preventing peritoneal sclerosis in dialysis patients.

FR-PO931

Background: To investigate the roles of miR-200c in the process of high glucose induced EMT and ECM accumulation in HMrSV5 cell lines.

Methods: HMrSV5 cells were exposed to 60mM D-glucose.The expressions of E-cadherin, vimentin, FN and COL-1 were examined by realtime PCR and western blo,

Results: Stimulation of HMrSV5 cells with high glucose resulted in a significant decrease of E-cadherin and increase of vimentin, COL-1 and FN, all in time-dependent manner. High glucose also repressed miR-200c.Compared to high glucose group, overexpression of miR-200c in HMrSV5 cells upregulated the miRNA and protein expression of E-cadherin, and downregulated the mRNA and protein expression of vimentin,COL-1 and FN. However, miRNA mimics negative control had no significant effect on the expression of E-cadherin, vimentin ,COL-1 and FN.

Conclusions: Our data suggest that microRNA-200c plays a significant role in the progression of high glucose induced peritoneal fibrosis.

FR-PO932
Interferon-Gamma Alters Mesothelial Cell Response to Transforming Growth Factor Beta-1, Promoting Peritoneal Fibrosis Donald Fraser, Tanya Jayne Bodenham, Timothy Bowen, Nicholas Topley. 1Institute of Molecular and Experimental Medicine, Cardiff Univ, Cardiff, Wales, United Kingdom; Institute of Infection, Immunity and Biochemistry, Cardiff Univ, Cardiff, Wales, United Kingdom.

Background: Peritonitis infections are a serious complication for patients receiving peritoneal dialysis (PD) leading to progressive fibrosis of the peritoneal membrane, one of the major reasons for treatment failure in PD patients. TGF-β1 is a key regulator of tissue repair and the fibrotic process and the interaction between TGF-β1 and pro-inflammatory signalling may affect how cells respond to this cytokine either by repair and resolution, or by fibrosis and disease.

Methods: In vivo and in vitro systems have been used to characterise the interplay between TGF-β1 signalling and Signal Transducer and Activator of Transcription (STAT) activation by Interleukin 6 (IL6) and Interferon gamma (IFN-y). The in vivo system consists of a murine model of inflammation driven fibrosis, where mice are injected with repeated inflammatory stimulation with lipopolysaccharides (LPS) to the peritoneum. The in vitro system comprises culture of primary human peritoneal mesothelial cells (HPMC) in the presence of TGF-β1/ +/- IFN-y.

Results: Stimulation of HPMCs with TGF-β1 results in induction of matrix metalloproteinase 3 (MMP3) at the mRNA and protein level, which is specifically inhibited in the presence of IFN-y. IFN-y did not alter other TGF-β1 responses. Increased matrix production has been shown in the in vivo system thus supporting the in vitro findings. Chemical inhibition of mitogen activated kinase pathway (MAPK) through blockade of ERK1/2 and NFκB signalling prevented the TGF-β1 dependent induction of MMP3. This induction was also blocked via inhibition of SMAD 3 phosphorylation, thus suggesting that MMP3 induction via TGF-β1 requires both SMAD dependent and SMAD independent signalling pathways.

Conclusions: Within HPMCs, IFN-y appears to promote fibrosis by favouring matrix accumulation over remodelling through specific inhibition of MMP3. Current investigations are directed at the mechanism by which IFN-y regulates MMP3 expression.

Funding: Private Foundation Support

FR-PO933
Heme Oxygenase-1 Attenuates Lipopolysaccharide (LPS)-Induced TLR4 and Proinflammatory Signaling in Human Peritoneal Mesothelial Cells (HPMCs) Jungho Shin, Jeongho Kim, Jinuk Jeong, Kitae Bang. Nephrology, Eulji Univ Hospital, Dae-jeon, Republic of Korea.

Background: Bacterial peritonitis is a major complication of PD and a leading cause of technical failure. Recognition of bacterial pathogens by the peritoneum is mediated in part by toll-like receptors. Heme oxygenase-1 gene expression by LPS in macrophages is not only induced via a TLR4-dependent mechanism, but also increased HO-1 activity has also been shown to have inhibitory effects on intracellular signaling, that is initiated by TLR-4 activation. This regulatory interplay between TLR-4 and HO-1 appears to form a negative feedback loop which might inhibit excessive activation of macrophage by LPS. However, the regulatory effects of HO-1 overexpression on LPS-induced inflammation, which plays a leading cause of technical failure, are unknown in HPMCs, yet. So, the objectives of this study are examine the effects of overexpression of human HO-1 on LPS-induced inflammation in HPMCs.

Methods: We treated HPMCs with LPS (1µmol/l) and HO-1 inducer(hemin,10µmol/l). To further investigate the pure effect of HO-1 on LPS-induced inflammation, Gene transfer of recombiant Adenosine-harboring human HO-1 to HPMCs was done. The involvement of MAP Kinase family and nuclear factor(NF)-κB in these processes was also studied.

Results: HPMCs constitutively expressed TLR4 and HO-1. LPS increased the expression of TLR4 and HO-1. A prominent induction of IL-8 was detected after LPS stimulation. Treatment of HPMCs with HO-1 inducer, hemin showed a suppression of LPS-induced changes in expression of TLR4 and IL-8 with increase of expression of HO-1. Human HO-1 gene transfection resulted in a significant increase in HO-1 expression and ameliorated LPS-induced changes. NF-κB expression was also detected but ERK and JNK were not detected in our study like other previous reports.

Conclusions: Our study suggest that HO-1 pathway is involved in LPS-induced inflammation and HO-1 can regulate LPS-induced inflammation in HPMCs.

FR-PO934
Competing Risks of Encapsulating Peritoneal Sclerosis: Results from PD-CRAFT Mark Lambie,1 David W. Johnson,2 Simon J. Davies,3 1Health Services Research Unit, Keele Univ, Stoke on Trent, United Kingdom; 2Queensland Univ, Brisbane, Australia.

Background: Encapsulating peritoneal sclerosis (EPS) is an uncommon complication of peritoneal dialysis (PD), where the risk increases significantly with increasing time on therapy. We hypothesised that, at the start of PD, risk factors for death would decrease the risk of developing EPS as death will act as a competing risk for EPS.

Methods: We combined 3 large datasets (AnzData, Global Fluid Study, Scottish Renal Registry) with complete datasets on EPS occurrence and the denominator population. All incident patients aged ≥15 years were included and a competing risks survival analysis used outcomes of censored, EPS (prior to death) or death and robust standard errors.
Comorbidity data was classified by either primary renal diagnosis (low comorbidity = glomerulonephritis, polycystic kidney disease, chronic pyelonephritis, high comorbidity = other) and diabetic status (all 3 datasets) or by Stoke comorbidity score (AnzData and Global). Results: There were 112 cases of EPS out of 17,912 patients. The cumulative incidence at 10 years varied from 0.04 in AnzData, to 0.25 in SRR. Competing risks models showed age (HR 0.64, 95% CI 0.54-0.72) and high comorbidity renal disease (SHR 0.54, 95% CI 0.41-0.73) decreased the risk of EPS which Cox models failed to demonstrate. The SHR had a SRR of 5.62 (95% CI 5.28-6.21) relative to AnzData but this was not through a decreased mortality (HR for mortality in SRR vs AnzData in adjusted Cox model 1.14, 95% CI 1.05-1.20) or through longer periods of PD (median months on PD, SRR 22.6, AnzData 21.1, p=0.2). The Global dataset had an intermediate risk (SRR relative to AnzData 2.11, p=0.32). The Global dataset had an intermediate risk (SHR relative to AnzData 2.11, SRR had a SHR of 5.62 (95% CI 5.28-6.21) relative to AnzData but this was not through a

Conclusions: For patients commencing PD, factors that increase the risk of death decrease the risk of developing EPS. Competing risks regression is an appropriate model for analysis of dialysis outcomes. The Scottish Renal Registry has a significantly higher rate of EPS than found in AnzData, possibly due to ascertainment bias or genetic factors.

Funding: Pharmaceutical Company Support - Baxter

FR-PO935

Peritoneal Membranes Are More Inflamed in Patients with Subsequent Encapsulating Peritoneal Sclerosis: Results from the GLOBAL Fluid Study

Mark Lambie, Nicholas Topley, Simon J. Davies. 1Health Services Research Unit, Keele Univ, Stoke on Trent, United Kingdom; 2Cardiff Univ School of Medicine, Cardiff, United Kingdom.

Background: Risk factors for Encapsulating Peritoneal Sclerosis (EPS), a serious, uncommon complication of Peritoneal Dialysis (PD), include a fast peritoneal solute transport rate (PSTR) and a fast PSTR is associated with increased peritoneal inflammation. Whether inflammation is present in patients with subsequent EPS is not known.

Methods: We performed a nested case control study on UK patients from a multicenter international, cohort study (the GLOBAL Fluid Study). All definite cases of EPS (n=11) were matched on centre, age and duration of control PD with 3 controls each. All 4-hour dialysate effluent and plasma samples from cases and controls collected by repeated sampling during routine peritoneal equilibration tests prior to PD cessation were assayed by electrochemiluminescence for IL-6, IFN-γ, TNF-α and IL-1β. Analysis was by multiple modelling of log-transformed cytokine levels accounting for clustering by person (level 2) and case-control strata (level 3) with EPS and time till PD end as predictors. A skewed distribution of IL-1β necessitated a logistic model.

Results: Dialysate IL-6 (β=0.78 of one log unit, cytokine concentrations, 95% CI 0.13, 1.44, p=0.02), IFN-γ (β=0.63, 95% CI 0.02, 1.24, p=0.04) and TNF-α (β=0.67, 95% CI 0.30, 1.03, p<0.001) were all significantly higher in cases with subsequent EPS. Dialysate IL-1β was not significantly different, possibly due to loss of statistical power through conversion to a binary variable. Plasma IL-6 (β=0.31, 95% CI 0.01, 0.63, p=0.06) tended to run slightly higher; whereas plasma IFN-γ was significantly lower in EPS patients (β=−0.51, 95% CI −0.81, −0.22, p=0.001) and there was no difference in plasma TNF-α. Dialysate and plasma IL-6 rose significantly towards the end of PD, while plasma IFN-γ fell.

Conclusions: Peritoneal membranes are more inflamed in PD patients who subsequently develop EPS.

Funding: Pharmaceutical Company Support - Baxter

FR-PO936

Detection of Pericytes in a Peritoneal Dialysis Rat Model and Its Functional Study

Nan Chen, Hong Fu Yan, Jingyuan Xie. Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong Univ, School of Medicine, Shanghai, Shanghai, China.

Background: Angiogenesis and vascular remodeling of peritoneum are associated closely with ultrafiltration failure(UF) in peritoneal dialysis (PD) patients. Pericytes may relate to angiogenesis and contribute to UF. Although it is still unavailable, the detection of pericytes and to develop an approach to measure the peritoneum vessels and neovascularization (NV).

Methods: 48 SD rats were divided into 7 groups; Dialysate (100 ml/kd) was injected into peritoneal cavity through the PD catheters. Rats in Group N (n=6) were subjected to sham operation; Group U (n=6) which were conducted 5/6 nephrectomy; Rats in Group PD1 (N=6), Group PD2D(N=6) and Group PD3(N=6) were injected by 1.5%, 2.5%, 4.25% PD fluid for one month 12w after the 5/6 nephrectomy; Group PD4 used 4.25% PD fluid injection for one month 12w after the 5/6 nephrectomy; Group PD5 used 4.25% PD fluid injection for two months 12w after the 5/6 nephrectomy; Group PD6 used 4.25% PD fluid injection for 3 months 12w after the 5/6 nephrectomy; Rats in Group N+P (n=6) were performed 4.25% PD fluid injection for one month.

Results: We detected pericytes in normal peritoneum, the markers of pericyte were various in different part of peritoneum, in the superficial part, marked by CD34/PDGF-β, while Desmin/PDGF-β was detected in deep peritoneum. However, during PD process, the DESMIN marker appears in the superficial part. We found obvious NV in the peritoneum, the degree was obviously associated with the glucose concentration. Spatial distribution of NV present obvious lateral and vertical inhomogeneity. By electron microscopy, we observed two rucks of angiogenesis; sprout new blood vessels and the angiogenesis of endothelial like tumor cells. The concentrations of VEGF secreted by the pericyte and VEGF-R2 secreted by the endothelial cells were both rised, associated with the glucose concentration and the PD duration.

Conclusions: We found the pericytes are exist in the peritoneum of PD rat and the surface markers of pericyte changes to match the pathophysiological circumstance. The function of pericytes is related to angiogenesis of peritoneum and has potential values in early prediction of the development of UF.

Funding: Government Support - Non-U.S.

FR-PO937

Tissue Advance Glycation End Products Deposits Are Reduced in Peritoneal Dialysis Patients Treated with Biocompatible Peritoneal Fluids

Arok M Nongnag, 1,2 1,2 Stanford Yan, Andrew Davenport. 1Renal Unit, Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand; 2Centre for Nephrology, Royal Free Hospital, Univ College London, London, United Kingdom; 3Dept of Nephrology, Barts & the London National Health Service Trust, Royal London Hospital, London, United Kingdom.

Background: Advance Glycation End Products (AGEs) are a novel biomarker for cardiovascular disease (CVD) and may be absorbed during the intraperitoneal dwell in peritoneal dialysis patients. The amount of AGEs present in standard acidic lactate PD fluids is greater than those found in neutral PD fluid. The objective of this study was to compare skin autofluorescence as a measurement of AGEs between standard and bicarbonate base PD fluid.

Methods: We measured tissue AGEs using skin autofluorescence (sAF) (DiagOptics, Groningen, Netherlands) on 145 peritoneal dialysis patients, 78 on standard PD solution and 61 on neutral PD solution.

Results: The results are shown in the table.

Funding: Private Foundation Support

FR-PO938

IL6 and Peritoneal Dialysis Adequacy

Sabrina Milan Manani, Grazia Maria Virzi, Alessandra Brocca, Giacomo Mason, Ilaria Tantillo, Carlo Crepaldi, Claudio Ronco. Nephrology Dep-IRRI, Italy.

Background: Inflammation is a predictor of all-cause mortality in the general population and in CKD patients. In these patients several factors can contribute to inflammation. Furthermore, in peritoneal dialysis (PD) patients, many systemic and local inflammatory mediators have been associated with membrane failure and increased mortality risk. Inflammation often coexists with malnutrition and there is a relationship between nutritional indices, as serum Albumin (Alb), and mortality. C-Reactive Protein (CRP) is an index of inflammatory activity. IL6 is a proinflammatory cytokine and modulates inflammation. The aim of the study was to investigate the systemic inflammatory biomarkers and assess their relationship with PD adequacy.

Conclusions: The more biocompatible neutral pH peritoneal dialysis solutions may have beneficial effect on reducing tissue AGE accumulating in PD patients. Further prospective studies are warranted to confirm these encouraging findings.

Funding: Private Foundation Support

FR-PO939

DESMIN marker appears in the superficial part, marked by CD34/PDGF-β, while Desmin/PDGF-β was detected in deep peritoneum. However, during PD process, the DESMIN marker appears in the superficial part.
No statistically significant relationship between IL6 and the wCcr was observed, but a positive trend was evident.

Conclusions: In conclusion, this study suggested that a low grade of IL6, as a marker of inflammation state, may be considered an index of PD adequacy. It is necessary to increase the sample size of PD subjects enrolled to validate our hypothesis.

FR-PO939
The Effect of Bicarbonate Containing Peritoneal Dialysis Solution on Epithelial-to-Mesenchymal Transition in Omentum-Derived Mesothelial Cells
Kyu-Iyang Cho,1 Jun-Young Do,1 Seokhui Kang,1 Jong-Won Park,1 Kyung woo Yoon,1 Tae woo Kim.1 1Dept of Internal Medicine, Yeungnam Univ Hospital, Daegu, Republic of Korea; 2Dept of Internal Medicine, Soonchunhyang Univ Gumi Hospital, Gumi, Republic of Korea.

Background: The purpose of this study is to investigate the effect of bicarbonate containing PD (peritoneal dialysis) solution on EMT (epithelial-to-mesenchymal transition) in omentum-derived mesothelial cells.

Methods: Omentum-derived mesothelial cells from 20 nonuremic patients undergoing abdominal surgery were incubated with lactate-buffered standard PD solutions (L group; Dianeb® and Stay-safe®), bicarbonate/lactate buffered PD solutions (LB group; Physioneal® and Balance®) or bicarbonate buffered PD solution (B group; BicaVera®) diluted 1:1 with culture medium. E-cadherin was measured as standard mesothelial marker by quantitative RT-PCR (real time-polymerase chain reaction) analysis. Snail and alpha-SMA (alpha-smooth muscle actin) were also measured as fibroblast marker by quantitative RT-PCR analysis. The number of CD54 (cluster differentiation 54) positive cells (indicative mesothelial cells) was counted among confluent omentum-derived mesothelial cells by FACS (fluorescence-activated cell sorter).

Results: There were no significant differences in level of E-cadherin, snail and alpha-SMA among three groups. The number of CD54 positive cells among confluent omentum-derived mesothelial cells was B group, BL group and L group in order but the difference did not reach the statistical significance.

Conclusions: Bicarbonate containing PD solution groups showed a trend of higher number of CD54 positive cells among confluent omentum-derived mesothelial cells in vitro but without significant statistical differences in this study. We need further studies to clarify the impact of bicarbonate containing peritoneal dialysis solution on EMT in mesothelial cells.

FR-PO940
Hepatocyte Growth Factor Signalizes Ultrafiltration Failure in Peritoneal Dialysis Patients
Ana Paula Bernardo,1 Olivia Santos,1 Maria João Carvalho,1 António Manuel Nunes Cabrita,2 AnaBela Rodrigues,1,2 Nephrology, CHP, Porto, Portugal; 3UMIB/ICBAS/Porto Univ.

Background: Ultrafiltration failure (UFF) is a leading cause of peritoneal dialysis (PD) drop-out. Increased submesothelial fibrosis is a key process linked with such complication. Hepatocyte growth factor (HGF) ameliorates peritoneal fibrosis both in animal models and in vitro studies, but no study explored dialysate HGF concentration in PD patients with UFF. Our aim was to assess the relation of dialysate HGF concentration with the UF profile, free water transport quantification (FWT), and small-solute transport (MTACcreatinine) in a group of prevalent PD patients.

Methods: We performed a 4-hour, 3.86% glucose PD with additional measurement of UF at 60 minutes in 68 PD patients (age 50±14 years, 52% male, on PD for 19±23 months). We calculated Dialysate (D)/Plasma (P) ratio of creatinine, MTACcreatinine, FWT and small-pore ultrafiltration. We measured HGF and CA125 in the effluent.

Results: Effluent HGF strongly correlated with UF measured in a 4h, 3.86% glucose PET (r=0.80, p=0.009), with FWT (r=0.69, p=0.04) and with MTACcreatinine (r=0.75, p=0.02). Patients with UFF had higher dialysate HGF concentration and HGF/CA125 ratio than patients without UF (103 pg/mL vs 77 pg/mL, p=0.018 and 6.2 pg/U vs 4.6 pg/U, p=0.68, respectively). Moreover, patients with severe UF forms, namely with FWT compromise, had higher dialysate HGF concentration compared with patients with UF but no FWT compromise (104 pg/mL vs 88 pg/mL, p=0.08). FWT545% without UF was documented in some patients: these also had a higher effluent HGF concentration, but a significantly lower HGF/CA125 ratio compared with those with preserved FWT (3.6 pg/U vs 5.6 pg/U, p=0.014).

Conclusions: Our study establishes that dialysate HGF concentration is significantly higher among patients with UFF, specially, if FWT is compromised. This increase possibly signalizes an ongoing counteracting process facing peritoneal membrane deterioration.

FR-PO941
Glucose Degradation Product Methylglyoxal Induces Immature Angiogenesis and Peritoneal Dysfunction in Peritoneal Membrane in Patients Undergoing Peritoneal Dialysis
Toshiaki Nakano,1 Tohru Mizumasa,2 Hiroshi Yoshida,1 Masahito Eriuchi,1 Masatomo Taniguchi,1 Kosuke Masutani,1 Hideki N. Hirakata,2 Kazuhiko Tsuuya,1 TakanaI Kitazono.1 1Dept of Medicine and Clinical Science, Kyushu Univ; Fukuoka, Japan; 2First Dept of Internal Medicine, Fukuoka Red Cross Hospital, Fukuoka, Japan.

Background: Angiogenesis in peritoneal membrane has been recognized to induce ultrafiltration failure and possibly lead to encapsulated peritoneal sclerosis in patients on CAPD. We investigated whether glucose degradation product methylglyoxal (MGO) is associated with angiogenesis in peritoneal membrane and induce a disturbance of angiogenesis in vitro.

Methods: Peritoneum obtained when CAPD catheters were removed from 61 CAPD patients was analyzed. Peritoneum was immunohistochemically stained with anti-CD34 (for endothelial cells), anti-eSMa (for pericytes) and anti-MGO antibodies. We evaluated the associations between the number of capillary vessels, peritoneal function (D/P Cr) and the degree of MGO deposition. In addition, we measured the levels of VEGF and PDGF-BB mRNA in culture endothelial cells (human umbilical vein endothelial cells) and culture smooth muscle cells (human aortic smooth muscle cells) after the administration of MGO 50µM in vitro.

Results: We defined CD34-positive and eSMa-negative vessels as capillary vessels in peritoneal membrane using serial sections. The number of capillary vessels was associated significantly with the value of D/P Cr and the degree of MGO depositions (both P<0.01). In vitro, the expression of PDGF-BB mRNA and protein in endothelial cells significantly decreased after the administration of MGO, though the expression of VEGF mRNA increased (both P<0.01). The expression of PDGF-BB mRNA in culture smooth muscle cells did not change after the administration of MGO, though the expression of VEGF mRNA increased (P=0.01).

Conclusions: Glucose degradation product MGO enhanced the production of VEGF and suppressed the production of PDGF-BB, suggesting it may lead to a disturbance of angiogenesis in peritoneal membrane. The accumulation of MGO in peritoneum may cause immature angiogenesis and peritoneal dysfunction.

FR-PO942
Fetuin Calcioprotein Particles May Be Formed in Peritoneal Dialysis Fluid and May Contribute to Peritoneal Inflammation
Edward Robert Smith,1 Stephen G. Holt.1 1Dept Renal Medicine, Eastern Health Clinical School, Monash Univ, Melbourne, VIC, Australia; 2Eastern Health Intermurated Renal Services, Monash Univ, Melbourne, VIC, Australia; 3Royal Melbourne Hospital, Melbourne Univ, Melbourne, VIC, Australia.

Background: Fetuin-A (Fet-A) is a protein synthesised in the liver circulating at high concentrations. Fet-A forms high molecular weight complexes with calcium phosphate nanocrystals called calcioprotein particles (CPP). CPP are detectable in the serum of patients with chronic kidney disease and/or inflammation, but not normal controls. CPP may be cleared by macrophages uptake via scavenger receptor-A, but in doing so cause inflammatory cytokine and oxidant species generation. CPP have been reported in the PD fluid of patients with calcific peritonitis. Since free Fet-A has a similar molecular weight to albumin and CPP are too big to pass through large peritoneal membrane pores, we tested the hypothesis that CPP might be formed in situ in peritoneal fluid (PDF).

Methods: We measured Free Fet-A, CPP and albumin in spent dialysate and in the serum of 20 patients undergoing PD without obvious complication.

Results: Mean (SD) total Fet-A concentration was 187 (30) and 88 (46) µg/l in serum and PDF respectively. The mean (SD) CPP-associated Fet-A concentration in serum and PDF were markedly different [31 (4) vs. 23 (6) %, P<0.001]. Thus, the ratio of Fet-A to albumin was significantly higher in serum than in PDF [45 (13) vs. 24 (16) mg/L, P<0.001]. The proportion of Fet-A present as CPP was not significantly different to serum [24 (7) vs. 23 (6) %, P=0.11]. Mean (SD) albumin concentrations in serum and PDF were markedly different [31 (4) vs. 1.2 (0.6) g/L, P<0.0001]. Thus, the ratio of Fet-A to albumin was significantly higher in PDF fluid than in serum [81 (44) vs 5 (1) mg/g, P<0.0001]. PDF CPP Fet-A concentration was significantly correlated with phosphate (r=0.54, P=0.001), total protein (r=0.48, P=0.031) and 8-iso-PGF2α (r=0.48, P=0.032), but not with calcium (P=0.37) or albumin concentrations (P=0.40).

Conclusions: CPP formation may occur within the peritoneal cavity. CPP may interact with peritoneal macrophages and contribute to inflammation and oxidant stress.

FR-P0943

The Mutual Relationship between Peritonitis and Peritoneal Transport

Sadie Van Esch, Anouk Van diepen, Raymond T. Krediet, Dirk Gijsbert Struijk.
Nephrology, Academic Medical Centre, Amsterdam, Netherlands.

Background: Preservation of the peritoneal membrane is required to achieve long-term PD. We investigated the effect of multiple peritonitis episodes on peritoneal transport.

Methods: We prospectively collected transport parameters from 709 incident adult PD patients treated between 1990 and 2010. Strict inclusion criteria were used to select patients: follow-up of at least 3 years with the availability of a standard peritoneal permeability analysis (SPA) in the first year after start of PD and a SPA after the third year of PD, without peritonitis preceding the first SPA. Patients either had to remain peritonitis-free (group 0, n=30) or experienced ≥3 peritonitis episodes (group ≥3, n=16) during follow-up.

Results: At baseline the groups were similar with regard to the transport of low molecular weight solutes and fluid. However, group ≥3 had lower peritoneal protein clearances and a higher restriction coefficient compared to group 0. This resulted in lower dialysate concentrations in group ≥3 vs group 0: albumin: 222±51 vs 146±51 mg/L, p<0.01, IgG: 36±16 vs 69±16 mg/L, p<0.01, e2-microglobulin: 2:4±5 vs 4±5 mg/L, p<0.01. Plasma concentrations were not different. After 3 years, group ≥3 showed a significant increase in the mass transfer area coefficient (MTAC) of creatinine and glucose absorption (GA) with a concomitant decrease in transcapillary ultrafiltration (TCUF) compared with group 0 (MTAC: creat: p=0.03, GA: p=0.04, TCUF: p=0.03). No changes in free water transport were found.

Conclusions: Slow initial peritoneal transport rates of serum proteins result in lower dialysate concentrations, and likely a lower osmotic activity, which is a risk factor for peritonitis. This disappears during follow-up. Patients with frequent episodes of peritonitis show a increase in the transport of low molecular weight solutes and a concomitant decrease of ultrafiltration, but no changes in free water transport; this was not found in long-term peritonitis-free PD patients. These findings suggest that frequent peritonitis leads to the development of an increase of the effective peritoneal surface area without the structural membrane alterations that may develop after long-term PD.

FR-P0944

Characteristics and Outcomes of Fungal Peritonitis in a Modern North American Cohort

Anne-Claire Nadeau-Fredette, Joanne M. Bargman.
Div of Nephrology, Dept of Medicine, Toronto General Hospital - Univ Health Network, Univ of Toronto, Toronto, Canada.

Background: Peritonitis remains a common complication of peritoneal dialysis (PD). Although representing only 1-12% of overall peritonitis in dialysis patients, fungal peritonitis (FP) is associated with serious complications, including technique failure (15-85%) and death (5-55%). Only scarce data has been published regarding FP outcomes in modern cohorts in North America. In this study, we aim to evaluate rates, characteristics and outcomes of FP in a major North American PD center.

Methods: We conducted a retrospective cohort study including all fungal peritonitis among peritoneal dialysis patients followed in a large PD center between January 2000 and February 2013. Our pre-specified end-points included rates of FP, characteristics, outcomes and determinants of death.

Results: Thirty-six episodes of FP were identified during the follow-up period (one per 671 patient-months), representing 4.5% of the total peritonitis events. Patients’ mean age and peritoneal dialysis vintage were 61±3.1 and 15.5±2.9 (1-5.4-8) years, respectively. Of the 36 episodes of FP, seven (19%) resulted in death and 17 (47%) led to more severe forms of infection. Calprotectin is a novel inflammatory biomarker widely used in the diagnosis of inflammatory bowel disease. The aim of this study was to assess the utility of peritoneal fluid calprotectin as a novel diagnostic and prognostic marker in PD-related peritonitis.

Methods: A total of 44 consecutive peritoneal fluid samples from patients were collected at the peritonitis onset and on days 3, 7 and 30. All samples were examined for cell count, bedside culture and calprotectin concentration. Moreover we evaluated C reactive protein and blood leukocytes on the same days of PD effluent collection.

Results: We investigated 44 patients: 26 men, 61±18 years, 23.5% diabetic, mean PD vintage 30±16 months. During the follow-up, peritonitis was diagnosed in 11 patients (8 men, 59±16 years). The PD effluent culture was positive in 9 patients. The mean calprotectin concentration was 263.7±81.4 on day 0 and 35.7±66.8 on day 3. Calprotectin was undetectable in PD samples in 6 patients on day 3 and in 9 patients on day 7, and in all patients on day 30. The only 2 patients with persistence of calprotectin on day 7 were those who presented with a worse clinical course, a long in-hospital stay and who underwent peritonitis recurrence after treatment suspension. In all patients, both PD cells count and calprotectin levels decreased significantly after the start of treatment (p<0.001). At the time of peritonitis onset, calprotectin concentration correlated well with both the neutrophil count in the PD effluent (r=0.68) and in the circulation (r=0.62).

Conclusions: Calprotectin was detected in PD fluids of all patients at the peritonitis onset and then slowly disappeared within 7 days. Persistence of calprotectin on day 7 or its reappearance after a previous disappearance should be regarded as a risk factor for a worse clinical course.

FR-P0945

Glucose-Based Peritoneal Dialysis Fluids Inhibit Complement-Mediated Host Defenses against Staphylococcus aureus

Parvati S. Kumar,1 Mattia Corradini,1 Maria Parmeggiani,2 Lucia Belloni,1 Alfredo Stefanì,2 Sonata Pasquali.1
1. Nephrology and Dialysis Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, 2. Laboratory and Molecular Biology Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy.

Background: While fungal peritonitis is still associated with a high frequency of death in modern cohorts in North America. In this study, we aim to evaluate rates, characteristics and outcomes of FP in a major North American PD center.

Methods: We conducted a retrospective cohort study including all fungal peritonitis among peritoneal dialysis patients followed in a large PD center between January 2000 and February 2013. Our pre-specified end-points included rates of FP, characteristics, outcomes and determinants of death.

Results: Thirty-six episodes of FP were identified during the follow-up period (one per 671 patient-months), representing 4.5% of the total peritonitis events. Patients’ mean age and peritoneal dialysis vintage were 61±3.1 and 15.5±2.9 (1-5.4-8) years, respectively. Of the 36 episodes of FP, seven (19%) resulted in death and 17 (47%) led to more severe forms of infection. Calprotectin is a novel inflammatory biomarker widely used in the diagnosis of inflammatory bowel disease. The aim of this study was to assess the utility of peritoneal fluid calprotectin as a novel diagnostic and prognostic marker in PD-related peritonitis.

Methods: A total of 44 consecutive peritoneal fluid samples from patients were collected at the peritonitis onset and on days 3, 7 and 30. All samples were examined for cell count, bedside culture and calprotectin concentration. Moreover we evaluated C reactive protein and blood leukocytes on the same days of PD effluent collection.

Results: We investigated 44 patients: 26 men, 61±18 years, 23.5% diabetic, mean PD vintage 30±16 months. During the follow-up, peritonitis was diagnosed in 11 patients (8 men, 59±16 years). The PD effluent culture was positive in 9 patients. The mean calprotectin concentration was 263.7±81.4 on day 0 and 35.7±66.8 on day 3. Calprotectin was undetectable in PD samples in 6 patients on day 3 and in 9 patients on day 7, and in all patients on day 30. The only 2 patients with persistence of calprotectin on day 7 were those who presented with a worse clinical course, a long in-hospital stay and who underwent peritonitis recurrence after treatment suspension. In all patients, both PD cells count and calprotectin levels decreased significantly after the start of treatment (p<0.001). At the time of peritonitis onset, calprotectin concentration correlated well with both the neutrophil count in the PD effluent (r=0.68) and in the circulation (r=0.62).

Conclusions: Calprotectin was detected in PD fluids of all patients at the peritonitis onset and then slowly disappeared within 7 days. Persistence of calprotectin on day 7 or its reappearance after a previous disappearance should be regarded as a risk factor for a worse clinical course.

FR-P0946

Eosinophilic Peritonitis: Possible Association with Laparoscopic Peritoneal Dialysis Catheter Insertion

Yuko Akioka, Tatsuo Asano, Kei Nishiyama, Noriko Sugawara, Kyonobu Ishizuka, Masataka Hisano, Hiroko Chikamoto, Motoshi Hattori. Pediatric Nephrology, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: The methods for peritoneal dialysis (PD) catheter insertion include the open technique and the laparoscopic technique. A major advantage of laparoscopy is the complete visualization of the peritoneal cavity with diagnosis of some potential problems such as inguinal hernias, which can be repaired at the same time. However, the specific complications of the laparoscopic insertion were not sufficiently reported. The purpose of this study was to examine the association of eosinophilic peritonitis with laparoscopic insertion.

Methods: We examined 14 pediatric PD patients who underwent laparoscopic catheter insertion. Age-matched 12 patients who underwent open insertion were also examined. The cell counts of the peritoneal fluid were routinely studied during the post-operative period. Eosinophilic peritonitis was defined as showing >100 leukocytes/mm3 effluent, of which >10% was eosinophils in the differential cell count.

Results: The incidence of eosinophilic peritonitis in the laparoscopic group was significantly higher than that of open group (64.3% vs. 16.7%, p<0.01). Eosinophilic peritonitis developed asymptomatically in 2, 4, 2.0 days, and resolved spontaneously in 14.0±7.6 days after laparoscopic insertion. The peak count of leukocytes was 798.0±748.6 cells/mm3 (ranging from 275 to 2100) with a mean eosinophil percentage of 72.0±20.5. In patients with laparoscopic insertion, there were no differences in the duration of pneumoperitoneum, serum IgE level, eosinophilia in peripheral blood, and the presence of allergic diseases or immunosuppressive therapy between those with or without eosinophilic peritonitis.

Conclusions: Although the larger numbers of study will be needed, this study suggests the possible association of eosinophilic peritonitis with laparoscopic PD catheter insertion.
FR-PO948
Predictors and Clinical Course of Culture-Negative Peritonitis in Peritoneal Dialysis Patients: Experience of a Center
Daniela Lopes, Clara Santos, Ana Marta Gomes. Servico Nefrologia, CHNG/E, VNGaia, Portugal.

Background: Peritonitis is the main infectious complication related to peritoneal dialysis (PD) and is a major reason for hospitalization and technique failure. Up to 20% are cases of culture-negative peritonitis (CNP). The aim of the study is to examine the frequency, predictors and clinical outcome of CNP in PD patients.

Methods: Retrospective cohort study of all episodes of PD-related peritonitis between 1998 and 2012. To determine the predictors and clinical outcome we compared 2 groups: positive-culture or CNP. Predictors: socio-demographic and clinical variables. Outcome analysis: resolution, hospitalization, catheter removal and hemodialysis transfer. Tests were employed multivariate logistic regression to estimate the association between the variables in analysis. The significance level for the models were determined as p < 0.05.

Results: We studied 163 episodes of peritonitis in 67 patients with a mean age of 55 ± 11 years, 70.5% male, yielding an overall rate of 0.59 episodes/patient/year. There were 40 episodes of CNP. When comparing the 2 groups there were no differences in bacterial aetiology regarding age, gender, etiology of kidney disease and major co-morbidities between the groups. A history of previous antibiotic treatment (past 30 days) was significantly more common with CNP than culture- positive (42.5% vs. 7.3%, p < 0.05). The reasons for the adhesions that developed were: infection (10.2%), non-infective (2 cases), peritonitis (1 case) and other medical reasons (14 cases). No association was found between the need for hospitalization (p = 0.33), cure (p = 0.46) and transfer technique (p = 0.95) with CNP. There was no association between previous antibiotic treatment and clinical outcome (p = 0.68).

Conclusions: In our study a history of previous antibiotic treatment was an important risk factor, this can be due to the fact that antibiotic can promote the change of the local flora and cause peritonitis with fastidious microorganisms or impairing the abilities of cultures to detect the infectious organism. Thus, most cases of CNP may be explained by recent antibiotic treatment but there is no differences in clinical outcome between groups.

FR-PO949
Global Pediatric Perspective on Peritonitis: A Report from the IPPN

Background: Peritonitis remains a frequent complication of peritoneal dialysis (PD) and is the most common reason for technique failure. Our previous published registry experience revealed world-wide variation in causative organisms. To build upon that experience, the International Pediatric PD Network (IPPN) has collected data pertaining to peritonitis and other PD related issues in children receiving PD since 2007.

Methods: Data on children on maintenance PD enrolled, in the IPPN on-line registry was analyzed for this report.

Results: To date, 1991 children receiving PD have been enrolled in the registry from 95 centers in 35 countries. One-third of the patients receiving PD have experienced > 1 episodes of peritonitis with an overall annualized rate of 0.47 (± .29, 42%) of all episodes were caused by Gm pos organisms, 19% by Gm neg organisms, 2.6% by fungus and 33% were culture neg. Staphylococcal and enterococcal infections were more common in Europe, whereas MRSA and pseudomonas episodes were more common in Latin American countries. South American and Turkish had the highest rate of culture neg results. Exit-site/tunnel infections (8%) and touch contamination (7%) were the most common identifiable sources of infection. Of 508 episodes of exit-site infection, 20% were associated with peritonitis. Presence of ostomy (RR 1.28), hypoalbuminemia (< 3.0 g/dL) (RR 1.42) and recent antibiotic use (0.47±0.29, 42%) were risk factors for occurrence of peritonitis. Dialysis modality, catheter configuration, number of cuffs, or exit-site orientation had no impact on the peritonitis rate. Relapse of peritonitis occurred in 60 patients; 73% of these occurred due to Gm pos organisms and 70% followed intermittent antibiotic therapy.

Conclusions: The frequency and rate of peritonitis remain high, but the risk factors are well known. Efforts to decrease the rate of infection and enhance treatment should focus on eliminating modifiable risk factors and improving culture techniques worldwide.

FR-PO950
Astragalus Membranaceus Based Chinese Medicine Formula Might Better Preserve Residual Renal Function in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis
Kazutaka Tabata, Terence Yin, Wai Kei Lo Medicine, Tung Wah Hospital, Hong Kong SAR, China.

Background: Astragalus membranaceus is a Traditional Chinese Medicine which has been shown to possess renal protective effects in animal studies. The aim of this study was to examine the effect of Astragalus membranaceus based Chinese Medicine formula on preservation of residual renal function (RRF) and daily urine volume in patients newly on CAPD.

Methods: We studied 163 episodes of peritonitis in 67 patients with a mean age of 55 ± 11 years, 70.5% male, yielding an overall rate of 0.59 episodes/patient/year. There were 40 episodes of CNP. When comparing the 2 groups there were no differences in bacterial aetiology regarding age, gender, etiology of kidney disease and major co-morbidities between the groups. A history of previous antibiotic treatment (past 30 days) was significantly more common with CNP than culture- positive (42.5% vs. 7.3%, p < 0.05). The reasons for the adhesions that developed were: infection (10.2%), non-infective (2 cases), peritonitis (1 case) and other medical reasons (14 cases). No association was found between the need for hospitalization (p = 0.33), cure (p = 0.46) and transfer technique (p = 0.95) with CNP. There was no association between previous antibiotic treatment and clinical outcome (p = 0.68).

Conclusions: In our study a history of previous antibiotic treatment was an important risk factor, this can be due to the fact that antibiotic can promote the change of the local flora and cause peritonitis with fastidious microorganisms or impairing the abilities of cultures to detect the infectious organism. Thus, most cases of CNP may be explained by recent antibiotic treatment but there is no differences in clinical outcome between groups.

FR-PO951
Evaluation of Protein Energy Wasting and Inflammation on Continuous Ambulatory Peritoneal Dialysis Patients and Its Correlation
Sham Sunder, Venkatesanaranjan K, Himanshu Verma, Satyanand Sathi, Rajesh Padmalatha Jayaraman, Prabhu K, Anurag Gupta. Nephrology, PGIMER & Dr. Ram Manohar Lohia Hospital, New Delhi, India.

Background: Protein energy wasting and heightened inflammation are highly prevalent and is a strong risk factor for morbidity and Mortality in CAPD patients. Evaluation of malnutrition, prevalence of inflammation as well as inter-relationship between various nutritional indices and inflammation has not been studied in much detail.

Methods: 63 CAPD patients were assessed for their nutritional status and inflammation. Nutritional status was assessed by dietary diary,Anthropometry, Subjective global assessment, multi- frequency BIA and serology. Inflammation was assessed by High-sensitivity CR - reactive and Interleukin-6. Diagnosis of malnutrition was made. Correlation between malnutrition and various indices were performed.

Results: Mean age of the patients was 57.6 ± 11.6 years. The overall average calorie and protein intake / Kg / day were 25.5±4.6 Kcal and 0.81±0.2 gm resp. The mean and standard deviation of BMI (23.7±5.7), MAC (26.3±4.5) Cm, TST (1.624±0.4) Cm MAMC (25.6±4.5), were respectively .The mean values of S.protein, S.Albumin S.Pre-albumin, S.transferrin, S.Cholesterol, S.Triglyceride, hsCRP and IL-6 were 5.9 gm/dl, 3.0 gm/dl, and 21.1 mg/dl, 130.6 mg/dl, 155.9 mg/dl, 136.1 mg/dl and 8.8±7.6 mg/dl and 8.1±12.2 mg/dl respectively on PD basis. According to SGA, 17%, 54%, 28% had S.albumin < 25% 21% 62% and BMI < 20%, 11% of CAPD patients had normal, moderate, severe malnutrition status resp. Based on hs-CRP and IL-6, 70% and 71.8% of CAPD patients had high inflammation resp. baseline or post-transplantation S.protein S.albumin S.transferrin.

Conclusions: Protein energy wasting (80-85%) by various methods and inflammation (70%) was very highly prevalent . Inflammatory markers showed significant negative correlation with Anthropometry and serological markers.Inflammatory markers should be included in the regular assessment of CAPD patients, for the better management of protein energy wasting.

FR-PO952
Peritoneal Permeability Is Not Associated with Patient Survival
Hiromi Nakamura, Makoto Higuchi. 1 Dept of Nephrology, Shinonoi General Hospital, Nagano, Japan; 2 Dept of Nephrology, Shinshu Univ, Matsumoto, Japan.

Background: Several studies have suggested a relationship between high peritoneal transport and adverse outcomes in patients with peritoneal dialysis (PD). However, there have been no adequate studies comparing the outcomes of high and low peritoneal permeability.

Methods: We investigated longitudinal changes in peritoneal permeability and patient survival, including transfer to hemodialysis after a dropout of peritoneal dialysis therapy, related to differences between PET categories at baseline. We performed a retrospective, single-hospital study of patients with PD treated from 1998 to 2009. Based on baseline dialysate-to-plasma creatinine (D/P Cr), the 76 patients were divided into two categories: L-A (D/P Cr < 0.65) and HA-H (D/P Cr > 0.65). Patient demographics and clinical features were compared. The changes in D/P Cr, ultrafiltration, Kt/Vi, dialysate glucose load, total protein loss, and urine volume were followed for 5 years. The overall mortality rate was evaluated using the Kaplan-Meier method.

Results: 1) A comparison with baseline showed no significant differences between the L-A and HA-H groups: age (57 vs. 61 years), gender (64 vs. 77%), diabetes (38 vs. 31%), APD (54 vs. 60%), 10-year survival (36 vs. 36%), serum albumin (3.5 vs. 3.4 g/dl), and serum creatinine (9.1 vs. 7.9 mg/dl). The D/P Cr value increased to 0.63 ± 0.68 at years 2 and 3 from 0.51 in the L-A group and decreased to 0.65 ± 0.68 at years 2 and 3, respectively from 0.79 in the HA-H group. In the HA-H group, ultrafiltration increased to 521 ml at year 3 from 215 ml at baseline. No significant changes were observed in patients with high protein loss or total protein loss between the two groups over the 5-year period. 2) There were no significant differences in mean PD duration (53 vs. 51 months) or mean survival time from PD initiation (71 vs. 62 months) in the L-A vs. HA-H groups, respectively. Kaplan-Meier curves showed no survival differences between groups (log-rank test: p = 0.362).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only. Underline represents presenting author/disclosure.
Conclusions: Both high and low peritoneal permeabilities at baseline were rated as regression to average status in years 2 and 3, but not were associated with overall patient survival.

FR-PO953

Free Water Transport (FWT) and Sodium Sievling in Different Clinical Settings

Javier De Arteaga, 1 Fabian Ledesma, 1 Bengt Rippe. 1 Nephrology, Hospital Privado, Catholic University, Cordoba, Argentina; 2 Nephrology, Lund Univ, Sweden.

Background: Peritoneal sodium sievling(Ss), an indirect measure of FWT, is mainly the consequence of aquaporin function. A high transport state and/or a plasma/dialysate Na gradient >5 mmol/l may influence this sievling effect with sodium diffusion from plasma. A diffusion correction may apply for assessing FWT. Upreregulated peritoneal aquaporins increasing FWT is possible and described in the posttransplant state, due mostly to steroids (NTD2011vol 26). Acisic pts on PD have a high UF and fast transport Objective: evaluate Ss and FWT in our pts in different clinical settings.


Results: Solute transport, FWT and Na dip

<table>
<thead>
<tr>
<th>Controls</th>
<th>UFF</th>
<th>Pts of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>44</td>
<td>8.5</td>
</tr>
<tr>
<td>TH</td>
<td>3.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Conclusions: As compared to controls, Ss is blunted incirrhic pts and enhanced in the posttransplant state. The cause of this in the former, we don’t know, but we can hypothesize that it could be due to ascitic fluid generated “per se”, a high Na P/D gradient and transport state. In the latter, an upregulation of aquaporins for steroid use is the most probable case. UF and NAR is significantly higher in cirrhics.

FR-PO954

Leptin Impact in Peritonitis Events of a Peritoneal Dialysis Population

Silvia Coelho, 1 Ana Paula Bernardo, 2 Maria João Carvalho, 2 Olivia Santos, 2 Guilherme Rocha, 2 António Manuel Nunes Cabrita, 2 Anabela Rodrigues, 2 Nephrology, Hospital Fernando Fonseca, Lisboa, Portugal; 1 Nephrology, CHP Hospital Santo António, Porto, Portugal.

Background: Leptin is a key link between nutritional status and immunity function. Hypoleptinemic states have been associated with increased risk of infection. In peritoneal dialysis-PD this link has not yet been studied.

We aimed to explore the clinical association between leptin levels and peritonitis events.

Methods: A cross sectional measurement of leptin was performed in a prevalent PD population. Peritonitis episodes occurring one year before and two years after were documented. Corporal composition was evaluated with BCM®.

Results: Patients (n=66) had a mean age of 50.3 years (SD 14.3), 48.5% female, 56.2% were on APD and 44% used icodextrin. Total k/t was 2.2 (1.8-2.9) and renal k/t was 0.9 (0.4-1.3). Nutrionally, they had a mean body mass index-BMI of 25.2 (SD 4.4), normalized protein catabolic rate-nPCR of 0.8 (SD 0.6) and serum albumin-sAlb 3.8 (SD 0.4). Peritonitis was observed in 36.4% with a median of 2 (1.0-2.75) episodes/patient during the study period.

Patients with peritonitis were predominantly women (p=0.006) and older (p=0.034) but did not differ in respect to BMI, LBM, FBM, nPCR and sAlb levels (p>0.05). Leptin and IL6 levels were similar in patients with or without peritonitis, p=0.178 and p=0.805, respectively. Considering the median value of leptin in our population (17.3ng/ml), patients were divided in high leptin (HL) and low leptin (LL) groups. The HL had higher BMI (27.3 vs 23.4) and FBM (14 vs 8.5), lower LBM (12.5 vs 14) and lower nPCR (0.7 vs 0.9), all p<0.05. There were no statistical differences (p>0.05) between the HL and LL groups with respect to the presence or number of peritonitis episodes, recruited leucocytes in the peritoneal effluent or the level of IL6.

Conclusions: Hyperleptinemia was associated with obesity but not with systemic inflammation. On the other hand, hypoleptinemia in the absence of other signs of undernutrition, was not associated with peritonitis events or outcome. The link between leptin and immunity in PD deserves further investigation.

FR-PO955

Comparison of Small Solute Transport between Two Different Peritoneal Equilibration Tests

Saisri Siriprapasvan, Kanjanap Thamprasertkit, Thatsaphan Srithongkul, Nipa Aiyasanon, Sukit Raksaatk. Renal Unit, Internal Medicine, Siriraj Hospital, Mahidol Univ, Bangkok, Thailand.

Background: Measurement of small solute transport have been developed and modified to obtain more information of solute and fluid kinetics in peritoneal dialysis(PD). However, the dialysate to plasma creatinine ratio at 4 hours(D/PCr4hr) of the original standard peritoneal equilibration test(PET) has still been used in clinical practice. The aim of this study is to compare the D/PCr4hr between the standard PET and the new modified PET with temporary drainage.

Methods: Two PETs(2.5%Dextrose(D)PET and 4.25%D PET with temporary full drainage at 1 hr) were performed consecutively in 59 stable chronic PD patients(sample size was calculated from a pilot study of 10 patients). The D/PCr4hr at the end of 4 hr was measured and dialysate Cr was corrected for the glucose concentration. Small solute transport was classified as fast, average and slow by the D/PCr4hr of <0.81, 0.81-0.50 and <0.50 respectively. Intra-class correlation coefficients was used to assess the agreement of D/PCr4hr and weighted kappa was used to evaluate the agreement of transport categories between the 2 PETs.

Results: The mean age of the patients was 68 years and median time of PD duration was 11.4 months. Intra-class correlation of D/PCr4hr between the 2 PETs was 0.73(CI 0.58-0.83,p<0.001). The agreement of peritoneal transport categories among the 2 PETs was moderate(weighted kappa=0.46,p<0.001). Most agreement(88.5%) were found in average group. The D/PCr4hr of standard PET tended to be higher in fast transportor but lower in slow transporter than D/PCr4hr of modified PET with temporary drainage.

Conclusions: The D/PCr4hr of the modified PET with temporary drainage well correlated with the standard PET in average transporter but may be underestimated in slow transporter and fast transporter, respectively in PD patients.

FR-PO956

Clinical Investigation of Relationship between Peritoneal Dialysis Effluent Cytokine Profiles and Peritoneal Solute Transport Rate

Guochun Chen, Feng Wen, Hong Liu, Xiang Zhou, Jing Liu, Fu-You Liu. Dept of Nephrology, The Second Xiangya Hospital of Central South Univ, Changsha, Hunan, China.

Background: Fast peritoneal solute transport rate (PSTR) is reportedly correlated with high mortality in peritoneal dialysis(PD) patients. The immune dysfunction provoked by incompatible solutions may contribute to variability of PSTR in peritoneal cavity.

Methods: This study was to apply the Lumines Max technology to detect the cytokine profiles in overnight dwelled PD effluent of stable continuous ambulatory peritoneal dialysis(CAPD) patients, including inflammatory cytokines(IL-6, MCP-1, TNFα, IL-17A, IL-21, IL-22, IL-23), angiogenic factor (VEGF), pro-KMT/fibrosis factor(TGF-β1). The clinical data were analyzed from 30 CAPD patients in the Second Xiangya Hospital from September 2012 to February 2013.

Results: According to the peritoneal transport characteristics, all patients were divided into low and low-average transport (L/A) (D/P Cr <0.64) group, high and high average transport (H/A) (D/P Cr ≥0.65) group respectively. Dialysate IL-6,MCP-1,TNFα, VEGF, and TGF-β1 level were above the detected limit Dialysate IL-17A, IL-17F, IL-21, IL-22, IL-23 could not be detected. Dialysate IL-6 in H/A group were higher than L/A group(P<0.05). Among PDE inflammatory profiles, IL-6 levels (r = 0.56, P<0.001), MCP-1 level (r = 0.62, P<0.001) was significantly associated with D/P Cr (Dialysate VEGF(r=0.425, P=0.019) and TGF-β1(r=0.425, P=0.019) were also correlated with D/P Cr. Among systemic markers, serum albumin but not CRP showed a negative correlation with D/P Cr(r=-0.369, P=0.045). Multivariate regression analysis showed that D/P Cr was independently correlated with dialysate IL-6. Besides, dialysate IL-6, MCP-1, VEGF and TGF-β1 correlated with each other.TGF-β1 was negatively correlated with eGFR(r=-0.370, P=0.048), and for these patients whose eGFR <60 ml/min/1.73m2, TGF-β1 level is much lower than the rest(P<0.018).

Conclusions: Our study indicated that these dialysate cytokines contributing to chronic inflammation, angiogenesis and fibrosis maybe contribute to high PSTR in stable CAPD.
FR-P0957
Decreased Cytokine Levels Is Associated with Oxidative Stress in Patients on Peritoneal Dialysis

Ji Sun Paeng,1 Hye-Young Kang,1 Hyung Jung Oh,2 Sung Jin Moon,1 Jae-Hyun Yoo,2 Shin-Wook Kang,1 Seung Hyeok Han,2
1Brain Korea 21; 2Dept of Internal Medicine, College of Medicine, Yonsei Univ, Seoul; 2College of Medicine, Kwandong Univ, Gyeonggi-do, Korea.

Background: Cytokines are known as an antiaging gene, which is predominantly expressed in the distal convoluted tubes of the kidney. Previous studies have shown that circulating cytokine levels are decreased in experimental kidney disease models and that cytokine exerts anti-oxidative and anti-inflammatory effects. Meanwhile, patients with end-stage renal disease (ESRD) are particularly characterized by increased inflammation and oxidative stress. However, little is known about the relationship between these features and cytokines in these patients.

Methods: We conducted a cross-sectional single-center study in 78 ESRD patients on peritoneal dialysis (PD). Serum concentrations of cytokine, interleukin-6 (IL-6), and 8-isoprostane were measured by enzyme-linked immunosorbent assay. To identify independent factors associated with cytokine, Spearman’s correlation coefficients were determined. Linear multiple regressions analyses were conducted.

Results: When patients were classified according to the median value of serum cytokine (329.6 pg/ml), serum 8-isoprostane and IL-6 levels were significantly higher in the ‘high’ cytokine group compared to patients with ‘low’ cytokine. In correlation analyses, log 8-isoprostane (r=0.310, P=0.006) and log IL-6 (r=0.343, P=0.002) were inversely correlated with log cytokine. After adjustment for age, gender, MAP, log iPTH, and log IL-6, log 8-isoprostane was independently associated with log cytokine (β=0.158, P=0.040). In contrast, the significant relationship between cytokine and IL-6 disappeared in an adjusted model.

Conclusions: Circulating cytokine concentrations were significantly associated with 8-isoprostane levels in ESRD patients on PD, suggesting a potential link between cytokine deficiency and enhanced oxidative stress in these patients. Further studies with a large number of patients are required to confirm the relationship between cytokine, oxidative stress, and inflammation in ESRD patients.

FR-P0958
Peritoneal Protein Clearance Rather Than Faster Transport Status Determines Outcomes in Peritoneal Dialysis Patients
Gayathri K. Rajakaruna, Ben Caplin, Andrew Davenport. UCL Centre for Nephrology, Royal Free Hospital, London, United Kingdom.

Background: Fast peritoneal transport status was shown to be associated with increased mortality risk for peritoneal dialysis (PD) patients. However fast transport could either be due to increased peritoneal capillary surface area or increased permeability. Peritoneal protein clearance (PCC) has been proposed to differentiate increased permeability from increased capillary surface area.

Methods: Patients underwent bioimpedance measurements of extracellular water (ECW) and total body water (TBW) attending for their first peritoneal transport assessment. We also measured PCC in PD patients and grouped them into high (top quartile) or low PCC groups and followed patient outcomes.

Results: 300 patients, median age 57.0 (44-66) years, 47.7% male, 29.0% diabetic and 56.3% Caucasian were studied. Mean PCC 87.7±3.8 ml/day. During a median follow up of the patients of 5.9 (1.6-9.1) years, 29.8% died, with a median duration of peritoneal dialysis of 28 (15.3-50) months, 37.3% transplanted and 30.3% transferring to haemodialysis. Overall mortality was greater for those in the high PCC group (log rank test p=0.01). On Cox proportional hazards modeling the high PCC group was associated with an increased risk of death hazard ratio 1.81, P=0.018), as was age (HR 1.04, P=0.000), increased ECW/TBW (HR 2.43, P=0.04) and Davies co-morbidity score (HR 1.55, P=0.01) independent of serum albumin and C-reactive protein.

Conclusions: We found an independent association between a high PCC and mortality. Protein clearance was also increased with age, co-morbidity and ECW/TBW. Peritoneal protein clearance may be a surrogate for capillary permeability, and can be relatively easily measured, and as such could be used to identify patients at risk of increased mortality to allow further interventional trials.

FR-P0959
Protein Binding of P Cresol Sulphate and Indoxyl Sulphate in Peritoneal Dialysis Effluent
John P. Collins,1 David B. Lee,2 Martin Roberts.2 1Renal Medicine, Auckland City Hospital, Auckland, New Zealand; 2VAGLA Healthcare System, David Geffen School of Medicine, UCLA, Los Angeles, CA.

Background: The small MW highly protein-bound solutes P Cresol Sulphate (PCS) and Indoxyl Sulphate (IS) are recognized uremic toxins. Hemodialysis removes a tiny fraction of the total toxins as a consequence of high plasma protein binding (> 90%). In The PD-based Automated Wearable Artificial Kidney (AWAK) peritoneal proteins are not dissolved but are continuously regenerated and re-turned to the patient Thus, the protein-content of the dialysate is anticipated to rise to levels higher than those seen in conventional PD effluent (PDE). Potentially the removal of protein bound toxins could be enhanced. However there is no data on PDE protein binding of PCS and IS.

Methods: 24 hour PDE was collected from 10 patients on CAPD/APD and total, free and protein-bound PCS/IS were measured with an HPLC method. One 24 hour PDE was compared to the total toxins as a consequence of high plasma protein binding (> 90%). In The PD-based Automated Wearable Artificial Kidney (AWAK) peritoneal proteins are not dissolved but are continuously regenerated and re-turned to the patient. Thus, the protein-content of the dialysate is anticipated to rise to levels higher than those seen in conventional PD effluent (PDE). Potentially the removal of protein bound toxins could be enhanced. However there is no data on PDE protein binding of PCS and IS.

Conclusions: We have shown that the protein binding of PCS and IS in PDE were 34% and 32% respectively - levels substantially lower than those reported in plasma. However when the PD protein concentrations were artificially raised to mimic those anticipated with the use of AWAK, binding was enhanced substantially for both PCS and IS. Clinical use of the AWAK may result in improved removal of these toxins.

Funding: Private Foundation Support

FR-P0960
Inflammatory Markers among Diabetic Women with End-Stage Renal Disease: A Role in Higher Cardiovascular Mortality
Sudha P. Chennasamudram,1 Essam N. Nakhi,2 Tarek H. Naguib,2 Tetyana L. Vasylyeva.1 Pediatrics, TUHSC,1 Internal Medicine, TUHSC. Amarillo, TX.

Background: Cardiovascular disease (CVD) mortality is higher for diabetic women, women under 65 years of age, and those under 70 years with end-stage renal disease (ESRD) than for comparable men. CVD also worsens mortality of persons with diabetes mellitus (DM) among ESRD population. Due to the implication of interleukin 1 beta (IL-1β) and endothelin 1 (ET-1) in CVD, we hypothesized that sex differences relative to the proinflammatory and endothelial markers may exist and play a role in the higher CVD mortality of women in this population. The study objective is to investigate whether endothelial function (EF) and proinflammatory markers vary by sex among persons younger than 65 years and DM and ESRD.

Methods: This is a post-hoc analysis of 15 subjects (average age of 54±9 years, 8 females), on peritoneal dialysis (PD), from an earlier study done for phosphate binder comparison. We evaluated EF by reactive hyperemia index (RHI). We measured serum levels of EF biomarkers: ET-1, plasmaminogen activator inhibitor 1 (PAI-1), soluble vascular adhesion molecule 1 (sVCAM) and soluble intercellular adhesion molecule 1 (sICAM); and proinflammatory markers: tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP). Wilcoxon test was performed for all the study parameters.

Results: Proinflammatory markers in males vs females were: TNF-α was 49.4±7.6 vs 36.8±3.0 pg/mL (P=0.054), IL-1β was 11.6±1.1 vs 14.0±2.1 pg/mL (P=0.158), IL-1β was 21.9±0.7 vs 28.0±3.3 pg/mL (P=0.028), CRP 25.8±9.7 vs 34.7±5.6 ng/mL (P=0.251). RHI was not significantly different between sexes. For serum markers of EF, see Table 1.

Conclusions: Diabetic women aged under 65 years on PD due to ESRD have higher levels of IL-1β and ET-1, than comparable men. These markers may have a role in the higher CVD mortality in women of this population.

Funding: Private Foundation Support

FR-P0961
Competing Risk Analysis of First Peritonitis for Technique Failure and Death in Peritoneal Dialysis
Jinn-Yang Chen, Div of Nephrology, Taipei Veterans General Hospital.

Background: Competing risks outcomes may be encountered in peritoneal dialysis (PD) treatment. Identifying the differential effects of risk factors on different outcomes may improve initial assessment and treatment of PD patients.

Methods: Records for patients aged 20 years and older, started dialysis therapy between January 2006 and December 2009, and had received peritoneal dialysis as their initial dialysis modality (modality used on 90th day after initiating dialysis) were reviewed for our study. Cause-specific hazard and subdistribution hazard models were performed. Technique failure and death during PD were defined as censoring events or competing events for each other. Demographics, comorbidities and first peritonitis episode as a time-dependent covariate were included in the model.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only
Results: Among 4553 incident PD patients, 665 (14.6%) patients experienced technique failure and 632 (13.9%) patients died during PD. Patients who experienced technique failure had higher peritonitis rate (0.68 episode/patient-year). Patients who died during PD were older (67.7 ± 13.1 years) and had higher prevalence of comorbidities. Using the subdistribution model, male sex (HR: 1.42; 95% CI: 1.21-1.66), diabetes (HR: 1.6; 95% CI: 1.34-1.91) and the first peritonitis episode (HR: 1.76; 95% CI: 1.5-2.06) increased the risks of technique failure. By contrast, age, diabetes, CHF, CVA/TIA, GI bleeding, liver disease and cancer significantly increased risks for death during PD. The first peritonitis episode was associated with death during PD in the cause-specific model (HR: 2.44; 95% CI: 2.06-2.88), but the risk became insignificant in the subdistribution model. Time-varying risk of technique failure prior to the first peritonitis was highest during the first six months (HR: 5.01; 95% CI: 3.93-6.39) and patients remained at increased risk of technique failure for another 6 months after the episode.

Conclusions: After the first PD peritonitis, the risk for technique failure was higher that for death. Patients of advanced age or multiple comorbidities had higher risks of death than technique failure. Male diabetic PD patients need the most aggressive care for peritonitis prevention.

Funding: Government Support - Non-U.S.

FR-PO962
Vascular Calcification Is Associated with Lower Weekly Phosphate Clearances in Peritoneal Dialysis

Background: Vascular calcification contributes to increase cardiovascular risk in patients on dialysis and is commonly associated with hyperphosphatemia. Lower phosphate clearance in hemodialysis might be associated with vascular calcification yet there is no data on phosphate clearance and its relation to vascular calcification in patients in peritoneal dialysis (PD).

The aim of this study was to evaluate the association between phosphate removal in patients treated with PD and vascular calcification assessed by radiographic studies (KDIGO guidelines).

Methods: We included 47 patients ≥18 years with at least 6 months on PD and stable clinical course for at least 2 mo. We measured 2 vascular calcification scores: based on radiographic films (hands and pelvis or lateral abdominal). Phosphate was measured in 24-hour dialysate. In patients with residual renal function (RRF), phosphate was determined in 24-hour urine collection. Weekly total phosphate clearance was calculated (L/week).

Other collected variables: age, time on dialysis, diabetes, body mass index (BMI, kg/m²), RRF (ml/day), and serum lipids, phosphorus, calcium, iPTH, and alkaline phosphatase.

Results: Forty-seven patients aged 38 ± 12.5 yr (range 18-66) were included, 29 female (62%). Negative correlations were observed between vascular calcification scores and weekly total phosphate clearance (hands and pelvis: r=-0.36, p<0.001 and abdominal lateral column r=-0.43, p<0.001). Relevant correlations were observed between vascular calcification scores and age (r=-0.54, p<0.001), time on dialysis (r=-0.36, p<0.01), BMI (r=0.30, p <0.04) and RRF (r=-0.26, p<0.04). Serum phosphorus, calcium, iPTH were not associated with vascular calcification. In a multiple regression analysis, weekly total phosphate clearance (p<0.01), age (p<0.001), and RRF (p<0.03) remained independently associated with vascular calcification scores.

Conclusions: Lower weekly total phosphate clearance is associated with increased vascular calcification and may be useful as a prognostic marker and treatment objective in patients on PD.

Funding: Government Support - Non-U.S.

FR-PO963
An Easy Way to Estimate Total Kt/V in Patients on Peritoneal Dialysis between Mandatory Routine Measurements
Fernando Sales, Rosilene M. Elias, Adrian Sanjuan, Benedito J. Pereira, Manuel C. Castro, Hugo Abensur. Div of Nephrology, Univ of Sao Paulo, School of Medicine, Sao Paulo, Brazil.

Background: For patients on peritoneal dialysis (PD), all guidelines recommend measurements of dialysis dose by calculating renal Kt/V every 2 months and peritoneal Kt/V every 4 months, in order to achieve a total Kt/V minimal of 1.7week. However, patients can lose their residual renal function between these intervals, while the physicians are blinded to the offered dialysis dose. In this meantime an estimated Kt/V is welcome. The purpose of our study was to compare measured total Kt/V (mKt/V) with estimated Kt/V (eKt/V) based on equations.

The purpose of our study was to compare measured total Kt/V (mKt/V) with estimated Kt/V (eKt/V). ROC determined that total eKt/V can predict a total mKt/V of 1.7 with sensitivity of 89% and specificity of 80% (AUC= 0.872; p=0.002).

Correlation
Measured Estimated Correlation
Total Kt/V (n=110) 1.92 ± 0.43 1.01 ± 0.53 r=0.683; p<0.0001
Peritoneal Kt/V (n=51) 2.72 ± 0.41 1.08 ± 0.32 r=0.75; p<0.0001
Capillary Kt/V (n=51) 2.19 ± 0.48 2.00 ± 0.43 r=0.828; p<0.0001

Conclusions: Our data showed how to estimate PD Kt/V. We are not proposing a replacement of the well validated method to calculate Kt/V. However, as a simple tool, this estimate might help to adjust the dialysis dose in the intervals we do not have measured Kt/V.

FR-PO964
Comparison of Various Antiseptics Impact on Torque Required for Transfer Set Disconnection and Implications for Safety
Catherine Finnek, Ira D. Davis, James A. Sloand, Dorota Wolpiuk, Audrey M. Hutchcraft, Mary E. Gellens. Medical Affairs, Baxter Healthcare Corporation, Deerfield, IL.

Background: To evaluate the security of the attachment of the Peritoneal Dialysis (PD) transfer set (TS) to the Baxter (B) titanium catheter adapter (TCA) following the submerged contact of the TCA threads using 5 antiseptics and measuring removal torque (T).

Methods: The Baxter TCA was soaked separately in Amuchina, Octenisept, Braunol Povidone Iodine 10%, Chlorhexamed Forte 0.2% and Purdue 10% Povidone Iodine (PI) before connecting theo B-TS with a clockwise torque range of 2.5-3.0 inch-lb.s. A test without antiseptic application (dry) was used as a control. One lot of TCAs was used and 28 units tested in each of the five antiseptics groups. Counter-clockwise torque off assessment of the removal of the TCA from the TS was evaluated with a hand torque device for 24 hrs prior to disconnection. Connection integrity was also measured using the tensile pull test.

Results: Connection integrity was measured. All antiseptic-containing and dry connections sustained a 0.2 in-lbf force for 10 seconds and endured a pull force of 75bf. No leaks were found with the leak and vacuum tests. The removal torque (in-lbf) mean result as follows:

Antiseptic Mean Removal Torque [in-lbf] ± Standard Deviation (SD)
Amuchina 1.46 ± 0.24
Octenisept 1.89 (0.62)
Braunol 1.86 (0.83)
Purdue PI 10% 1.36 (0.81)
Chlorhexamed 0.59 (0.59)

Conclusions: Our data suggests that the use of Purdue 10% PI at the connection site is associated with a tighter TCA-TS connection compared to four other antiseptics and compared with a dry connection. Enhanced tightness of the TCA-TS connection would be expected to reduce the probability of a complete or partial TCA-TS disconnection and the possibility of peritonitis.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

FR-PO965
Greater Omentum Folding in Open Surgical Placement of PD Catheters: A Randomized Controlled Study and Systemic Review

Background: Mechanical catheter dysfunction caused by omentum entrapment remains a major complication of PD therapy. The purpose of this study was to determine the outcomes of omentum folding at the time of primary open catheter insertion.

Methods: From March 2008 to December 2012, total 67 PD subjects were enrolled in the study and randomly assigned to receive either Regular Open Insertion (ROI group, n=33) or Open Insertion with Omentum Folding (OIOF group, n=34). The primary outcome was defined as PD catheter tip migration with dysfunction. A systematic review was performed to analyze the outcomes of omentum management in PD catheter implantation, based on published data from 1990 to 2011.

Results: There was no statistical difference of baseline patient characteristics between ROI and OIOF groups. 9 (27.3%) patients in the ROI group presented with the catheter malposition in the late stage (~60 days) of the study, significantly higher than 2 (5.9%) of the OIOF group (P=0.049). Significant differences of catheter survival rate between 2 groups were observed in the late stage (P=0.030) and the full time of the study (P=0.028). A higher incidence of irreversible catheter dysfunction was shown in the ROI group (15.2%), whereas none occurred in OIOF group (P=0.031). No statistical difference was determined in other catheter-related complications or patient survival rate. There were no statistical differences of peritoneal transport characteristics or dialysis adequacy between 2 groups upon evaluation of 3-, 6- and 12-month. Systemic review of current publications suggested that PD catheter placement with omentum management could lead to less irreversible catheter dysfunction and improved outcome of catheter survival.

Conclusions: Our data suggest that omentum folding at the initial time of open catheter placement can significantly reduce the risk of catheter tip migration with dysfunction and improve the outcome of PD technique.
FR-PO966
Which Fluid Space Is Affected by Ultrafiltration? Mihaly B. Tapolyai,1 Maria Faludi,1 Tibor Fulop,2 Klara Berta.2 1Fresenius Medical Care, Semmelweis Univ, Budapest, Hungary; 2Medicine, Div of Nephrology, Univ of Mississippi, Jackson, MS. 3Medicine, Div of Nephrology, WJB Dorm VA Medical Center; Columbia, SC.

Background: Ultrafiltration (UF) is a common and everyday procedure performed with almost all dialysis session. During UF several liters of fluid are removed, however, what proportion of this fluid is removed from which fluid space could not be easily and clinically measured until now; we designed this study to evaluate the fluid spaces most affected by UF.

Methods: This is a prospective cohort study of 40 prevalent chronic dialysis (HD) patients in receiving thrice weekly hemodialysis. We measured the patients’ fluid spaces using a whole body bioimpedence apparatus to evaluate the changes of fluid spaces right from the beginning of the HD session and immediately after. We recorded the fluid spaces: UF volumes, and blood pressures.

Results: 40 prevalent HD patients (mean age: 60 ±52 year; 15 male; 11 diabetic; mean weight: 71.63 ±15.48 kg had bioimpedence (BCM, Fresenius) measurements before and after HD. On the average 2.38 ±0.98 L of UF was achieved (measured overload: 2.35±1.44 L). The Extracellular Volume decreased from 16.84 ±3.52 to 14.89 ±3.06 Liters (p: <<0.0001); Intracellular Volume from 16.88 ±4.40 to 16.55 ±4.48 Liters (p: 0.45); the degree of volume overload from 3.60 ±7.30 to 3.83 ±8.32 % (p: <0.0001) of the extracellular space. The Mean Arterial Pressures also decreased from 122.95 ±19.02 to 108.50 ±13.91 mmHg (p: <0.0001).

Conclusions: We conclude that UF almost exclusively reaches the extracellular fluid space and the fluid in the intracellular fluid space is not significantly affected when fluids are measured immediately after a 4 hour dialysis session.

FR-PO967
Dialysability and Safety of Gadoterate Meglumine (Dotarem®) in Hemodialysis Patients Eric F. Gheuens,1 Ronald Dalemans,1 Sofie Mesens.2 1Dept Nephrology-Hypertension, Ziekenhuis Netwerk Antwerpen, Antwerpen, Belgium; 2Clinical Pharmacology Unit, SGS, Antwerpen, Belgium.

Background: To evaluate the dialysability and safety of gadoterate meglumine (a macrocyclic gadolinium based contrast agent) in hemodialysis patients.

Methods: Phase I, monocentric, non-comparative, non-randomized, open-label clinical trial, including 10 patients, requiring hemodialysis 3 times a week for 4 hours. Gadoterate was injected intravenously (0.1 mmol/kg). The primary evaluation criterion was the decrease in serum gadoterate concentration (SGC) after each hemodialysis session. To calculate the dialysability, blood samples were drawn simultaneously from the inflow and outflow of the circuit during the first hemodialysis session, and from the vascular access before and after each of the 3 hemodialysis sessions. These started at 1, 2 hours, 2 days and 4 days, following the gadoterate injection. The total SGC was measured by inductively coupled plasma mass spectrometry. The secondary evaluation criteria were the clinical safety (vital signs, injection site tolerance) and laboratory assessments which were evaluated during the 4-day follow-up after gadoterate injection. Adverse events (AEs) and serious AEs were evaluated after 3 weeks, 3 months and 1 year.

Results: All 10 subjects were Caucasian, 50.0% were female. Median age was 64.0 (31-79) years; median weight was 70.6 (61-116) kg. During the first hemodialysis, the mean gadolinium clearance (ml/min) was 224.6 ±0.5 at 2 hours and 225.7 ±1.5 at 4 hours. The SGC decreased over time by 88 to 93% and 97% at 0.5, 1.5, and 4h after start of dialysis. After the third hemodialysis session the SGC dropped by 99.7% compared to the pre-dialysis value of the first session. No AEs related to gadoterate were reported. No AEs occurred at the injection site during the observation period. There were no clinically relevant changes in mean laboratory values and vital signs. No cases of Nephrogenic Systemic Fibrosis have been reported so far.

Conclusion: This is the first study to document the excellent dialysability of gadoterate (recently FDA approved). After 3 hemodialysis sessions the serum concentration dropped by 99.7%. Furthermore we confirm the safety in hemodialysis patients.

Funding: Pharmaceutical Company Support - Guerbet-group

FR-PO968

Background: The independent prognostic values of T3 levels for all-cause and CV mortality were also determined. Accumulating evidence has indicated that a reduced triiodothyronine (T3) level in prevalent hemodialysis (HD) patients is a prognostic factor for adverse clinical outcome. However, little is known about the association between low T3 and mortality in end-stage renal disease (ESRD) patients starting HD and whether the impact of T3 on mortality is mediated by malnutrition, inflammation, or cardiac dysfunction in these patients.

Methods: In a randomized controlled trial 40 chronic hemodialysis patients were dialysed with HCO or regular Highflux membranes for three weeks following a cross-over design. Serum samples were drawn before dialysis. Afterwards, vascular smooth muscle cells were incubated with calcification media and these serum probes (10%). After ten days calcification was measured using alizarin red staining and set in relation to the number of proliferating cells using WST-8.

Results: After ten days of incubation, SMCs incubated with serum obtained after 3 weeks dialysis with HCO showed significantly reduced calcification compared to SMC incubated with serum during Highflux dialysis (0.144±0.0052 vs. 0.161±0.0008, p=0.003).

Conclusion: Calcification of SMC in vitro is lower using serum during dialysis with HCO compared to serum during Highflux dialysis. This effect may be caused by improved elimination of pro-calcifying mediators with HCO membranes.


FR-PO970
The Impact of Low Triiodothyronine Levels on Mortality Is Mediated by Malnutrition and Cardiac Dysfunction in Incident Hemodialysis Patients Hyang Mo Koo,1 Fa Mee Doh,1 Ji Sun Paeng,1 Hyung Jung Oh,1 Tae-Hyun Yoo,2 Shin-Wook Kang,1,2 1Dept of Internal Medicine, Yonsei Univ College of Medicine; 2 Severance Biomedical Science Institute, Brain Korea 21, Yonsei Univ, Seoul, Korea.

Background: Accumulating evidence has indicated that a reduced triiodothyronine (T3) level in prevalent hemodialysis (HD) patients is a prognostic factor for adverse clinical outcome. However, little is known about the association between low T3 and mortality in end-stage renal disease (ESRD) patients starting HD and whether the impact of T3 on mortality is mediated by malnutrition, inflammation, or cardiac dysfunction in these patients. A recently developed, highly permeable High-cutoff (HCO) membrane allows elimination of proteins with a molecular size of up to 45 kda.

Methods: In a randomized controlled trial 40 chronic hemodialysis patients were dialysed with HCO or regular Highflux membranes for three weeks following a cross-over design. Serum samples were drawn before dialysis. Afterwards, vascular smooth muscle cells were incubated with calcification media and these serum probes (10%). After ten days calcification was measured using alizarin red staining and set in relation to the number of proliferating cells using WST-8.

Results: After ten days of incubation, SMCs incubated with serum obtained after 3 weeks dialysis with HCO showed significantly reduced calcification compared to SMC incubated with serum during Highflux dialysis (0.144±0.0052 vs. 0.161±0.0008, p=0.003). SMCs incubated with FCS showed a very low degree of calcification. (0.09±0.007).

Conclusion: Plasma A VP levels are higher in HD patients compared with healthy controls, but show little or no increase during standard HD. A VP levels during HD may therefore be pathophysiologically involved in the onset of IDH.

index (LVMI) and lower LV ejection fraction (LVEF). All-cause (113.4 vs. 18.2 events/1000 patient-years, P < 0.001) and CV mortality rates (49.8 vs. 9.1 events/1000 patient-years, P = 0.001) were significantly higher in the ‘lower’ T3 group compared to the ‘higher’ T3 group. Kaplan-Meier analysis also showed significantly worse cumulative survival rates in the ‘lower’ T3 group (P < 0.001). In Cox regression analysis, low T3 was a significant independent predictor of all-cause mortality, even after adjusting for traditional risk factors (HR, 3.76; P = 0.021). However, this impact was mitigated when LBM-Ct, nPCR, LVMI, or LVEF was incorporated into the successive Cox model.

Conclusions: Low T3 was a significant independent risk factor for all-cause mortality in incident HD patients, which was partly attributed to malnutrition and cardiac dysfunction.

FR-P0971
Prominent Accumulation in Hemodialysis Patients of Solutes Normally Cleared by Tubular Secretion 
Tammy L. Sirich,1 Natalie Plummer,1 Thomas H. Hostetter,1 Timothy W. Meyer.1 Medicine, Stanford Univ; 2Medicine, Case Western Reserve Univ;

Background: The native kidney clears many solutes efficiently by secretion while hemodialysis clears solutes by passive diffusion. We tested whether concentrations of solutes which the kidney clears by secretion therefore rise to high levels in dialysis patients.

Methods: We compared the plasma concentrations and clearances of solutes normally cleared by secretion - p-cresol sulfate (PCS), indoxyl sulfate (IS), and hippurate (HIPP) - with those of urea in patients maintained on hemodialysis (HD; n=9) and in normal subjects (N; n=8). Values were expressed in terms of the free, unbound solute concentrations as these are the levels to which body tissues are exposed.

Results: Results showed (mean±SD; n): p<0.05 dialytic versus native kidney clearance; *p<0.05 secreted solutes vs urea;

<table>
<thead>
<tr>
<th>Solute</th>
<th>Clearance HD/Nl</th>
<th>Clearance Nl</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS</td>
<td>0.18±0.05</td>
<td>3.5±0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>IS</td>
<td>0.05±0.01</td>
<td>2.8±0.3</td>
<td>0.04</td>
</tr>
<tr>
<td>HIPP</td>
<td>0.04±0.01</td>
<td>0.3±0.01</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Conclusions: These results show that plasma concentrations of solutes normally cleared by tubular secretion remain very high in hemodialysis patients. Adoption of urea as our index solute for dialysis efficacy has had the unintended effect of completely negating how poor conventional treatment replaces the native kidney’s secretory function.

Funding: NIDDK Support

FR-P0972
Dialysate Containing Nitric Oxide Suppresses Blood Coagulation during Hemodialysis in a Rat Hemodialysis Model
Shunichiro Urabe,1 Yukie Kartya,2 Kenichi Kokubo,3 Hiroshi Tsukao,4 Hiroshi Kobayashi.1,2 Kitasato Univ Graduate School of Medical Science, Sagamihara, Kuganawa, Japan; 3Tokyo Univ of Technology School of Health Sciences, Tokyo, Japan;

Background: In blood vessels, nitric oxide (NO) generated by NO synthase on endothelial cells suppresses the aggregation and activation of platelets. Therefore, the biocompatibility of dialysis membranes could likely be improved using an NO-containing dialysate capable of delivering NO to blood through the membrane. The present study examined whether an NO-containing dialysate suppressed blood coagulation during hemodialysis without any effects on blood pressure in a rat hemodialysis model.

Methods: Hemodialysis was performed using 10-12-week-old male rats (Sprague Dawley) for 4 h. Blood was removed from the carotid artery of a rat, forced to stream through the intracapillary lumen of a small arteriole, and returned to the tail vein. NO was added using gas exchange membranes during intermittent treatment.

Results: The arterial-side blood pressures during hemodialysis were stable and similar between the control (without NO) and NO-addition groups, indicating that NO did not affect the blood pressure during hemodialysis. However, the venous-side pressures in the control group were unstable and in some cases had increased at 150 to 240 min after the start of dialysis, whereas the pressures in the NO-addition group were stable throughout hemodialysis.

Conclusions: These results show that plasma concentrations of solutes normally cleared by tubular secretion remain very high in hemodialysis patients. Adoption of urea as our index solute for dialysis efficacy has had the unintended effect of completely negating how poor conventional treatment replaces the native kidney’s secretory function.

Funding: Government Support - Non-U.S.

FR-P0973
Vascular Refilling Is Independent of Fluid Overload in Hemodialysis Patients
Mauro Pietribski,1 Krassimir Katsarski,2,3 Magda Galan,1 Joanna Stachowska-Pietrka,1 Daniel Schneditz,1 Bengt Lindholm,2 Jacke Waniowski,1 1Institute of Biocybernhetics and Biomedical Engineering, Warsaw, Poland; 2Baxter Novum and Renal Medicine, Karolinska Institutet, Stockholm, Sweden; 3Diaverum, Stockholm, Sweden; 4Institute of Physiology, Medical Univ of Graz, Graz, Austria.

Background: Fluid removal by ultrafiltration during a hemodialysis (HD) session is brought about by vascular refilling, the increase in plasma oncotic pressure (rp). Inadequate refilling rate (Qr) is suspected to contribute to hypertensive crises. The refilling process was quantified by the refilling coefficient (Kr) expressing Qr driven by a unit increase in rp. We calculated Kr for two groups of HD patients differing by treatment fluid status and session time, but similar in ultrafiltration rate (Qf).

Methods: Nine stable patients underwent two HD sessions: short session of 3.5 h (SH, after 2 day break) and long session of 4.5 h (LH, after 3 day break). Relative blood volume changes were measured online with Gambio AK 200 Ultra HD machine module, and solute concentrations were measured before and after HD, and regularly during the session. The volume of body fluid compartments was measured by bioimpedance analysis.

Results: Patients were more hydrated before LH session: initial body weight, total body water (31.7±5.1 kg vs 32.5±5.1 kg for LH) and extracellular water (16.6/2±1 kg for SH vs 17±2 for LH) were higher. rp was similar for both sessions. Qr was higher for LH. Kr decreased with dialysis time, but showed no statistically significant difference between sessions both at the beginning and at the end of HD (Kr at 1h: 268±127 ml/h/mmHg for SH and 396/198 ml/h/mmHg for LH). The final, stable value of Kr was reached at similar times (3 h) and was similar for both sessions (137±55 ml/h/mmHg for SH and 166/94/ml/h/mmHg for LH).

Conclusions: Patients undergoing LH, despite being more volume expanded, did not have higher initial Kr, even with higher initial Qr. Final Kr values stabilized on similar levels at similar times, notwithstanding differences in initial fluid status or Qr in the two groups, suggesting that Kr is relatively insensitive to the initial fluid status of the patient.

Funding: NIDDK Support

FR-P0974
Prevalence and Risk Factors of MRSA Infections and Effect of Program for MRSA Eradication in HD Patients on Hemodialysis: Single Center Study
Young-II Jo,1 Jung-Hwan Park,1 Jung-Ho Lee,1 Eun Hye Seo,2 Jeong-hwa Choi,1 Hyun-kyun KJ.3 1Div of Nephrology, Konkuk Univ School of Medicine, Seoul, Republic of Korea; 2Dept of Infectious Disease, Konkuk Univ Medical Center, Seoul.

Background: Hemodialysis (HD) patients with meticillin-resistant Staphylococcus aureus (MRSA) infections face high morbidity and mortality. This study was designed to estimate the prevalence of MRSA nasal carriage, to define the risk factors of MRSA nasal carriage, and to investigate the effect of anti-infective program on the prevalence of MRSA nasal carriage among HD patients.

Methods: A total of 126 HD patients without signs of overt clinical infection (M:F 59:67, duration of dialysis 48.9±47.8 months) were enrolled in 2011. Nasal carriers for MRSA were identified using standardized bacteriological techniques. Anti-infective program including education and hand washing has been taken place for all patients. All patients were followed up for elimination and infections for 1 year.

Results: The prevalence of nasal carriage for MRSA was 16.4% including 4.0% for the first year and 6.9% for 2nd year. After anti-infective program for 1 year, the prevalence of nasal carriage for MRSA was 4.5%. Mupirocin eliminated MRSA in 75.0% (3/4) of patients. The 5.1% (4/77) patients without nasal carriage for MRSA showed nasal colonization of MRSA in follow-up screening in 2012.

Conclusions: Compared with previous reports, the prevalence of MRSA nasal carriage in outpatient was markedly lower. However, the prevalence in inpatients was high, and the long duration of hospitalization and ICU care was risk factor of nasal carriage for MRSA. Anti-infective program appears to be an effective preventive strategy.

Funding: NIDDK Support

FR-P0975
Free P-Cresol Sulfate Is Associated with Septicemia in HD Patients
Tanushree Banerjee,1 Timothy W. Meyer,2 Tariq Shafi,3 Michal L. Melamed,1 Thomas H. Hostetter,1 Yang Liu,1 Neil R. Powe,4 1Univ of California, San Francisco; 2Stanford Univ; 3Johns Hopkins Univ; 4Albert Einstein College of Medicine; 5Case Western Reserve Univ.

Background: The uricemic syndrome is attributed to progressive retention of compounds which, under normal conditions, are excreted by the healthy kidneys. P-cresol sulfate (PCS), a prototype protein-bound uricemic retention solution, has been shown to exert toxic effects in various ways. These studies have identified putative relationships between increased levels of PCS and adverse clinical outcomes in hemodialysis (HD) patients. We explored the relationship between free PCS with septicemia in HD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: In a U.S. cohort of 294 incident HD patients enrolled in 1995-1998 and followed for an average of 3.4 years, we measured free PCS using mass spectroscopy. We linked 1996-2005 Medicare billing records to ascertain septicemia over follow-up. We used Poisson regression to calculate incidence rate ratios (IRRs) for septicemia.

Results: Mean age was 57 years, 59% White and 44% female. The incidence of septicemia per 1000 patient-years was 43 in the lowest tertile, 87 in the middle tertile and 120 in the highest tertile of free PCS levels when compared with the lowest tertile (p=0.07, 0.002, respectively). After adjustment for age, sex, race, body mass index, comorbid disease, albumin, creatinine, Kt/V, and residual kidney function; those with levels in the middle tertile had 5% higher risk of septicemia [IRR (95% CI) = 1.05 (0.65-1.69)] and those with highest tertiles had a 31% higher risk of septicemia [IRR (95% CI) = 1.31 (0.83-2.07)] when compared with the lowest tertile of PCS levels.

Conclusions: These results suggest an association between higher levels of free PCS and septicemia in HD patients. Better methods of dialysis should be developed to evaluate the utility of removing PCS and its effect on the outcomes.

Funding: NIDDK Support

FR-P0976

Will Haemodialysis Patients Previously Immunized with a Hepatitis B Vaccine Respond to a Booster Dose Using a Different Product? Single Centre Experience on 115 Patients

Background: Maintaining immunity to hepatitis B in the haemodialysis (HD) population is important in order to reduce the chances of patients contracting this infection. Little et al. [1] determined whether those vaccinated with a particular type of hepatitis B vaccine will continue to maintain immunity if given a booster with a different type of hepatitis B vaccine.

Aim: To determine the effectiveness of a single booster dose of the recombinant Hep B DNA vaccine (Fendrix) in naive HD patients previously immunised with HBVaxPro.

Methods: All patients with established immune response to HBVaxPro had annual hepatitis B surface antibody titres measured. A titre < 10mIU/ml required a booster. All patients from October 2010- May 2013 were given booster doses using Fendrix. Data were collected through computerised systems. Davies co-morbidity scores were calculated for all patients to determine whether this affected response rates.

Results: 115 HD patients received boosters over this period. 62 male, 44 female. Median age 71.9 years with a median time of 2228 days on HD. 106 (92.9%) responded to a booster. Those that responded had similar Davies co-morbidity score to the responders. 9 that showed no response went on to have a course of Fendrix; of these 100% responded to a full course.

Conclusions: Those with previous immunity to HBVaxPro showed a good response to a booster dose of Fendrix. Those that did not respond to a single booster went onto develop full immunity following a full course. Gender, age, median length on HD, type 2 diabetes or Davies co-morbidity score were not independent predictors of response. Our data show that in patients who previously responded to vaccination with the Hep B vaccine, this immunity is likely to be maintained despite changing to a different Hep B vaccine.

FR-P0977

Does It Matter which Type of Hepatitis B Vaccine is Given to Haemodialysis Patients?
Rosa M. Montero, Raja Mohammed Kaja Kamal, Maggi Steele, David Makanjuola. Epsom & St. Helier Univ Hospitals NHS Trust.

Background: Maintaining immunity to hepatitis B in the haemodialysis (HD) population is important in order to reduce the chances of patients contracting this infection. Little et al. [1] determined whether those vaccinated with a particular type of hepatitis B vaccine will continue to maintain immunity if given a booster with a different type of hepatitis B vaccine.

Aim: To compare the response (R) and Non response (NR) between Hep B vaccine naive and patients vaccinated with Fendrix compared with a historical cohort who had HBVaxPro.

Methods: A single centre retrospective study. Data were collected on all patients from October 2010 until May 2013. Fendrix was administered at 0, 1, 2 and 6 months. Patients with previous immunity to HBVaxPro were classified as R, those with titre <10mIU/ml received a second course. Those that did not respond following 2 courses were classified as NR. Comparison was made with a historical cohort vaccinated with HBVaxPro from 1999-September 2010. The HBVaxPro course consisted of vaccinations given at 0, 1 and 6 months.

Results: 432 patients (3 were excluded for missing data) were in the historical cohort. 353/429 (82.3%) were immune following a single course with HBVaxPro. 212 male; 144 female, median age 66.8 years with median length of HD days 1690. 72 (17.7%) were given a second course and only 4 (0.9%) were NR. NRs had median age of 80.7 years with median length of 1544 days on HD. In contrast, the Fendrix cohort was 428 patients. 363 (84.8%) were immunised after 258 male; 105 female with median age 70.8 years. 65 (15.2%) had a second course, of which 9 had no response (2.1% of the total cohort). The median age of NRs was 74.3 years and median time on HD was 1004 days. There were no significant correlations between response rates and ethnicity, diabetes, or the Davies co-morbidity scores in either group.

Conclusions: Response rates were similar between the two vaccines in our HD population. NR rates were slightly higher with Fendrix but this did not reach statistical significance. There was a trend towards non-response to the vaccines with male gender and increasing age. Overall, we found that both vaccines provided good levels of immunity.
Methods: Incident renal replacement therapy patients starting between 2002 and 2006 in England with available data until 2009 from the UK Renal Registry were analysed. However, the data were limited to identify HHD attendance pattern, comorbidity, and associated cost. The model factored the cost of an additional HD session per fortnight, and a saving and survival benefit with the reduction in excess hospitalisation and mortality rates over the 2 day gap to that of the rest of the week. Estimated survival was calculated using a Weibull multivariable model. Quality of life for patients on HD and time hospitalized were obtained from existing literature.

Results: 5790 patients were analysed. Compared to the rest of the week excess emergency admissions (2.29 vs 1.36 per patient, P<0.001) and mortality (21.3 vs 15.7 deaths per 100 patient-years, P<0.001) were identified after the 2 day gap, with greater differences for heart failure patients. For all patients mean survival was predicted at 7.7 years. Additional HD sessions cost $34,328 USD, generated a hospitalization cost saving of $2,411 and accrued 0.40 quality adjusted life years (QALYs). The cost per QALY was $79,067. For heart failure patients surviving a mean of 4.4 years, additional HD cost $20,722, saved $1,768 in hospitalisations and accrued 0.26 QALYs. The cost per QALY was $73,539. If survival and hospitalisation advantages were increased from approximately 10% to 16% the cost per QALY was $49,496 in all patients.

Conclusions: Alternate day dialysis would not be deemed cost effective based on a reduction in admissions and mortality after the two day gap to the rest of the week, but may be cost effective with a more global reduction in rates.

FR-PO981

Association of Initial Twice-Weekly Hemodialysis Treatment with Preservation of Residual Kidney Function in ESRD Patients

Mingmin Zhang, Mengjing Wang, Haiming Li, Ping Yu, Jing Chen, Kamyar Kalantar-Zadeh.

Methods: A historical cohort study was performed in 85 maintenance HD patients to compare RKF loss and clinical outcomes, in which 30 patients on twice-weekly HD for more than 6 months initially, the other 55 patients starting and maintaining thrice-weekly HD. Then, a subcohort study was implemented in 48 incident HD patients whose residual GFR was examined serially, to assess the potential predictors of the decline of RKF.

Results: The main cohort study showed that the HD adequacy and the clinical outcomes were same in 85 patients receiving HD treatment for more than 5 years. However, the rate of RKF loss (defined as urine volume <200 ml/day) was significantly lower in twice-weekly group (60%) compared to thrice-weekly (82%), especially during the first year of HD initiation (10% versus 40%, p<0.03). In the subcohort study, the residual GFR of 48 patients, treated with 2.69±0.43 times per week HD for 10.27±3.53 months, declined from baseline 6.95±2.66 to 2.12±1.97 ml/min/1.73m² and 40% of patients lost their RKF over an average period of 7.6±4.5 months of HD initiation. Multivariate logistic regression analysis showed that odds ratio of RKF loss for each additional HD treatment per week was 7.2 in HD patients.

Conclusions: Initial twice-weekly HD during the first year of dialysis therapy appears associated with better RKF preservation.

Funding: Government Support - Non-U.S.

FR-PO982

The Returns of the MACs: A Natural Experiment Relating More Than Twice-Weekly Home Hemodialysis and Patient Outcomes


Methods: A prospective multi-center cohort study was conducted in 11 HD centers. The participants aged of 18 to 80 years, undertaken twice-weekly or thrice-weekly HD therapy. The participants were seen in a dedicated CKD clinic prior to HD. Uremia was the main indication for initiation. The average inter-dialytic weight gain was low (1.5 ±0.8 kg) suggesting preserved RRF. The serum albumin was maintained at an average of 3.68±0.5 mg/dl. The hospital rate was lower at only 2.27 days / patient year when compared to the USRDS rate of 12 days / patient year.

Results: Patients have been maintained on twice weekly HD for an average of 2.9 years ± 2.2 years. The majority of patients were non- diabetic males and Caucaians aged 75+/-15. Seventy percent were seen in a dedicated CKD clinic prior to HD. Uremia was the main indication for initiation. The average inter-dialytic weight gain was low (1.5 ±0.8 kg) suggesting preserved RRF. The serum albumin was maintained at an average of 3.68±0.5 mg/dl. The hospital rate was lower at only 2.27 days / patient year when compared to the USRDS rate of 12 days / patient year.

Conclusions: Patients can be maintained for extended periods of time on twice weekly HD with a low rate of hospitalization and preserved volume and nutritional status. Further studies comparing outcomes to patients on thrice weekly dialysis are needed.

FR-PO984

Outcomes of Patients with End-Stage Renal Disease Undergoing Twice-Weekly and Thrice-Weekly Hemodialysis


Methods: A prospective multi-center cohort study was conducted in 11 HD centers. The participants aged of 18 to 80 years, undertaken twice-weekly or thrice-weekly HD for at least 3 months were recruited. Baseline characteristics were recorded at recruitment. Outcomes including death and first hospitalization were recorded. Kaplan-Meier method and Cox regression analysis was computed. Results: A total of 673 participants, 504 in 2-HD/wk and 169 in 3-HD/wk group were recruited. They were male in 59% with mean age of 56 years and 39.8% were DM. Median follow-up time was 13.7 months. During the total follow-up time, 9,254 patient-months, 45 patients died, 33 in 2-HD/wk group (6.5%), and 12 in 3-HD/wk group (7.1%). The one year survival probability of 2-HD/wk group, 0.94 (95% confidence interval (CI); 0.92 to 0.96) was comparable to that of 3-HD/wk group, 0.94 (95% CI; 0.89 to 0.96), hazard ratio = 0.99, 95% CI, 0.5 to 2.0, p = 0.99.

Conclusions: There were no significant differences in survival between patients on twice weekly HD and thrice weekly HD.
There was no significant difference in incidence of first admission between 2-HD/wk (24.2/100 patient-years) and 3-HD/wk group (19.7/100 patient-years), log rank test p-value = 0.25.

**Conclusions:** Participants who were treated with 2-HD/wk had a similar one year survival rate but tended to associate with higher incidence of hospitalization when compared to those with 3-HD/wk. Twice-weekly HD is an alternative treatment scheme in resource-limited settings.

**Funding:** Private Foundation Support

**FR-PO985**

**Challenges Recruiting to a Study Investigating Extended Treatment Time on Haemodialysis Outcomes** Seema Singh, Albert J. Power, Charles D. Pusey, Neill D. Duncan, Edwina A. Brown. Imperial College Renal & Transplant Center, United Kingdom.

**Background:** Outcomes on conventional haemodialysis (HD) remain suboptimal with observational data suggesting better survival with extended treatment times (TT).

**Methods:** Randomised cross-over study of in-centre HD patients with TT of either 6 hrs or 4 hrs for a period of 24 wks with a 4wk washout period between the two arms (NCT01721421). Assessments of nutritional status (malnutrition inflammation score, bioimpedance analysis, hand grip), in quality of life domains (KDQoL). BNP) are made before and after each treatment phase. Time to recovery is assessed and first admision between 2-HD/wk and 3-HD/wk group. A high flux dialyzer (Polyflux Revaclear) was used 3-4 h per session. Dialysate (Dox) and Pox were measured hourly via enzymatic oxalate oxidasde.

**Results:** Oxalate production was estimated from historical Uox measured when GFR was > 50 mL/ min.73m2. HD regimens were adjusted according to historical Uox, amount of oxalate removal at HD, residual Uox, and predialysis Pox.

**Results:** Mean reduction in Pox was 79±7% (Figure), with a mean pre and post dialysis Pox of 68±9±37.5 μM/L and 13±6±5.8 μM/L. 12 patients had urine output at the time of study with an average Uox of 1±1.0±0.8 mmol/24h. Based upon HD oxalate removal and Uox clearance, 7 patients required HD 6 times a week, 2 patients 5 times a week, and 5 patients 3 times a week. Combined renal and HD oxalate clearance was 16±8±7.6 μM/L, which exceeded endogenous oxalate production (13±4±3.9mmol/wk). 8 patients received a kidney or combined liver-kidney transplant after a mean period of 4 mos on HD. The final pre-dialysis Pox before transplantation was significantly lower than the initial pre-dialysis Pox before individualizing HD (45±4±23.1 vs 78±8±38.0 μM/L, P=0.002).

**Conclusions:** In conclusion, a method to measure Dox was validated that can be used to individualize the HD prescription of PH patients to prevent systemic oxalosis, and to reduce the risk of oxalate nephropathy in the transplanted kidney.

**Funding:** NIDDK Support, Other NIH Support - National Center For Advancing Translational Sciences (NCATS)

**FR-PO986**

**Oxalate Quantification in Hemodialysate to Assess Dialysis Adequacy for Primary Hyperoxaluria** Xiaojing Tang, Nick Voskoboiev, Stacie L. Wannmark, Julie B. Olson, Dawn S. Milliner, John C. Lieske. Mayo Clinic, Rochester, MN.

**Background:** Aggressive hemodialysis (HD) is required to prevent systemic oxalosis in primary hyperoxaluria (PH) patients with renal failure, and the required amount of HD increases as residual renal function declines. Due to extravascular oxalate deposition, plasma oxalate (Pox) does not reflect systemic oxalate loads. This study validated a method to accurately measure oxalate removal via HD.

**Methods:** 14 stable PH1 patients treated with HD by physicians in the Rare Kidney Stone Consortium were included. A high flux dialyzer (Polyflux Revaclear) was used 3-4 h per session. Dialysate (Dox) and Pox were measured hourly via enzymatic oxalate oxidasde.

**Results:** Oxalate production was estimated from historical Uox measured when GFR was > 50 mL/ min.73m2. HD regimens were adjusted according to historical Uox, amount of oxalate removal at HD, residual Uox, and predialysis Pox.

**Results:** Mean reduction in Pox was 79±7% (Figure), with a mean pre and post dialysis Pox of 68±9±37.5 μM/L and 13±6±5.8 μM/L. 12 patients had urine output at the time of study with an average Uox of 1±1.0±0.8 mmol/24h. Based upon HD oxalate removal and Uox clearance, 7 patients required HD 6 times a week, 2 patients 5 times a week, and 5 patients 3 times a week. Combined renal and HD oxalate clearance was 16±8±7.6 μM/L, which exceeded endogenous oxalate production (13±4±3.9mmol/wk). 8 patients received a kidney or combined liver-kidney transplant after a mean period of 4 mos on HD. The final pre-dialysis Pox before transplantation was significantly lower than the initial pre-dialysis Pox before individualizing HD (45±4±23.1 vs 78±8±38.0 μM/L, P=0.002).

**Conclusions:** In conclusion, a method to measure Dox was validated that can be used to individualize the HD prescription of PH patients to prevent systemic oxalosis, and to reduce the risk of oxalate nephropathy in the transplanted kidney.

**Funding:** NIDDK Support, Other NIH Support - National Center For Advancing Translational Sciences (NCATS)

**FR-PO987**

**Calcium Equivalent Citrate Dialysis** Jan P. Sternby, Anders Nilsson, Gunilla Grundstrom, Maria Alquist. Research Dept, Gambro.

**Background:** Citrate has in recent years been introduced as a more physiological alternative to acetate in bicarbonate hemodialysis. Citrate entering the blood complex binds calcium (Ca). Some protein bound Ca is then released to maintain the equilibrium between protein bound and free ionized Ca. Both free and citrate bound Ca can pass the dialysis membrane which increases the Ca transport from the blood. We developed an algorithm to calculate the mass balance of Ca transfer over the membrane. The objective was to establish which Ca concentration in a citrate containing dialysis fluid gives the same total Ca mass transfer as a citrate-free dialysis fluid. The same was also done for magnesium (Mg).

**Methods:** The mass transfer area coefficients for ions and complexes were assumed proportional to their diffusive mobility. The electrical membrane potential was considered by requiring electroneutrality. As transfer of complexes across the membrane affects their diffusive mobility, the electrical membrane potential was considered to be given by the concentration gradients for both complexes and individual ions, we included in the calculations the (pH dependent) binding of ions like hydrogen, Ca and Mg to albumin and of Ca and Mg to bicarbonate and citrate. The dialyzer was considered being composed of serial segments. For each segment the transport of each solute and complex were calculated separately. The given inlet concentrations for each solute the outlet concentrations for a dialyzer segment were calculated from the transports. From total outlet concentrations new distributions between free concentrations and complexes were calculated and used as input to the next subsegment. Parameters used: Plasma concentration of total Ca 2.2-2.4 mM (mmol/l), plasma citrate 0.1-0.3 mM, blood flow rate 200-400 ml/min, dialysis fluid flow rate 500 and 800 ml/min, urea K0.7 and 1000 and 1000 ml/min, Ca concentrations in dialysis fluid without citrate 1.0, 1.25, 1.5 and 1.75 mM, and citrate levels in the dialysis fluid 0.25–2 mM.

**Results:** In all cases the need for extra Ca and Mg in the dialysis fluid increases almost linearly with the citrate level. Each mM of citrate requires 0.15 mM additional Ca to maintain the same Ca mass balance.

**Conclusions:** Calcium equivalent citrate dialysis requires 0.15 mM more calcium in the dialysis fluid for each mM of citrate.

**Funding:** Pharmaceutical Company Support - Gambro

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Biofeedback Controlled Haemodialysis Increases Ionic Mass Removal

Isabelle Kazes, 1 Coralie Barbe, 2 Khaled Gaha, 1 Herve Maheut, 1 Philippe Rieu. 1
Nephrology Dept, Univ Hospital, Reims, France; 2 Clinical Research Unit, CHU, Reims, France.

Background: The Hemocontrol® system controls blood volume changes by acting on the actual ultrafiltration rate and the actual dialysate conductivity during the whole dialysis session.

Methods: Between 2007 and 2011, part of chronic dialysis patients at the University Hospital of Reims (France) were dialysed using both HD and HC haemodialysis. One or the other mode of dialysis was used with each patient in an occasional manner, only depending on organizational obligations. 35 439 dialysis sessions were analyzed. In total 2101 pairs, containing 2197 patients (4202 sessions) were matched on 6 different criteria: the patient him/herself (the patient being his own control), the dialysis membrane, the blood pump speed (±15ml/min), patient weight before dialysis (± 100 gr), prescribed dialysate variations among patients treated with different dialysate bicarbonate concentrations to find the optimal dialysate bicarbonate.

Methods: We conducted a retrospective data analysis on 90 patients who received HD 3 times a week from a single dialysis unit. Total study duration was 6 months. Data was collected retrospectively for first 3 months, when we were using 38 mL/h bicarbonate dialysate concentration with acetate 8 mL/h. Then we individualized the bicarbonate concentration to maintain the serum pre-dialysis bicarbonate 22±2 mEq/L and collected data for the following 3 months. We compared the different variables in the both study groups.

Results: The mean serum pre-dialysis bicarbonate before and after individualized bicarbonate bath was 25.4±4.29 mEq/L and 22.8±2.36 mEq/L respectively (P <0.001).

After individualizing dialysate, 67.8% of patients required 35mEq/L, 14.4%<35mEq/L and 17.8%>35mEq/L of bicarbonate concentration. Most patients before individualized dialysate bicarbonate had serum pre-dialysis bicarbonate <25mEq/L in 65.6% and >29mEq/L in 5.6%.

After individualizing, serum pre-dialysis bicarbonate was >25mEq/L in only 8.8% and >29mEq/L in 1%. There was no statistically significant difference in the other variables like Kt/V, Albumin, phosphate, pH/T, ESA, sensipar, and vitamin D requirements in both groups. In subgroup analysis, there was no statistically significant difference in those variables in patients who required dialysate bicarbonate concentration 35 mEq/L, less than 35 mEq/L or more than 35 mEq/L.

Conclusions: Our data suggests that there is no standard dialysate bicarbonate bath in HD patients. We suggest individualizing the dialysate bicarbonate concentration to maintain serum pre-dialysis bicarbonate 22±2 mEq/L. Monthly serum pre-dialysis bicarbonate was the only laboratory parameter which influence the choice of dialysate bicarbonate concentration.
Conclusions: In this study it could be shown that treating patients with FX CorDix 60 dialyzers instead of FX 60 results in significantly increased reduction ratios of middle sized molecules without clinically relevant changes in albumin loss. This change could represent an improvement in the removal capacity that could be transferred to potential clinical benefits.

FR-PO993

Intra-Dialyzer Oxidative Stress (OS) Is Ameliorated by Molecular Hydrogen-Enriched Hemodialysis (HD) Solution (H₂-HD) | Wan-jun Zhu,1,2 Hiroyuki Terawaki,1 Masaaki Nakayama,1,2 Yasuhito Takahashi,1 Shigeru Kabayama,2 Kaoru Sakuragi,1 Sadayoshi Ito.1 1Dialysis Center, Fukushima Medical Univ, Fukushima, Japan; 2Center for Advanced and Integrated Renal Science, Graduate School of Medicine, Tohoku Univ, Sendai, Japan.

Background: OS is the leading cause of HD patients’ mortality. HD exacerbates OS via removing antioxidants and excess oxidative burst of neutrophils in the dialyzer. We hypothesized that H₂ could act as an anti-OS mediator using H₂-HD in the clinical setting. This study aimed to clarify H₂-HD’s possible anti-OS effect during HD session.

Methods: A HD cross-over study was performed using standard solution (S-HD) and H₂-HD in the mid-week (n=8, 4 hours each). Blood samples of inlet and outlet were obtained from the dialyzer at the start and end. The redox state of human serum albumin (HSA) were examined as an OS marker; non-oxidized human mercapto-albumin (HMA), reversibly-oxidized human non-mercaptoalbumin-1 (HNA-1) and irreversibly-oxidized form (HNA-2) by HPLC.

Results: H₂ level of H₂-HD in blood and solution were 50 times of S-HD. In H₂-HD, HMA increased and HNA-1 decreased significantly (p<0.05, start of HD), respectively, furthermore, HNA-1 decreased significantly (p<0.05, end of HD), while no changes in S-HD, suggesting H₂-HD’s anti-OS effect.

Conclusions: H₂-HD could suppress intra-dialyzer OS induced by HD session.

Funding: Private Foundation Support

FR-PO994

Different Impact of Membrane Flux on Mortality between Incident and Prevalent Hemodialysis Patients | Yong Kyun Kim,1 Hyung Wook Kim,2 Su Hyun Kim,2 Su Jin Choi,1 Young ok Kim,1 Ho Cheol Song,1 Yong-Lim Kim,3 Yon Su Kim,1 Shin-Wook Kang,3 Chul Woo Yang.1 1Clinical Div of Nephrology, Medical Univ of Graz (MUG), Austria; 2Institute of Physiology, MUG; 3Div of Gastroenterology and Hepatology, MUG.

Background: The effect of flux membrane on mortality has been controversial. Previous study reported that the effect of high-flux dialysis on mortality may vary depending on the duration of dialysis. We evaluated the effects of dialyzer membrane flux on mortality in incident hemodialysis (HD) patients and prevalent HD patients.

Methods: 1244 observational HD patients, 857 incident and 1,353 prevalent HD patients with HD were included. In incident HD patients, 589 patients were dialyzed using low-flux dialysis membrane and 228 were dialyzed using high-flux dialysis membrane. In prevalent HD patients, 801 patients were dialyzed using high-flux dialysis membrane and 552 patients were dialyzed using high-flux dialysis membrane. All-cause mortality was primary outcome.

Results: After a median 20 months of follow-up, mortality was not significantly different between the high-flux group and low-flux group in incident HD patients (HR 1.45, 95% CI, 0.86-2.58, P = 0.155). In prevalent HD patients, HD using high-flux dialysis membrane was associated with decreased mortality compared to HD using low-flux dialysis membrane in univariate (HR 0.43, 95% CI, 0.25-0.74, P = 0.002), multivariate (HR 0.40, 95% CI, 0.21-0.77, P = 0.006) or propensity score-matched (HR 0.35, 95% CI, 0.18-0.67, P = 0.001) analyses.

Conclusions: Our data showed that HD using high-flux dialysis membrane had survival benefit in prevalent HD patients, but not in incident HD patients. These findings suggest that the effect of flux membrane on mortality may be different between incident and prevalent HD patients and high-flux dialysis might be recommended for the prevalent patients with HD treatment.

Funding: Government Support - Non-U.S.
Conclusions: These results indicate that on-line hemocencentration captures the true plasma volume changes during HD in patients with moderate UF volumes. Failure of on-line H-monitoring to predict intradialytic morbid events is therefore unlikely to depend on systematic overestimation of intravascular volume.

FR-PO997

Determinants of Aortic Stiffness by Cardiovascular Magnetic Resonance in Patients New to Haemodialysis Ayughou Oduduh,1,1 Mohamed Tarek Eldelh,2 Mark A. Horsfield,3 Gerry P. McCann,3 Chris W. McIntyre,3 1Div of Medical Sciences, Univ of Nottingham; 2Dept of Renal Medicine, Royal Derby Hospital; 3NIHR Cardiovascular Biomedical Research Unit, Leicester, United Kingdom.

Background: Aortic stiffness is a novel cardiovascular risk factor in HD patients. Prior prevalent studies estimated stiffness by pulse wave velocity (PWV) with external devices. These are limited by inaccuracy of aortic length & determinants are unclear. Cardio Magnetic Resonance (CMR) can accurately measure cardiac structure & function & directly measure aortic distensibility (AD) & PWV. We aimed to investigate the determinants of directly-measured AD by CMR & the utility of MR-determined PWV (MR-PWV) in a cohort of patients within 6 months of commencing HD.

Methods: 30 HD patients with 19 age & sex-matched controls (NC, n=19) were studied. AD and MR-PWV were determined from velocity-encoded imaging of the aortic arch using standard techniques. Carotid-femoral PWV was measured with an external oscillometric device (Ex-PWV). Skin autofluorescence (SAF), a marker of advanced-vascular end-products, high-sensitivity troponin-T & NT-Pro-BNP were measured in the HD cohort.

Results: Means±IQR of data are presented. AD was reduced in HD compared to NCs, despite similar blood pressure & Ex-PWV (2.0±1.8mmHg-1×10-3 vs 4.0±4.8mmHg-1×10-3, p<0.001). Univariate analysis showed significant inverse correlations of AD to age (r=-0.67, p<0.001), MR-PWV (r=-0.72, p<0.001), Ex-PWV (r=-0.41 p<0.005) & left ventricular mass (r=-0.34, p=0.016). AD was positively correlated to ejection fraction (r=0.43, p=0.002) & strain (r=0.53, p=0.012). In HD patients, AD was inversely correlated to high sensitivity troponin-T (r=-0.53, p=0.014) & SAF (r=-0.57, p=0.013). There was no relation to anthropometric measures, NT-Pro-BNP or Calcium-Phosphate product. Multiple regression analysis identified MR-PWV & age as the strongest independent determinants of AD (adjusted R2=0.70 p<0.001).

Conclusions: In a cohort of incident HD patients, age & PWV by CMR were independent determinants of directly-measured aortic stiffness. Long-term follow-up will investigate aortic stiffness as an independent risk factor for HD-associated cardiomyopathy.

Funding: Government Support - Non-U.S.

FR-PO998

Overhydration Index Measured with BCM Is Correlated with Mean Arterial Pressure in Dialysis Patients Eun Kyong Lee,1 Ji Eun Lee,1 So Mi Kim,2 Hyun woo Kim.2 1Dankook Univ Hospital; 2Jeu National Univ Hospital.

Background: It is important to maintain euvoelma to prevent further cardiovascular events and to reduce mortality in dialysis patients. But in daily practice fluid status is assessed by using clinical methods such as body weight, clinical sign (blood pressure, edema, dyspnea), laboratory data (hemoconcentration or hemodilution) or chest X-ray because there is rare objective method to assess uid status.

We evaluated fluid status in dialysis patients using the portable whole-body multifrequency BIA device, Body Composition Monitor BCM (Fresenius Medical Care, Germany).

Methods: We measured the body composition in 48 dialysis patients (M:F=29:19, age 52±12.6, CAPD:HD=32:16, DM:HTN:CGN:etc=19:14:12:3) from Dankook University Hospital using the BCM. We compared the overhydration index (OH) which was measured by BCM with blood pressure and cardiothoracic ratio (CTR).

Results: Mean overhydration index was 3.8±2.9 Liter and mean value of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and CTR were 147±22 mmHg, 82±12 mmHg, 104±14mmHg and 0.5±0.08, respectively. Correlation coefficient between overhydration index and SBP was 0.68 (p<0.001). It was 0.494 (p<0.08) with MAP but there was no significant correlation between overhydration index with DBP(r=0.343, p=0.109).

Conclusions: Overhydration index which was measured by BCM could be used as a relatively objective guide to decide ultrafiltration event in dialysis patients.

FR-PO999

Plasma Sodium Levels and Cardiovascular Stability in Hemodialysis Patients Eduardo Baamonde,1 Elvira Bosch,1 German Perez Suarez,1 Cesar Garcia-cantón,1 Mar Lago alonso,2 Dolores Checa.2 1Nephrology, AVERICUM, Telde, Las Palmas, Spain; 2Nephrology, Hospital Insular de Gran Canaria, Las Palmas de Gran Canaria, Las Palmas, Spain.

Background: A relationship between pre-hemodialysis (HD) plasma sodium and mortality has been described. Lower sodium levels are associated with higher mortality. We analyze the relationship between pre-HD plasma sodium levels and intra-HD hemodynamic stability in a group of patients on standard HD and constant dialyzed sodium.

Methods: Retrospective analysis of 231 prevalent patients in HD classified into three groups (G) according to their pre-HD sodium levels corrected for glucose (cNa): G0: cNa < 137 mEq/L (n=59); G1: cNa 137 to 139.9 mEq/L (n=126); G2: cNa > 140 mEq/L (n=46). Patients were followed up for two years. Mean blood pressure (MBP), inter-dialysis weight gain (HDWG), ultrafiltration rate (UF), dry weight (DW) and dialysis hypotension (DH) was calculated in every single session. Laboratory tests, HD adequacy and antihypertensive treatment (AT) were analyzed.

Results:

<table>
<thead>
<tr>
<th></th>
<th>G0</th>
<th>G1</th>
<th>G2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Sodium</td>
<td>136±0.6</td>
<td>137±0.6</td>
<td>140±0.6</td>
</tr>
</tbody>
</table>
| cNa level was negatively correlated with UF rate (r: 0.325; p:0.000), percent weight gain (r: 0.279; p: 0.000) and % DH: (r: 0.146; p: 0.027).

Conclusions: Pre-dialysis plasma sodium was inversely related with cardiovascular stability. Patients with lower sodium levels showed higher tendency to hypotension may be related with higher inter-dialysis gain and UF rates.

FR-PO1001

Hemoglobin Levels, Cardiovascular and All Cause Hospitalization Rates, and Mortality in Pediatric Chronic Hemodialysis Patients Blanche M. Chavers,1,2 Julia T. Molony,1,2 Craig Solid,1 Michelle N. Rheaum,1 Thomas Nevin,1 Charles A. Herzog.2,3 1Univ of MN, Pediatrics, Minneapolis, MN; 2U.S. Renal Data System/CVSSC; 3Univ of MN, Medicine.

Background: Our objective was to describe the association of pt hemoglobin (Hgb) levels with risk of all cause and cardiovascular disease (CVD) hospitalization and mortality in pediatric chronic hemodialysis pts.

Methods: Pediatric pts (ages <18) from the CMS ESRD Clinical Performance Measures (CPM) project, from 2000 to 2008, were merged to the USRDS database. Prior Hgb and EpoGen (EPO) use were determined from CPM data, and beginning annually on Jan. 1st, pts were followed for up to 1 yr and censored at the first date of death, lost to follow-up, or Dec. 31st. Outcomes included mortality and hospitalizations (all cause and CVD). We calculated the rates of outcome events per time at risk and stratified by pt Hgb levels.

Results: Pts with an average Hgb>10g/dL prior to follow-up had the highest unadjusted 1-yr mortality and at all cause hospitalization (5.85 and 278.89, respectively, per 100 pt yrs), and both rates declined with increasing entry Hgb levels. In contrast, the unadjusted rates of CVD hospitalizations were relatively constant across Hgb groups except for pts with Hgb<13g/dL who had the lowest rate. EPO use also differed by Hgb levels with the highest average dose per prescription [at least 2 out of 3 months (Oct-Dec) with an EPO prescription] and the highest average dose per prescription.

Conclusions: There is an association between a pt’s Hgb levels and their risks of hospitalizations and mortality in the year following Hgb measure. Future analyses will adjust for pt characteristics and clinical profile.

Funding: NIDDK Support

FR-PO1002

Association between Blood Pressure Levels and Adverse Clinical Outcomes in Korean Incident Hemodialysis Patients Fa Mee Doh,1 Hyang Mo Koo,1 Hyung Jung Oh,1 Tae-Hyun Yoo,1 Shin-Weok Kang.2 1Dept of Internal Medicine, College of Medicine; 2Brain Korea 21, Yonsei Univ, Seoul, Korea; 1On behalf of the Clinical Research Center for ESRD Investigators.

Background: BP control is an important issue in ESRD patients on HD. In general, it is recommended that target pre- and post-dialysis BP should be <140/90 mmHg and <130/80 mmHg, respectively. However, there is much controversy about the optimal BP in these patients.

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

Underline represents presenting author/disclosure.

S90A
Methods: A prospective cohort of 807 incident HD patients from 36 dialysis centers of the CRC for ESRD in Korea was included in this study. Time-averaged BPs were expressed as mean of the 6-month SBP and pre-and post-dialysis DBP. The composite of all-cause mortality or cardiovascular (CV) events was clarified by multivariate Cox regression analysis.

Results: The mean time-averaged BPs were as follows: pre- and post-dialysis SBP, 146±19 mmHg; and pre- and post-dialysis DBP, 77±12 mmHg and 77±12 mmHg. During a mean follow-up duration of 20.5 mo, 65 patients died and 49 CV events occurred. Compared to patients with pre-dialysis SBP of 140-149 mmHg, HRs for the composite outcome were 2.16 (p=0.044), 1.90 (p=0.073), 2.28 (p=0.021), and 2.42 (p=0.016) in the pre-dialysis SBP groups of <130, 130-139, 140-149, and ≥150 mmHg, respectively, after adjustment for potential confounders. Similar relationship was also observed across post-dialysis SBP categories, where post-dialysis SBP ≥150 mmHg was associated with a significantly higher risk for the composite outcome. In terms of DBP, HRs for the composite outcome in the pre-dialysis DBP groups of <60, 60-69, 70-79, and ≥80 mmHg were 0.56 (p=0.171), 0.50 (p=0.011), 0.87 (p=0.596), and 2.55 (p=0.024), respectively, when compared to patients with pre-dialysis DBP of 70-79 mmHg. Similarly, post-dialysis DBP ≥90 mmHg exhibited a significantly higher risk for the composite outcome.

Conclusions: Pre-dialysis SBP of 140-149 mmHg and post-dialysis SBP of 130-149 mmHg were revealed to be the optimal BP levels associated with a favorable clinical outcome in incident HD patients. In addition, maintaining pre- and post-dialysis DBP <90 mmHg may provide a more beneficial effect to these patients.

FR-PO1004

Global Pediatric Hemodialysis Dialysis Experience: The PICCOLO MONDO Consortium

Background: The MONDO consortium consists of HD data from US Renal Research Institute clinics; dialysis facilities of Fresenius Medical Care in Europe, Asia Pacific, Latin America (Germany); Imperial College (UK), Hadassah Medical Center (Israel); and University of Maastricht (The Netherlands) (Usvyat, Blood Purif 2013) with 62,345 incident patients from 1,052 units in 26 countries. The PICCOLO MONDO consortium includes incident 1 to 18 year old patients between 2000 and 2012.

Methods: Analysis of 494 patients (8.8% of the population), revealed that 17 patients were from the Asia Pacific (41% males, mean age 13.35); 43 from the USA (49% males, mean age 15.13); 87 from Europe (64% males, mean age 15.91); and 347 from Latin America (52% males, mean age 14.3). The Asia Pacific units reported the youngest incident patients (mean age 10.83) and diabetes in 18%, whereas the Europeans had the oldest patients (mean age 15.35). The use of HD catheters is greatest in the Americas (75%), followed by Europe (52%) while Asia Pacific had 0%. The USA cohort had the greatest prevalence of hypertension (58%) and cardiovascular comorbidities (58%), followed by the European cohort (26% & 18% respectively).

Conclusions: The PICCOLO MONDO cohort provides an opportunity to compare pediatric hemodialysis populations and outcomes at an international level. The prevalence of diabetes in the Asia Pacific units is unexpectedly high and requires additional investigation. The units in the Americas have the greatest use of HD catheters and the USA has the greatest prevalence of cardiovascular disease.

FR-PO1005

US Dialysis Facilities Target Hemoglobin (Hb) outside of Guidelines and Conduct Frequent Hb Measurements Despite Lack of Belief in Effectiveness of These Practices: A 2013 Survey of US Dialysis Facilities

Background: With the recent implementation of the CMS ESRD bundle, an updated FDA label for ESAs, and shifting QIP measures, changes in the approaches to anemia management have implications to the quality of care and management of patients on dialysis. Szezech et al (2012) demonstrated a lack of association between more frequent Hb measurements and decreased Hb excursions and between more frequent ESA titrations and decreased Hb excursions. In this study, we evaluated current anemia management practices.

Methods: In this study, >2000 nephrology professionals were screened against inclusion criteria: US nephrology professional, dialysis practice setting, >1 yr of nephrology experience, and consent. 367 eligible study candidates were invited with eventual 175 study participants (48%). Hb targets, Hb threshold for ESA holds, and frequency of Hb measurements and ESA titrations were evaluated. Analyses presented here were conducted across all study participants with no excluded data for any reason.

Results: 30% of study participant facilities use a Hb <10g/dl as lower range for target Hb, and 36% use a Hb >11g/dl as upper range for target Hb. 22% hold ESA dose at Hb ≥11g/dl; 88% make ESA dose adjustments on average once a month or more frequently for each dialysis patient. Respectively, 14% and 15% of study participants believe that more frequent Hb measurements and more frequent ESA titrations reduce Hb excursions.

Conclusions: Many US dialysis facilities seem to have Hb targets outside of the recommended ranges. Despite guidance to not make frequent ESA dose adjustments, nearly all facilities report frequent Hb testing and frequent ESA dose adjustment. Furthermore, nearly all participants do not believe these frequent Hb measurements and ESA dose titrations reduce Hb excursions, the purported reason to measure Hb and titrate an ESA. These apparent disconnects may represent the struggle between clinical beliefs, regulatory guidance, reimbursement constraints, and corporate directives.
FR-PO1006

Early vs Late Initiation of Dialysis on Clinical Outcomes of Quality of Life and Survival: A Propensity-Matched Analysis
Jeonghyun Lee,1,6 Jung-woon Noh,1,6 Yong-Lim Kim,2,6 Yoon Su Kim,4,6 Chun Soo Lim,2,6 Jung Pyo Lee,1,6 1Dept of Internal Medicine, Hallym Univ Hanang Sacred Heart Hospital, Seoul, Korea; 2Dept of Internal Medicine, Hallym Univ Gangnam Sacred Heart Hospital, Seoul, Korea; 3Dept of Internal Medicine, Kyungpook National Univ School of Medicine, Daegu, Korea; 4Dept of Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; 5Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; 6CRC ESRD Investigators Group.

Background: There is controversy on the adequacy timing of the initiation of renal replacement therapy for the patients with end-stage renal disease.

Methods: We enrolled a total of 1779 adult patients who start dialysis from 2007 to 2012 in a multi-center, prospective cohort of the Clinical Research Center for End Stage Renal Disease in Korea. All patients were interviewed and answered the questionnaire about Karnofsky performance score (KPS), Beck depression inventory (BDI), and kidney disease quality of life (KDQOL). Patients were classified, according to the mean values of estimated glomerular filtration rate (GFR) which is >7.37 ml/min/1.73 m² as early start group or late start group when GFR was above or below the mean values at the time of dialysis start.

Results: Before propensity-score matching, early start group showed poor score of KDQOL (15.6 ± 13.4 vs. 61.7 ± 14.6, P < 0.001), KPS (75.5 ± 15.4 vs. 78.8 ± 14.9, P = 0.002), and survival (P = 0.002). 1554 patients were eligible for matching and 395 patients were selected in each group. KPS (76.1 ± 15.0 vs. 78.6 ± 14.5, P = 0.086), BDI (16.4 ± 10.4 vs. 15.3 ± 10.4, P = 0.290), and KDQOL (57.8 ± 15.0 vs. 60.1 ± 14.5, P = 0.113) were similar between early start group and late start group. Overall survival was not different between groups (P = 0.259). In the subgroup analysis of patients with age above 65 years old, KPS (72.7 ± 15.2 vs. 73.2 ± 14.9, P = 0.869), BDI (16.8 ± 9.3 vs. 18.1 ± 11.0, P = 0.467), KDQOL (55.3 ± 12.4 vs. 54.6 ± 15.0, P = 0.791), and survival (P = 0.845) was comparable between groups.

Conclusions: Early initiation of dialysis was not associated with poor survival or quality of life even in the old age group.

FR-PO1007

Impact of Dialyzer on Serum Albumin Levels in End Stage Renal Disease Undergoing Chronic Hemodialysis
Alla Goldberg,1 Haife Hussain,1 Aruna Ray,1 Farahaneh Yousaf,1 Bruce S. Spinowitz,1 Chaim Charytan,1 New York Hospital Queens, Flushing, NY; 2Lutheran Medical Center, Brooklyn, NY.

Background: Serum albumin level is an important predictor of morbidity and mortality in end stage renal disease. However, very little is known about impact of different dialyzers on filtration of albumin molecules which may affect serum albumin. The purpose of our study was to evaluate the effect of different dialyzers on serum albumin levels.

Methods: Patients undergoing chronic hemodialysis at a single dialysis unit between January 1st to December 31st 2012 were included in present study. Patients who were hospitalized during year 2012 were excluded from current analysis. Medical records and lab values were reviewed. Patients were divided into 6 groups based on dialyzer; Optiflux 160NR, Optiflux 200NR, Optiflux 180NR, Optiflux 180NR, Rexeed 25S, Exeltra 210, and Exeltra 190. Univariate analysis of variance was used to analyze the data.

Results: 179 patients met the inclusion criteria with 46 % females. Mean age of patients was 67 years. Mean serum albumin was found to be statistically significant different (p<0.05) except Optiflux 180NR versus Optiflux 180NR and Exeltra 210 versus Exeltra 190. Age, gender, and cholesterol levels were independent predictors of serum albumin levels. However, serum albumin levels in different dialyzer groups were still significantly different even after controlling for age, gender, and cholesterol.

Conclusions: Our study suggests that the choice of dialyzer may affect serum albumin levels in end stage renal disease. Dialyzer may be selected based on patients serum albumin levels and malnourished patients may benefit from specific dialyzers such as Rexeed 25S. Further studies are warranted to confirm these results.

FR-PO1008

Correlation between Dt/V Derived from Ionic Dialysance and the Kt/V of Urea Using Daugirdas Formula in African-American Hemodialysis Patients
WhiB A. Gebregorgis, Nishi Pradhan, Stephen D. Migdal, Lakshminarayanan Nandagopal, Reddy Singasani, Tehmina Mushtaq, Yahya M. Osman Malik. Internal Medicine, Div of Nephrology, Wayne State Univ/Detroit Medical Center, Detroit, MI.

Background: Dialyzer obtained by using ionic dialysance (D) as a surrogate for urea clearance has been suggested as an adjunct measure of hemodialysis adequacy & has been shown to have variable correlation with the Kt/V of urea. We investigated the correlation between Dt/V & Kt/V of urea in African American HD patients & evaluated the impact of body size & ultrafiltration (UF) volume on the correlation.

Methods: A prospective single center observational study was conducted over a period of 3 months in 81 African-American HD patients. Each patient had 1-3 sessions of HD during which simultaneous evaluations of online Dt/V & spkt/V-urea were made. spkt/V-urea was estimated using the second generation Daugirdas formula. The ‘D’ was evaluated using conductivity probes at the dialysate inlet & outlet and ‘V’ was estimated using the Watson’s formula. Patients were categorized into three groups based on their body size & UF volume. The correlation between Dt/V & Kt/V was evaluated for the entire cohort & each pre-specified subgroup.

Results: A total of 81 patients had 186 HD sessions. The mean Kt/V was greater than the mean Dt/V (1.72 ± 1.50). There was an overall moderate correlation between Dt/V & Kt/V with an r2 of 0.602. The correlation was stronger in the medium BMI group compared to those in the lower & higher cohorts (r2 of 0.604, 0.653, 0.545 for those with BMI < 25, 25-30 & >30 kg/m2 respectively). The same trend was seen with the 3 weight groups. The correlation between Dt/V & Kt/V had inverse relationship to the UF volume; the lower the UF volume, the better the correlation between Dt/V & Kt/V (r2 of 0.698, 0.621 & 0.558 for those with UF volume of < 1.5, 1.5-3.0 & > 3 L respectively). 99.3% of the patients with Dt/V < 1.3 also had Kt/V > 1.3.

Conclusions: There is a moderate degree of correlation between Dt/V & Kt/V in African American chronic HD patients. Body size & UF volume affect the correlation between Dt/V & Kt/V. A Dt/V of > 1.3 strongly predicts adequate dialysis as defined by Kt/V of > 1.3.

Funding: Private Foundation Support
FR-PO1010

Comparison Study on Optimal Timing of Hemoperfusion Combined with Maintenance Hemodialysis

Chen Yu. Dept of Nephrology, Tongji Hospital, Shanghai, China.

Background: Hemodialysis (HD) combined with hemoperfusion (HP) was superior to HD in regularly eliminating middle and large molecule uremic toxins accumulated in the body. According to the different combining time of HD with HP, there were two types: Early type (HP was operated in the first two hours of HD) and Late type (HP was operated in the last two hours of HD). The purpose of this study is to compare the eliminating efficiency between these two types.

Methods: Twenty HD patients (4 hours each time, 3 times each week for more than 3 months) were enrolled. All patients were alternately given Early type and Late type of HD + HP. Serum concentration of creatinine (sCr), BUN, immunoreactive parathyroid hormone (iPTH), ß (2) microglobulin (ß (2)-MG), interleukin-1, interleukin-6-IL 6- and tumor necrosis factor-α (TNF-α) were determined before and after each treatment. Adverse events (low blood pressure, blood coagulation and so on) were observed.

Results: 1) Serum creatinine of all above mentioned were significantly declined after each type of treatment (p<0.01). 2) The eliminating efficiency of serum iPTH, ß (2)-MG, TNF-α, IL-1, IL-6 and IL-6 was better in the Late type of HD + HP (p<0.05). 3) There were no significant differences of the eliminating efficiency of Scr, BUN between the two types of HD+HP. 4) There was no significant difference in the incidence of adverse events (low blood pressure, blood coagulation and so on) between these two types.

Conclusions: Both two types of HD + HP are efficient in eliminating uremic toxins for MHD patient. Comparatively, the Late type of HD+HP (HP was operated in the last two hours of HD) has a better efficiency on elimination of middle and large molecule uremic toxins, like iPTH, ß (2)-MG, IL-1, IL-6 and TNF-α. However, there were no significant differences on elimination of small molecules, like sCr and BUN, between these two types of treatment. There was no significant difference of incidence of adverse events in the two types of HD+HP.

FR-PO1011

Markers of Financial Efficiency and Patient Quality Outcomes Are Interrelated in Dialysis Clinic Operations


Background: Dialysis providers face an increased pressure to reduce cost while trying to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients. With ESRD Seamless Care Organizations (ESCO) and other commercial integrated care arrangements, this pressure is even further to provide highest quality service to its patients.

Methods: We used data from 1700 FMCNA dialysis clinics. For calendar year 2012, we computed measures of financial and operational efficiency: employee retention ratio (max of 100%) and EBIT per treatment as well as measures of quality such as percent financial and operational efficiency measures. We divided measures of financial efficiency into quartiles and computed mean quality related measures in those groups. Comparisons between quartiles are performed by using independent t-tests.

Results: We found that clinics with higher employee retention ratios had lower SMR (max of 100%) and higher percent of patients with albumin ≥4.0 g/dl and standardized mortality ratio (SMR). We divided measures of financial efficiency into quartiles and computed mean quality related measures in those groups. Comparisons between quartiles are performed by using independent t-tests.

Conclusions: This analysis suggests that dialysis operational efficiency is tied to patient outcomes: clinics with higher employee retention ratios and highest EBIT/treatment also have the lowest SMR and highest albumin levels. While these relationships are not always significant in this analysis, they are performed on a clinic-wide basis with much variability in other clinic related characteristics, but highlight the positive association between quality outcomes and financial performance.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
593A

FR-PO1012

Dialysis Modality Decision Making

Suma Prakash,1,2 Steven A. Lewis,1,2 Anna McGrail,1 Jesse D. Schold,1 Mary Ellen Lawless,1,2 Ashwini R. Sehgal,1 Adam T. Perzynski,1,2 1MetroHealth Medical Center, Cleveland, OH; 2Case Western Reserve Univ, Cleveland, OH; 3Cleveland Clinic Foundation, OH.

Background: Preparing patients for dialysis is part of patient centered care for late stage chronic kidney disease. Stage of change (SoC) algorithms can be useful tools to assess patient’s readiness to make decisions and take health care actions. SoC algorithms classify patient readiness as pre-contemplation, contemplation (thinking SoC) preparation and action (acting SoC). The aims of this study were: 1) to develop a SoC tool for dialysis modality decision making, 2) determine associations between SoC and dialysis modality decision making and 3) determine additional factors associated with SoC and dialysis modality decision making.

Methods: Cross-sectional, observational study of adult patients with eGFR<20 mL/min/1.73m2. Qualitative interviews were conducted to support development and refinement of the survey. Survey responses were compared by SoC and by whether a dialysis decision was made using Fisher exact tests (dichotomous variables) and Wilcoxon’s two sample tests (continuous measures).

Results: 49 patients are enrolled. 69%-female, 38%-White, 60%-Black, 92%-high school graduates and 82% had annual income<$25,000. 10% were in pre-contemplation, 55%-contemplation, 8%-preparation and 27%-action. 63% made a dialysis modality decision. Thinking versus acting SoC patients were less likely to have made modality decisions (50% vs. 88%, p<0.01). More patients made modality decisions with higher knowledge scores (1.4-decided vs. 0.2-undeclared) and with physicians explaining modality options (41% vs. 74%) (both p<0.05). Modality decision barriers included: feeling home dialysis too difficult, others’ opinions, body image with peritoneal dialysis catheter, fears about dialysis and feeling overwhelmed (all p<0.05). Composite barrier score was higher in the thinking compared to acting SoC (means of 1.1 vs. 0.7) (p<0.01).

Conclusions: Modality decision making is associated with SoC. Findings from this measurement development study suggest that helping patients overcome self-identified barriers may allow them to feel ready and make dialysis modality decisions.

FR-PO1013

Post-Transplant Donor Specific Antibodies in Kidney Transplant Recipients with Graft Dysfunction

James E. Cooper, Jane Gralla, Alexander C. Wiseman. Kidney Transplant Center, Univ of Colorado, Denver, Aurora, CO.

Background: Post-kidney transplant donor specific antibodies (DSA) are important contributors to graft loss and no effective therapeutic options exist. In the largest reported series of post-transplant DSA IVIG treatment to date, we describe outcomes in patients with de novo DSA and graft damage treated with a long-term high dose IVIG protocol.

Methods: Retrospective analysis of 28 kidney transplant recipients with DSA and graft damage in the form of either a recent prior acute antibody-mediated rejection (AMR) episode (n=9, group 1) or chronic graft dysfunction (n=20, group 2) prescribed a standard regimen of high dose (5 g/kg) IVIG dosed over 6 months at our center.

Results: Mean fluorescence intensity (MFI) of 70 total DSA decreased by 520 at the end of treatment (T1, p=0.14) and by 708 at last follow up (T2, p=0.035) compared to treatment initiation (T0) MFI. The most robust treatment effect was seen in group 1 DSA (-1354 at T2 vs. T0, p=0.008) (figure 1a) and in class I DSA (-849 at T2 vs. T0, p=0.05) (figure 1b). Group 1, class I DSA underwent the largest MFI reduction (-1636 at T2 vs. T0, p=0.01). Antibody clearance, defined as MFI falling below 500, occurred in 68% of class I DSA vs. 16% of class II (p=0.001) and in 63% group 1 vs. 24% of group 2 DSA (p=0.001). Graft function stabilized in group 1 patients but continued to decline in those in group 2.

Conclusions: High dose IVIG resulted in modest DSA MFI reductions in patients with previous graft damage, while graft function either stabilized or continued to decline despite treatment. The most robust MFI effect was seen in Class I DSA in patients with recent acute AMR. This already-at-risk cohort may benefit from IVIG therapy in order to reduce the degree of future chronic DSA-mediated graft damage.
Hernández,1 Araminta Guichard,1 Norma O. Uribe-uribe,1 Nubia Banuelos,2 Los Angeles, CA.

albuminuria and glomerular association between post-transplant HLA antibodies and the key markers of renal injury: glomerular injury, is also considered a risk factor for graft failure. This report examine the term graft loss mainly due to endothelial damage. Albuminuria, a recognized marker of rebound after PP, due to exchange of DSA from interstitial

Jose

Filtration Rate Post-Transplantation

HLA Antibodies and Albuminuria Precede Decline in Glomerular Filtration Rate Post-Transplantation Lluvia A. Marino-vazquez,1,2 Araminta Guichard,1 Ahn Nguyen,2 Josefin Alberu,2 Luis E. Morales-Buenrostro.1 1Nephrology and Transplant, INCMNSZ, Mexico, DF, Mexico; 2Terasaki Foundation Laboratory, Los Angeles, CA.

Background: HLA antibodies have been shown to be a predictive marker of long-term graft loss mainly due to endothelial damage. Albuminuria, a recognized marker of glomerular injury, is also considered a risk factor for graft failure. This report examine the association between post-transplant HLA antibodies and the key markers of renal injury: albuminuria and glomerular filtration rate (eGFR).

Methods: We included 266 renal transplant recipients, transplanted between 1984 and 2012, and at least one-year follow-up. HLA antibodies were determined by Lumineux single antigen bead assay (One Lambda, Canoga Park, CA). Albuminuria was determined using turbidimetry measured in urine collected over a 24 hr period. The result was normalized to the creatinine content in the same sample (albuminuria/creatinine index). eGFR was calculated from serum creatinine values using MDRD equation.

Results: Of the 266 patients, 33.5% developed donor-specific HLA antibodies (DSA), and 45.1% had non-donor-specific HLA Antibodies (NDSA). 35 of the DSA patients had HLA Class I antibodies, while 64 had HLA Class II DSA. Patients with DSA had significantly higher albuminuria compared to patients with no antibodies (p=0.008). Interestingly, NDSA also showed higher proteinuria than the negative group. There was no significant difference between eGFR among the antibody and control groups at this point of follow-up.

Conclusions: Albuminuria is highly associated with the presence of HLA-DSA, and mildly correlated with NDSA. The fact that DSA and albuminuria were detected while eGFR remained at normal range, suggests that antibodies and albuminuria are earlier markers of graft injury than eGFR or serum creatinine.

Funding: Government Support - Non-U.S.
FR-PO1017

Background: Successful kidney transplantation in sensitized patients remains a challenge with high rates of antibody mediated rejection (AMR). 

Methods: Our protocol for live donor kidney transplantation with a flow positive crossmatch is pre- and post-transplant plasmapheresis (PP) with IL2 receptor antagonist induction, IV methylprednisolone tapered to prednisone 20 mg on postop day 4, with tacrolimus/mycophenolate maintenance therapy. To reduce AMR rates, in 2008, we added intraoperative Rituximab (375 mg/m2) and intravenous immunoglobulin (IVIG) 2gm/Kg in divided doses at months 0, 2, 4, 6. This study compares the 17 patients (grp 1) who received this AMR prophylaxis to a historical cohort of 14 pts (grp 2) that received the same maintenance regimen without this AMR prophylaxis.

Results: There were no significant differences between groups in terms of age (46.4±12.5 vs 45±9.8 yrs, p=0.92), gender (females 53% vs 79%, p=0.26), or prior transplant (76% vs 38%, p=0.06). Overall biopsy proven rejection rates were similar (82 v 86%, p=0.99). However, in the Rituximab/IVIG arm, rates of AMR were lowered significantly (see figure, Log Rank = 12, p=0.017), cases of concomitant ACR and AMR (4% vs 36%, p=0.012) were eliminated, and likely contributed to a small improvement in rejections with a complete response to therapy (85% vs 58%, p=0.2). Creatinine at one year was lower in grp 1, but not significantly different (1.5±0.6 vs 1.8±0.6 mg/dL, p=0.2). 

Conclusions: The addition of IVIG and Rituximab post-transplant appears to lower rates of AMR in patients receiving live donor positive flow crossmatch kidneys and should be considered in all such patients.

FR-PO1018

Nephrology, Transplantation & Pathology, National Institute of Medical Sciences and Nutrition SZ, Mexico City, DF, Mexico.

Background: Treatment for acute humoral rejection (AHR) has been an adaptation of the desensitization schemes. Includes removal of circulating HLA-antibodies (HLAabs) by plasmapheresis (PP), neutralization of HLAabs with IVIG, rituximab (RTX), and Bortezomib (Borte) intended to decrease HLAabs-producing plasma cells derived from B-cells, as well as use of rATG looking to control the cellular component (or interaction between T- and B-cells). This study compare different treatment protocols in order to guide future decisions.

Methods: Between May/08 and Apr/13, we prospectively recruited all 60 patients who had AHR. The histological description was made according to modified Banff 97 classification. DS-HLAabs were determined by Luminex single antigen bead assay (One Lambda). Kaplan-Meier survival curve with Log Rank test were used for compare graft survival.

Results: We included 60 KTR. Mean age 33.2±11.9; male gender 70%; first transplant 85%; living donor 76.7%; induction therapy 56.7%; maintenance triple therapy with CI 89.9%. The most used treatment schemes were PP+IVIG+RTX(36.7%), PP+IVIG+RTX+Borte(35%), PF+IVIG+Rtx+Borte(6.7%), others (21.6%). A 41.7% received more than one treatment (2-7). A 95% of the patients used PP, and 55% received Borte. There were not differences in graft survival when Borte, RTX, or IVIG were added to PP. Also, receive more than one treatment cycle, or the time after KT did not showed difference. The figure shows the eGFR behavior, and graft survival according to Borte use.

Conclusions: A higher rate of AMR observed in the ALE group did not translate into adverse short term graft and patient outcomes. Increased AMR incidence associated with ALE induction could be related to lesser suppression of humoral immune response when compared to r-ATG. Similar rates of ACR between the groups imply adequate suppression of T cell mediated immunity by ALE. Long-term impact of these observations is less clear.

FR-PO1019
Five-Year Patient and Graft Survival in Desensitized Patients with Positive Complement-Dependent Cytotoxicity Crossmatch Is Similar to Unsensitized Patients Kassern Safa,1 Jude A. Yagan,2 Helen Mah,3 Jamil R. Azzi,1 Edgar L. Milford,2 Anil K. Chandraker,1 Leonardo V. Riella.1 Surgery, Columbia Univ; 2Nephrology, Columbia Univ; 3Surgery, Brigham and Women' s Hospital, Boston, MA.

Background: More than 30% of potential kidney transplant recipients have pre-existing anti-HLA antibodies. Desensitization has been widely used and is accepted as an important strategy for overcoming this barrier. However, limited data is available regarding long-term outcomes, in particular for the highest risk group with a positive complement-dependent cytotoxicity crossmatch (CD-CXM) prior to desensitization.

Methods: Between 2002 and 2010, 39 patients underwent living-kidney transplantation across a positive CD-CXM against their donors at our center. The desensitization protocol involved pre-transplant immunosuppression, plasmapheresis, low-dose intravenous immunoglobulin ± rituximab. Measured outcomes included patient and graft survival, renal function and rates of rejection, infection and malignancy.

Results: The mean and median follow up was 5.2 years. Patient survival was 95% at 1 year, 95% at 3 years and 86% at 5 years. Graft survival was 87% at 1 year, 79% at 3 years and 72% at 5 years. Death-censored graft survival was 94% at 1 year, 88% at 3 years and 84% at 5 years. Chronic antibody-mediated rejection (AMR) caused 0.4% of 6 graft failures; 24 subjects (61%) developed acute AMR with the majority occurring in the first month after transplant; one patient lost their graft due to hyperacute rejection. Chronic rejection/transplant glomerulopathy developed in 15 patients (38%). Acute cellular rejection occurred in 9 patients (24%). Infectious complications included pneumonia (17%), BK nephropathy (10%), and CMV disease (5%). 10% of patients developed skin cancer; there were no cases of lymphoproliferative disorder.

Conclusions: Desensitization in living-donor kidney transplantation results in acceptable 5-year patient and graft survival, despite high acute rejection rates. This approach represents a reasonable strategy for sensitized patients with no access to other alternatives such as paired kidney donation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
FR-PO1020
Donor Specific Antibodies at Time of Transplant with a Negative or Weakly Positive Crossmatch Have Little Impact on Post Kidney Transplant Outcomes

Background: We wanted to retrospectively study the impact of pretransplant donor specific antibodies DSAs on kidney allograft rejection and graft survival.

Methods: We included all recipients of kidneys from July 2010 to January 2013 excluding multiorgan. HLA and crossmatch (CMX) data was reviewed including the presence of DSAs at time transplant. A DSA was considered if the MFI >1000. HLA Luminex testing and protocol biopsies were obtained at 4 months and 1 year in addition to indication biopsies. Follow up data was available till May 2013. We also included transplants with weakly positive CMX in the analysis.

Results: 44/506 recipients identified to have at least one DSA at transplant, 26 recipient with no available pretransplant HLA data and 436 with no DSAs. The group with DSAs were more likely to have a kidney from a deceased donor, receive rATG for induction and be on steroid maintenance. Also more likely to have a previous transplant and a higher PRA. There was no difference in rejection or graft failure. AMR was increased in the DSA group but not significant.

Conclusions: Employing rATG induction and steroid maintenance, recipients with pretransplant DSAs and negative/weakly positive CMX can be safely and successfully transplanted with at least similar short term outcomes compared to recipient with no DSAs.

FR-PO1022
Safety of Transplanting Patients with Pre-Transplant Donor-Specific (DSA) Anti-HLA Antibodies without Pre-Transplant Desensitization Therapy
Maria Ajajmy, Kwaku Marfo, Adriana Colovai, Enver Akalin. Kidney Transplantation, Montefiore-Einstein Center for Transplantation, Bronx, NY.

Background: Patients with strong DSAs develop higher rates of acute and chronic antibody-mediated rejection (AMR) despite pretransplant desensitization treatment. We created a pre-transplant immunologic risk assessment protocol based on mean fluorescence intensity (MFI) of DSAs and channel shift of values of flow-cytometry cross-match.

Methods: Patients with DSA MFI values between 1,000-5,000 and flow-cytometry T or B cross-match channel shift values of 50-150 and 100-250, respectively were accepted for transplantation. All patients with DSA received anti-thymocyte globulin (total 6 g) and IVIG (2 g/kg) induction treatment.

Results: Between May 2009 and December 2012, 66 kidney transplant recipients with a mean number of DSAs (1.63 ± 0.82), MFI (2904 ± 2776), Flow T (136 ± 50), B cell channel shift (162 ± 60) were compared to 308 patients without DSAs (Table). During a median 2.3 years follow-up, there was no difference in terms of patient and graft survival and graft function between 2 groups. Acute rejection was only observed in 8% of the DSA+ patients. Total of 73 DSAs were lost, and mean number of DSAs (0.54 ± 0.79) and MFI (2077 ± 3483) values significantly decreased posttransplant.

Conclusions: Successful kidney transplantation with a low acute rejection rate could be achieved in DSA+ patients with an immunologic risk assessment based on MFI and flow channel shift values and without pretransplant desensitization therapy.

FR-PO1023
Early De Novo Donor Specific Antibodies (dnDSA) after Kidney Transplantation: Impact on Rejection and Histology Findings

Background: Our aim was to study (1) the frequency of dnDSA during the first year post-transplant and (2) the impact of dnDSA on protocol biopsy findings and rejection.

Methods: All patients receiving a solitary kidney transplant between 7/2010 and 1/2013 were included. Luminex Single Antigen Bead (SAB) assay was performed at 1, 4 and 12 months post-transplant. Only DSAs with MFI>1000 were included. The cohort was grouped by the presence of a dnDSA at any time point during the first 12 months. Protocol kidney biopsy (Bx) done was done at 12 months.

Results: 506 patients were transplanted during the study period. Exclusions: 51 with pre-transplant DSA, 26 without pre transplant testing, 9 with early non-immune related graft loss. 415 of the remaining 420 patients had at least one Luminex SAB assay during the first 12 months. 61 (15%) had dnDSA: 39 (6%) class I, 41 (11%) class II, 7 (2%) both.

The dnDSA group was younger (50.4±13.5 vs. 55.4±13.1 yrs, p=0.007). Otherwise baseline patient characteristics were similar: female 39%, Black race 7%, deceased donor 50%, previous transplant 9%, 9% had pre transplant PRA>50%, and mean HLA mismatch 3.7±1.7. The control group was more likely to receive induction with a non depleting agent (18% vs. 3%, p=0.003). eGFR at 1 year was different. The dnDSA group had more glomerulitis, tubulitis, interstitial inflammation and ptc=0 on the 1 yr Bx. Banff 94 and C4d staining were not different. There was more antibody mediated rejection (AMR) in the dnDSA group.
Impact of Transplant Nephrectomy on HLA-Sensitization and Re-Transplantation  
Saad Ajmal,1 George P. Bayliss,2 Jason T. Machan,3 Claire Kassakian,3 Paul E. Morrissey,1 1Surgery, Alpert Medical School, Providence, RI; 2Medicine, Alpert Medical School, Providence, RI; 3Biostatistics, Alpert Medical School, Providence, RI.

Background: The management of a failed renal allograft is controversial. Transplant nephrectomy can lead to anti-HLA antibody formation (allo-sensitization). We evaluated the effect of transplant nephrectomy on allo-sensitization and the rate of subsequent transplantation.

Methods: We conducted a retrospective review of data from prospectively collected institutional and UNOS databases of kidney transplant recipients from 1997-2012 at a single academic transplant unit: some 933 renal transplants were performed out of which 183 failed (19.6%). Patients with failed transplants were divided into two groups: transplant nephrectomy for-cause (TN=53/172) and those who retained allograft (RA=119/172). Panel Reactive Antibody (PRA) values of patients who were re-listed, the main outcome measure, were collected at selected time points after graft failure.

Results: Age at transplantation, race, gender, living vs. deceased transplant, etiology of ESRD and time to graft failure were similar in both groups. No differences in co-morbidities were observed except for more patients with diabetes mellitus in the RA group (47.4% vs. 26.4%; p<0.0097). TN group demonstrated a significant increase in PRA values immediately following TN (30.5 % vs. 43.8 %; p<0.027). Patients with a failed allograft did not have significant change in PRA values (p= 0.67) over 1 year post-failure. 5/28 (17%) patients in TN group became highly sensitized (PRA>60) compared to 3/52 (5.7%) in RA group (p=0.08). Re-transplantation rates were similar at 4 years from graft failure in both groups (TN=9/53; RA=20/119; p=0.30). There was no statistically significant survival advantage offered by transplant nephrectomy; but peri-operative morbity was high, and there were two deaths within 30 days of nephrectomy.

Conclusions: Although a mild increase in PRA was observed immediately following transplant nephrectomy, TN does not decrease the opportunity for re-transplantation. TN should only be performed for cause.

Funding: Clinical Revenue Support

FR-PO1025
Some Renal Transplants Diagnosed as Glomerulonephritis Probably Have Antibody-Mediated Rejection

ANDRE BARRETO PEREIRA, 1,2 JESSICA CHANG, 1 KONRAD S. FAMULSKI, 1 PHILIP F. HALLORAN, 1,2.
1. Alberta Transplant Applied Genomics Centre, Edmonton, Canada; 2. Department of Nephrology and Transplant Immunology, University of Alberta, Edmonton, Canada;

Background: In renal transplants recurrent and de novo glomerulonephritis (GN) is common, but distinguishing GN from antibody-mediated rejection (ABMR) is difficult. We hypothesized that a recently developed test for ABMR would reveal that some GN causing failure in renal transplants is actually ABMR.

Methods: From a prospective study of transplant indication biopsies taken >1 year post transplant, we selected assessed 64 diagnosed as GN and assessed their microarray by pt self-report and CV% of TAC.

Results: 9/64 (16%) of transplants diagnosed as GN had positive ABMR scores (Table 1). In microarray analysis, S+ biopsies were later and had higher expression of DSA associated (DSAST), IFNG-induced (GRIT), and NK cell (NK) transcripts, typical of ABMR, and had higher AKI scores, than S-. S+ biopsies also had higher histologic cg and ci scores, and a higher frequency of failures than the 55 S- biopsies (Table 1). However, the TCMR scores were not different.

Conclusions: 16% of transplants diagnosed as GN in late biopsies have positive ABMR scores. These have an increased frequency of molecular features of ABMR, glomerular double contours and glomerulitis, and increased risk of graft failure. With treatment options emerging for ABMR, microarray diagnosis may aid in correctly distinguishing ABMR from GN.

FR-PO1028

The Role of Medication Nonadherence in the Generation of De Novo Donor Specific Antibodies

JULIA W. TZENG, 1 ROBERT B. ETTENGER, 1 ELAINE F. REED, 1 DAVID W. GJERTSON, 2 TING-YAN CHAN, 1 DECHU P. PULIYANDA, 2 EILEEN W. TSAI. 1
1. Pediatrics, Mattel Children’s Hospital UCLA, LA, CA; 2. Pediatrics, Cedars-Sinai Medical Center, LA, CA.

Background: Medication nonadherence (MNA) has been associated with development of de novo donor specific antibodies (DSA) and rejection (rej) in kidney transplant (Tx) patients (pts). However, these studies linking MNA and DSA were limited, since the technique of identifying MNA was not rigorously defined. We recently showed that the percent coefficient of variation (CV%) of tacrolimus (TAC) is significantly associated with DSA, using a standardized interview and by CV% of TAC (standard deviation divided by mean multiplied by 100%).

Methods: We studied 125 pediatric pts txed from Jan 2005 to Dec 2011. Pts were nonadherent (MNA) and all patients demonstrated low CsA and/or EVE trough levels.

Results: 9/64 (16%) of transplants diagnosed as GN had positive ABMR scores (Table 1). In microarray analysis, S+ biopsies were later and had higher expression of DSA associated (DSAST), IFNG-induced (GRIT), and NK cell (NK) transcripts, typical of ABMR, and had higher AKI scores, than S-. S+ biopsies also had higher histologic cg and ci scores, and a higher frequency of failures than the 55 S- biopsies (Table 1). However, the TCMR scores were not different.

Conclusions: 16% of transplants diagnosed as GN in late biopsies have positive ABMR scores. These have an increased frequency of molecular features of ABMR, glomerular double contours and glomerulitis, and increased risk of graft failure. With treatment options emerging for ABMR, microarray diagnosis may aid in correctly distinguishing ABMR from GN.

Table 1. CN1 in lobe combined biopsy (1 random biopsy per patient).

<table>
<thead>
<tr>
<th><em>p</em></th>
<th>0.001</th>
<th>0.01</th>
<th>0.05</th>
<th>0.10</th>
<th>0.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>e</td>
<td>0.01</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>DQA1</td>
<td>0.01</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>MHC class I (identity)</td>
<td>0.01</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>C4d+</td>
<td>0.01</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>GRIT</td>
<td>0.01</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>NK</td>
<td>0.01</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Conclusions: Rigorously defined MNA, DSA, and ABMR are conclusively associated. Thus, DSA can potentially be used as a novel marker to monitor MNA.

Funding: Private Foundation Support
Impact of Donor-Specific Antibodies and Biopsies of the Grafts on the Therapy of Pancreas-Kidney Transplantation Patients

**FR-PO1030**

**Impact of Donor-Specific Antibodies and Biopsies of the Grafts on the Therapy of Pancreas-Kidney Transplantation Patients**

Luis Eduardo Becker,1 Sebastian Schäfer,1 Ruediger Waldherr,2 Martin G. Zeier,1 Caner Süss,1 Christian Morath,1 1Nephrology, Univ of Heidelberg, Germany; 2Pathology, Univ of Heidelberg, Germany; 3Immunology, Univ of Heidelberg, Germany.

**Background:** While the role of donor-specific antibodies (DSA) in simultaneous pancreas kidney transplantation (SPKT) is still unclear, the histological evaluation of the pancreas allograft remains essential to judge immunological processes in the graft. Because of the growing clinical significance of DSA in the kidney-alone transplant setting, we performed a critical retrospective analysis of the indications and the further therapeutic consequences of these diagnostic tools on SPKT patients from our program.

**Methods:** All 17 cadaveric SPKT (from a total of 29) patients who underwent one or more biopsies of the pancreas allograft between Oct 2009 and Jan 2012 at our facility were included in the analysis. A total of 51 percutaneous biopsies (22 of the pancreas, 29 of the kidney) was performed in a median follow-up of 24 months. Analysis of DSA IgG against HLA antigens occurred prior to transplantation and by the time of the pancreas or kidney allograft biopsies.

**Results:** Adequate samples according to Banff were obtained in 15 of 22 procedures (68%). Successful pancreas biopsy led to a significant change in the immunosuppressive therapy in eleven episodes (73%) and justified the employment of antibody directed therapy in six (40%). In the remaining six patients, the therapy was the result of a concomitant kidney biopsy or the presence of DSA; antibody directed therapy was employed in one patient. Nine patients (60%) had at least one DSA positivity, eight of them with concomitant pancreas or kidney allograft rejection (88%), three with c4d positivity (33%). Six patients had negative DSA, four of them (67%) having sings of rejection in the kidney or pancreas histology, but none with antibody mediated rejection (AMR).

**Conclusions:** Even with the employment of Luminex tests in the routine and a possible association of DSA and the presence of AMR in our patient collective, the result of pancreas histology remained pivotal for the employment of a targeted, often more aggressive immunosuppression.

Antibody Mediated Kidney Renal Association with HLA-Cw Specific Alloantibodies

**FR-PO1031**

**Antibody Mediated Kidney Renal Association with HLA-Cw Specific Alloantibodies**


**Background:** It is unclear whether donor-specific antibodies (DSA) directed against HLA-Cw increase risk for antibody-mediated rejection (AMR) after kidney transplant.

**Methods:** Since 2008, kidney transplant recipients (KTR) at Columbia University Medical Center are screened for DSA against HLA-Cw pretransplant and at the time of graft dysfunction. We identified 84 KTR with Cw alloantibodies including 22 KTR with HLA-Cw DSA, either in isolation (45.5%) or combined with other class I or class II DSA (54.5%).

**Results:** Our cohort was 68.2% male, with a median age of 56.7yrs (IQR 46.5–67.6 yrs); the majority (68.2%) had no previous organ transplant. Nine KTR had an AMR (3 with pre-existing Cw DSA vs 6 with de novo Cw DSA, p=0.007). KTR with isolated Cw DSA were less likely to experience AMR (10% vs 66.7%, p=0.03 and OR=0.56, p=0.02) and have a longer time to AMR (p=0.002) despite similar MFI (Cw DSA MFI median 1600 vs 3600, p=0.08) to patients with additional DSA. No KTR with isolated pre-existing Cw DSA (n=9) experienced AMR while 50% (3/6) with other pre-existing DSA had AMR (p=0.04). Seven KTR developed de novo Cw DSA at a median of 126 days (IQR 53–909 days) post transplant but only 1 developed Cw DSA in isolation; 85.7% (6/7) had AMR. KTR with de novo Cw DSA had significantly shorter time to rejection than pts with pre-existing Cw DSA at transplant (p=0.007) despite similar MFI (median 2000 vs 2200, p=0.32). After adjustment for the presence of other HLA DSA, KTR with de novo Cw DSA were still more likely to develop AMR than those with pre-existing Cw DSA.

**Conclusions:** Our results suggest a lower incidence of AMR among KTR with isolated pre-existing HLA-Cw DSA compared to KTR who have multiple DSA. However, de novo HLA-Cw DSA even in isolation is associated with a higher risk of AMR than preformed HLA-Cw DSA.

Significance of Donor Specific Anti-HLA Antibodies Identified Using Recombinant HLA Coated Single Antigen Beads in Kidney Graft Recipients with a Negative Donor Flow Cytometry Crossmatch

**FR-PO1032**

**Significance of Donor Specific Anti-HLA Antibodies Identified Using Recombinant HLA Coated Single Antigen Beads in Kidney Graft Recipients with a Negative Donor Flow Cytometry Crossmatch**


**Background:** Flow cytometry crossmatch (FCXM) and recombinant HLA coated single antigen bead assay (SAB assay) are highly sensitive assays for detection of donor specific antibodies (DSA). Many transplant centers consider a positive FCXM as a contraindication to kidney transplantation. We investigated the clinical significance of DSA using SAB assay, in the context of negative FCXM.

**Methods:** We evaluated 204 patients who underwent prospective FCXM and SAB testing prior to kidney transplantation. Sera were profiled using LabScreen SAB assay & DSA with mean fluorescence (MFI) value >1000 MFI were scored as positive. Donor FCXM was scored as positive when the mean channel displacement was >40 for donor T cells and/or >50 for donor B cells.

**Results:** Of the 204 renal transplant recipients tested, 43 had a positive FCXM with donor T and/or B cells. In the remaining 161 recipients with a negative FCXM result, 50 were positive for DSA. Seven of 50 patients with the positive DSA by SAB assay experienced AMR and four experienced graft loss. In a multivariable logistic regression analysis, DSA detected by SAB assay in patients with a negative flow cross match result was an independent risk factor for AMR. Risk of graft loss was also increased (OR=4, 0.9, 17, p=0.007).

**Conclusions:** Donor specific antibodies, not detected by flow cytometry but identifiable by SAB assay, is associated with an increased risk of antibody mediated rejection with a trend toward increased graft loss in kidney graft recipients. Standardized screening of sera using SAB assay, in addition to identification of patients at risk for AMR, offers opportunities for personalized immunosuppressive therapy in kidney graft recipients.

**Funding:** Clinical Revenue Support

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

**Underline represents presenting author/disclosure.**
Lower Rejection Rates with Class 1 versus Class 2 Donor Specific Antibodies in Sensitized Kidney Transplant Recipients

Background: Renal transplant recipients with donor specific antibodies (DSA) have high rejection rates. Determination of which class of DSA are associated with worse outcomes will aid in donor selection and paired kidney exchange participation.

Methods: Since 2004, we have performed 57 live donor positive cytotoxic or flow crossmatch (+XM) renal transplants. All patients received pre- and post- transplant plasmapheresis(PP) with intravenous immunoglobulin (IVIG) replacement (100mg/kg) for a minimum of 2 treatments and until CDC crossmatch was negative. Induction therapy varied with time but included either an IL-2 receptor blocker or Thymoglobulin® with or without intra-operative Rituximab. Maintenance therapy is tacrolimus and mycophenolate. All patients received IV methylprednisolone with taper to prednisone 20 mg daily by post-operative day 4. Protocol biopsies are done at 1, 2, 4, 13, 26 and 52 weeks; then annually.

Results: Of the 57 patients, 40 had results of DSA measurement by single antigen beads available. Among the 18 patients with cytotoxic +XM, rejection rates were higher regardless of DSA type (Class 1- 99, class 2- 3/4, class 1&2- 5/5). Analysis was then restricted to the 22 patients with only flow +XM. Patients with class 2 and class 1&2 antibodies behaved similarly and were grouped together for analysis. There were significant differences in outcomes between patients with class 1 compared to only those with class 2 or both class 1 and 2 DSA.

<table>
<thead>
<tr>
<th>LOW CROSSMATCH RECIPIENTS ONLY</th>
<th>Class 1 DSA (n=5)</th>
<th>Class 2 DSA (n=10)</th>
<th>Class 1&amp;2 DSA (n=17)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>54.9±9</td>
<td>45±10</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Antibody</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.69±1.47</td>
<td>1.69±1.47</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Recent creatinine (mg/dl)</td>
<td>1.69±0.26</td>
<td>1.69±0.26</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Recent rejection type</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>AMR</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Recurrent rejection</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Among sensitized patients, those with only flow +XM donor specific antibodies restricted to class 1 MHC have fewer rejections and less recurrent rejections than those with class 2 or class 1 and 2 antibodies.

FR-PO1034
Elevated Urinary CCL2: Cr at 6 Months Is Associated with the Development of Renal Allograft Interstitial Fibrosis and Inflammation at 24 Months

Background: We have previously demonstrated that 6 month urinary CCL2: Cr is an independent predictor of interstitial fibrosis and tubular atrophy on 24 month biopsy and subsequent death-censored graft loss. Patients with graft loss frequently have a combination of graft interstitial fibrosis plus inflammation (GIF & “i”), i.e. >0 p<0.05. The study was done to determine if 6 month urinary CCL2: Cr is an independent predictor for the development of GIF & “i”.

Methods: The patients were from a prospective, multi-centre adult renal transplant study (n=111) that had 6 month urine and 24 month protocol biopsies. CCL2 was measured with ELISA, corrected for urinary creatinine. Renal histopathology was reported using the Banff schema. Stepwise logistic regression was performed with the potential covariates: 6 month urinary CCL2: Cr, donor age >50 years, delayed graft function, living vs. deceased donor, ACR/ABR exposure, PRA and HLA match.

Results: Six-month urinary CCL2: Cr was significantly higher in GIF & “i” [26.8 ± 17 ng/mmol, p=0.003, n=28] and transplant glomerulopathy patients [36.3 ± 36 ng/mmol, p=0.004, n=15] compared to normal hologeny [15.4 ± 10/mgmmol, n=30] at 24 months. By multivariate analysis, 6 month urinary CCL2: Cr was an independent predictor for developing GIF & “i” at 24 months [OR 1.04, CI 1.01-1.08, p<0.01]. Finally, 6-month urinary CCL2: Cr had an AUC 0.695 [95% CI 0.571-0.819], with a sensitivity specificit[71.8% and a cut-off value of 15ng/mmol for identifying 24 month GIF & “i”.

Conclusions: This study demonstrates that 6-month urinary CCL2: Cr is an independent predictor for developing 24 month GIF & “i”. Urinary CCL2: Cr may be used to stratify patients at risk for GIF & “i”, who may require more intensive post-transplant surveillance and avoidance of drug minimation withdrawal protocols. Finally urinary CCL2: Cr may help identify patients for novel interventional trials targeting GIF & “i”.

Funding: Pharmaceutical Company Support - Astellas Canada, Private Foundation Support

FR-PO1035
Protocol Biopsy at 0, 14 and 90 Days to Identify Renal Allograft Dysfunction – Single Center Study

Background: To identify histological changes of renal allograft by protocol biopsy for detection of early graft dysfunction.

Methods: Thirty five kidney transplant recipients were included in this study over a period of 3 years in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Results: Of the 57 patients, 40 had results of DSA measurement by single antigen beads available. Among sensitized patients, those with only class 2 and class 1&2 antibodies behaved similarly and were grouped together for analysis. There were significant differences in outcomes between patients with class 1 compared to only those with class 2 or both class 1 and 2 DSA.

<table>
<thead>
<tr>
<th>LOW CROSSMATCH RECIPIENTS ONLY</th>
<th>Class 1 DSA (n=5)</th>
<th>Class 2 DSA (n=10)</th>
<th>Class 1&amp;2 DSA (n=17)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>54.9±9</td>
<td>45±10</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Antibody</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.69±1.47</td>
<td>1.69±1.47</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Recent creatinine (mg/dl)</td>
<td>1.69±0.26</td>
<td>1.69±0.26</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Recent rejection type</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>AMR</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Recurrent rejection</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Among sensitized patients, those with only flow +XM donor specific antibodies restricted to class 1 MHC have fewer rejections and less recurrent rejections than those with class 2 or class 1 and 2 antibodies.

FR-PO1036
Complications Associated with Renal Graft Biopsy in Transplant Patients

Background: Percutaneous biopsy of renal grafts is a diagnostic method for the assessment, management and clinical monitoring of renal transplant, so it is necessary to know its complications. There are few data in the literature regarding complications from biopsies in renal grafts.

Methods: We performed a retrospective observational study, including data from 256 patients who underwent renal graft biopsies from January 2000 to September 2012. Major complications were defined as: anemia requiring blood transfusion, intraparenchymal arteriovenous fistula or arterial bleeding requiring embolization, nephrectomy, other surgery and exitus. And as minor complications: anemia without blood transfusion, intraparenchymal arteriovenous fistula without embolization, hematomas or perirenal collections, hematuria and fever. Kidney biopsies were performed with ultrasound guidance and automatic devices. We are not described.

Results: We performed 390 kidney graft biopsies. Total complications in renal graft biopsies were 49, which corresponds to an overall rate of 12.6%, of which 22 were major complications (5.6%) and 27 minor complications (6.9%). Among the 22 biopsies with major complications, 12 presented anemia which required blood transfusions (3.1%), 6 embolizations, of which one was for arterial bleeding and 5 were for intrarenal fistulas (1.5%), 1 tracheostomy secondary to important bleeding for laceration of the renal lower pole post-graft biopsy (0.3%), 1 required surgery for perirenal hematoma evacuation (0.3%) and two finally died (0.5%). Among the other 27 biopsies with minor complications, 12 were perirenal collections (3.1%), 9 were arteriovenous fistula not requiring embolization (2.3%), 3 haematuria (0.8%), 2 presented anemia who did not require blood transfusion (0.5%) and 1 episode of fever (0.3%). The success rate of tissue obtained for histopathological study was 97.9%.

Conclusions: The rate of complications related to renal graft biopsy observed in our center are similar to those described for native kidneys, and therefore we believe it remains a safe and effective technique, and an important diagnostic tool in transplant patients.
survival. The balance between acute and chronic lesion scores determines the magnitude likely informs short term creatinine trajectory. Post-biopsy creatinine improvement was not

Conclusions: Biopsy derived indices provide valuable short and long-term prognostic information. The “t” score likely reflects reversible short term injury and the “cg” score likely informs short term creatinine trajectory. Post-biopsy creatinine improvement was not sustained with higher “t” scores. The “ci” score informs prognosis regarding long term graft survival. The balance between acute and chronic lesion scores determines the magnitude and sustainability of functional improvement after treatment of allograft rejection.

FR-PO1038
Revisiting the Natural History of IF/TA in Renal Transplantation Based on Protocol Graft Biopsies
Ken Sakai,1 Tatsu Matsuikyo,1 Kiyoto Koibuchi,1 Hiroki Hase,2 Sonoo Mizuiri.1
1Nephrology, Toho Univ, Tokyo, Japan; 2Nephrology, Harada Hospital, Hiroshima, Japan; 3Nephrology, Toho Univ Ohashi Hospital, Tokyo, Japan.

Background: The landmark study by Nankivell et al in 2003, suggested two distinct phases of injury involved in IF/TA: an early tubulo-interstitial damage from allograft rejection and, beyond 1 year, an interstitial injury interpreted as secondary CA toxicity. According to the improvement of current immunosuppression, we re-examined the natural history of IF/TA in this era.

Methods: 1hour, 1year, 3year and 5year protocol biopsy was performed after kidney transplantation. Protocol biopsy specimens up to 5 years after KTx. They took protocol biopsy completely underwented protocol biopsies up to 5 years after KTx. Protocol biopsy derived indices provide valuable short and long-term prognostic information. The “t” score likely reflects reversible short term injury and the “cg” score likely informs short term creatinine trajectory. Post-biopsy creatinine improvement was not sustained with higher “t” scores. The “ci” score informs prognosis regarding long term graft survival. The balance between acute and chronic lesion scores determines the magnitude and sustainability of functional improvement after treatment of allograft rejection.

Thus the discordant kidneys were more injured and actual function was influenced by other factors e.g. recipient age. AKI score was similar in pre- and 1h post implant biopsies, indicating that it is established before kidney removal.

Conclusions: Thus the molecular measurements in either kidney can be used in the future to predict function of both and may prove useful in organ utilization decisions.

FR-PO1040
Glomerular Abnormalities in Cirrhotic Patients: Immune Mediated?
Anjali Gupta, Awas Aljanabi, James M. Pullman, Paul Joseph Gaglio, Enver Akalin, Graciela De boccardo. Montefiore Medical Center.

Background: We previously demonstrated universal glomerular abnormalities in kidney biopsies after orthotopic liver transplantation (OLT). We hypothesize that these changes exist prior to OLT and may play a role in the development of renal failure after OLT. We investigate the mechanism of kidney disease in patients listed for OLT by microarrays. The clinical and pathological data of 25 cirrhotic patients listed for OLT who underwent kidney biopsy was analyzed. Gene expression profile of biopsies (n=58) was studied by Affymetrix HuGene 1.0 ST expression assay and compared with pre implantation tissue.

Conclusions: Contemporary use of CNI with CD25 antibody significantly stabilized CNI toxicity defined as newly appearance of Ah. Interstitial inflammation and tubulitis

resulted in increasing IF/TA not caused by CNI toxicity in this era. Such graft damage have an identifiable cause that is not idiopathic IF/TA or CNI toxicity and that alloimmunity remains the most common mechanism.

FR-PO1039
Molecular Acute Kidney Injury Score in Deceased Donor Kidney Predicts Post-Transplant Function of Both Kneys
Konrad S. Famulski,1 Chatchai Kecepal,2 Declan De freitas,3 Philip F. Halloran.1 1Univ of Alberta, Edmonton, Canada; 2Srinakarinwirot Univ, Nakornayok, Thailand; 3Beaumont Hospital, Dublin, Ireland.

Background: Shortage of deceased donor (DD) kidneys for transplantation prompts clinicians to use more old and injured kidneys. Molecular acute kidney injury (AKI) score in DD kidneys can be measured by expression of injury-repair transcripts and at transplantation predicts impaired early function. We hypothesized that AKI score in each kidney predicts future function (Cr at day 7) of the mate kidney.

Methods: We analyzed microarray data, histology and clinical data of 15 kidney pairs from brain dead DD.

Results: The AKI score was highly similar within pairs r=0.95, while histology score (Remuzzi) was much more variable r=0.65. AKI score correlated with the future function of the opposite kidney, but histology did not.

Conclusions: Thus the discordant kidneys were more injured and actual function was influenced by other factors e.g. recipient age. AKI score was similar in pre- and 1h post implant biopsies, indicating that it is established before kidney removal.

Correlation with function
gene increase in DD
OSMR 0.42 0.37 2.7 0.79
MEGF11 0.51 0.41 2.5 0.77
OLFM4 0.40 0.44 3.4 0.75
CDH6 0.35 0.43 2.2 0.95
NNMT 0.38 0.37 3.3 0.54
MEGF11 0.42 0.37 2.7 0.77
OSMR 0.51 0.41 2.5 0.77
OLFM4 0.40 0.44 3.4 0.75
CDH6 0.35 0.43 2.2 0.95
NNMT 0.38 0.37 3.3 0.54

AKI score reflected the effect of brain death, it was higher in DD compared to living donors (LD). In pairs with discordant outcomes - one recipient with poor, another with good function, AKI score was high in both kidneys.
genes implicated in immune response, including T-cell, leucocyte and platelet activation and differentiation. Pathogenesis-based transcripts revealed significantly increased expression of cytotoxic T-cell, macrophage, B-cell, natural killer cell and endothelial cell associated transcripts, indicating an ongoing inflammatory immune response.

**Conclusions:** Our study demonstrates universal presence of glomerular abnormalities in biopsies of cirrhotic patients. Majority had in mesangial matrix, podocyte effacement and widespread expansion and duplication of GBM. Increased gene expression profiles related to immune activity indicates immune-mediated mechanisms in development of kidney disease.

**FR-PO1041**

**Increased Rejection-Associated Gene Transcripts in Biopsies of DSA+ Patients without Histopathologic Findings of Rejection**

**Nicole A. Hayde,** Yi Bao, James M. Pullman, Michelle L. Lubetzky, Graciela De boccado, Enver Akalin.

**Montefiore/Einstein Transplant Center, Bronx, NY.**

**Background:** The presence of donor specific antibodies (DSA) without allograft injury questions whether accommodation or other preventative mechanisms exist or if this is a state of pre-rejection. A set of genes was shown to be upregulated in the blood of tolerant patients in microarrays. We investigated the gene expression of kidney and whole blood samples of DSA+ patients with antibody-mediated rejection (AMR) and without rejection, including the tolerance genes.

**Methods:** DSA were measured by Luminex. The biopsy and whole blood samples of 28 DSA+/AMR+, 14 DSA+/AMR- and 20 DSA negative patients with normal histopathology (control) were analyzed by Affymetrix HuGene 1.0 ST expression arrays.

**Results:** Both DSA+/AMR+ and DSA+/AMR- biopsies showed increased cytotoxic T (CAT), constitutive macrophage (CMAT), natural killer cell (NKAT), and endothelial cell associated (ENDAT) pathogenesis based transcripts, and donor specific antibody selective transcripts seen in AMR (DSAT) compared to DSA- biopsies. However, there were no significant differences in the whole blood gene expression profiles of DSA+/AMR- and DSA- patients. DSA+/AMR+ patients had increased CAT, CMAT and interferon-γ and rejection induced transcripts (GRIT) in their blood. There was also no difference in expression of tolerance-associated genes in whole blood and biopsy samples of DSA+/AMR- compared to DSA-.

**Table 1: Pathogenesis Based Transcript Comparisons**

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSA+/AMR+</td>
<td>DSA+/AMR-</td>
</tr>
<tr>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>CAT</td>
<td>0.01</td>
</tr>
<tr>
<td>BAI</td>
<td>0.02</td>
</tr>
<tr>
<td>CMAT</td>
<td>0.02</td>
</tr>
<tr>
<td>NKAT</td>
<td>0.02</td>
</tr>
<tr>
<td>ENDAT</td>
<td>0.03</td>
</tr>
<tr>
<td>DSAT</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Conclusions:** We identified complex overlap between microcirculation injury, DSA and endothelitis. The absence of microcirculation injury at the time of biopsy did not exclude a humoral process as the potential cause of TMA. The high prevalence of endothelitis (−lesion) was high (n=9): 2/6 patients with probable CNI toxicity had DSA at the time of TMA. In 6/9 cases showing rejection with a humoral component, TMA preceded the presence of microcirculation injury. This prodmote of microthrombi with subsequent development of rejection could not be attributed to reduced immunosuppression.

In contrast, TNFAIP3, BLCL2 were upregulated in biopsy and blood samples of DSA+/AMR+ patients. CD79B, FCR1L, MS4A1 and SH2D1B were upregulated in DSA+/AMR- biopsies.

**FR-PO1042**

**Uncontrolled Complement after Renal Transplantation and C5b9 Deposits on Graft Predict Favorable Outcome in Adult Renal Transplant with C3 Glomerulopathy**

**Moglie Le Quintron,** Marion Rabant, Maria Chiara Marinozzi, Frank Bridoux, Michel Delahousse, Christophe M. Legendre, Veronique Fremaux-bacch. 

**Nephrology and Renal Transplantation, Hopital Foch, Suresnes, France; Anatomopathologie, Hopital Necker, Paris, France; Inserm UMR 872, Cordeliers Research Center, Paris, France; Nephrology and Renal Transplantation, Chenue de Poitiers, Poitiers, France; Nephrology and Renal Transplantation, Necker Hospital, Paris, France; Laboratoire d’Immunologie, Hopital Eproue Georges Pompidou, Paris, France.

**Background:** C3 glomerulopathy (C3G) is a severe disease strongly associated with abnormal control of complement alternative pathway activation. Few data are available on recurrence risk and graft outcome.

**Methods:** We studied 47 patients with DDD (n=15), GNC3 (17) and MPGN type I (n=15) who received renal transplantation. Plasma C3 and sMAC were measured by Elisa, C3 and C5b9 staining by immunocytochemistry.

**Results:** Graft survival was 98% and 77% at one and five years respectively: 48% of patient (n=23) had a clinical graft recurrence biopsy proven; 60% (14/23) of them occurred in the first year after transplantation. The recurrence occurred in 33% (5/15), 47% (8/17) and 60% (9/15) of patients with DDD, GNC3 and MPGN type I respectively. At five years, 54% of graft lost was due to recurrence (n=6/11). Before transplantation, a low C3, positive C3 Nef were documented in 63% of patients. After renal transplantation, a low C3, positive C3 Nef were documented in 20% (7/34), 33% (11/33) and 37% (6/16) of patient respectively. Only 34% (7/17) of patients with low C3 before transplantation had a recurrence. At time of recurrence, 60% (11/18) of patients had a low C3 or/and high sMAC (84/24) if no recurrence occurred. All patients who lost graft before 5 years due to recurrence had low C3 and/or sMAC high. All patients with recurrence had positive C3 staining, C5b9 staining (6/34) was possible in only lost graft due to early recurrence from patients who had severe recurrence and poor graft outcome.

**FR-PO1043**

**Clinicopathological Correlation of Transplant-Associated Thrombotic Microangiopathy**

**Miriam Berry,** Victoria Bardales, Meryl Helen Griffiths, Nicholas Torpey, Verena Broecker. 

**Transplant Unit, Addenbrooke’s Hospital, Cambridge, United Kingdom; Dept of Histopathology, Addenbrooke’s Hospital, Cambridge, United Kingdom.

**Background:** Transplant associated thrombotic microangiopathy (TA-TMA) is found in 1% of renal transplant biopsies. Clinicopathological correlation is required to identify the cause. However, there are often discrepancies between the histological, clinical and serological results at the time of diagnosis. This uncertainty has significant therapeutic implications.

**Methods:** We retrospectively re-evaluated 69 renal transplant biopsies from 16 patients with TA-TMA over 5 years, identified by a database search. Biopsies were graded according to Banff criteria. Clinical parameters were collected and correlated with histology.

**Results:** TA-TMA was diagnosed at median 0.6 months (range 1 week to 3 years) post transplant. Donor specific antibodies (DSA) were present in 50%.

Histological diagnoses were: rejection with a humoral component (microcirculation injury (~9), consistent with CNI toxicity (~6); pure cellular rejection (Banff II) (~1)). Over 80% of patients with endothelitis (−lesion) had DSA at the time of TMA. In 6/9 cases showing rejection with a humoral component, TMA preceded the presence of microcirculation injury. This predrome of microthrombi with subsequent development of rejection could not be attributed to reduced immunosuppression.

4 patients lost their graft and 1 died with a functioning graft. There was no significant reduction in eGFR from baseline (45 vs 47 ml/min) in the remaining grafts.

**Conclusions:** We identified a complex overlap between microcirculation injury, DSA and endothelitis. The absence of microcirculation injury at the time of biopsy did not exclude a humoral process as the potential cause of TMA. The high prevalence of endothelitis suggests an endothelial insult which may be triggered by DSA in some cases, however TMA may arise in the absence of humoral pathology. The outcome was bimodal, i.e graft loss or recovery to baseline renal function. TA-TMA is a histological finding rather than a diagnosis; it may be an early sign of humoral pathology and should prompt serological investigations.

**FR-PO1044**

**Web-Based Virtual Microscopy to Validate Histologic Classification Schemes of Renal Diseases: Are We There Yet?**

A. Gasim, Harsharan Kaur Singh, Surya V. Seshan, Jennifer Melton, Volk Nickelet.

**1 Div of Nephrology, University of North Carolina, Chapel Hill, NC; 2Pathology, Weill Cornell Medical Center, New York, NY.

**Background:** Attempts are made to stage polyomavirus nephropathy (PVN) (A: early disease; B: florid; C: sclerosed). During the validation phase of the proposed PVN classification scheme, web-based recruitment of pathologists world-wide and virtual slide microscopy was used for interobserver reproducibility studies. How good are the results?
Methods: A) Web-based study on 19 PVN biopsies. 110 pathologists from 6 continents participated and used virtual microscopy to stage PVN. Four web-based mandatory study modules were designed: 1) introduction to PVN, 2) demographic data collection, 3) training module on PVN staging, 4) test set with 19 PVN cases. B) Conventional approach with exchange of glass slides on 190 cases: PVN disease staging on conventional glass slides from 9 centers was conducted. Outside results were compared to central review UNC data that served as “gold standard diagnoses” in both study groups.

Results: Evaluation of conventional glass slides versus web-based virtual microscopy generated similar scoring results. Only 2 significant differences were noted estimating mild degrees of intra renal polynucleovirus load levels and mild degrees (ci<1) of Banff fibrosis scores. These differences do not appear to play a major role in a validation study. In this web-based study group (A) results did not significantly differ among demographic groups or according to the level of expertise in pathology.

FR-PO1045
miRNA and mRNA Regulation in Donor and Follow-Up Kidney Biopsies Diagnosed with Acute Rejection and Acute Renal Failure
Julia Wülflingseder,1 Alexander Kainz,2 Judith Sunzenauer,1 Eva Toronyi,3 Robert M. Langer,1 Rainer Oberbauer.1,2
1Nephrology, KH der Elisabethinen, Linz, Austria; 2Nephrology, KH der Elisabethinen, Linz, Austria; 3Transplantation and Surgery, Semmelweis Univ Budapest, Hungary.

Background: We previously showed that miRNAs are involved in the regulation of post-transplant events such as biopsy confirmed acute rejection (BCAR) and acute renal transplant failure (ARF) however, only few studies examined the concomitant regulation of miRNAs and mRNAs in the same biopsy samples.

Methods: We prospectively collected zero-hour and follow-up kidney biopsies of renal allograft recipients. Of these 242 donor kidney biopsies, we identified ten biopsy sample pairs of each clinical condition (1) BCAR (2) ARF, and (3) management biopsies without pathology within ten days after TX and subjected to miRNA and mRNA genome wide analyses. ARF was defined as acute tubular necrosis. An integrative bioinformatics approach was chosen to combine differentially regulated miRNA and mRNA targets before and after transplantation. miRNA target prediction was verified by correlation analysis and experimental data. Target genes were further evaluated based on their functional annotation.

Results: Preliminary results show that allografts with acute renal failure exhibit a distinct molecular pattern compare to acute rejection and management biopsies on the mRNA and miRNA levels. T-cell and B-cell activation (p<0.002 and p=0.03, respectively) in the zero-hour biopsies, Integrin signalling pathway (p=0.008) in the follow-up biopsies and p53 pathway (p=0.02) and Ras pathway (p=0.04) in the development are significantly enriched pathways associated with ARF. A detailed analysis of the miRNAs and target genes will be presented at the meeting.

Conclusions: Based on these data we identified miRNAs as major molecular regulators of post-transplant events. mRNA-182 is mainly involved in the development of ARF and mRNA-155 was identified as a classifier of BCAR. These two miRNAs will be further investigated as potential diagnostic and/or prophylactic targets towards the prevention of ARF and BCAR.

FR-PO1046
Spleen Tyrosine Kinase (SYK) Expression in Renal Allograft Rejection

Background: Rejection is a leading cause of renal allograft failure. Spleen tyrosine kinase (SYK) has an important role in BCR and FcR immunoreceptor signalling, and may therefore represent a treatment target in rejection. In work previously reported by our group, SYK inhibition has shown efficacy in a rat model of renal allograft rejection. SYK expression, however, in experimental and clinical renal tissue has not been characterised.

Methods: We conducted immunohistochemical analysis for total and phosphorylated SYK in experimental renal allograft rejection (Brown Norway to Lewis rats) and in clinical renal allograft biopsies: normal surveillance biopsies, n=3; acute cellular rejection (ACR), 4; antibody-mediated rejection (AMR), 12.

Results: Experimental Samples: Normal rat tissue was positive for total SYK in distal tubules only. Rejecting kidney tissue showed positive staining for both total SYK and phosphorylated SYK, localised to cellular infiltrates in the interstitium. Clinical Samples: Staining for total SYK in normal surveillance biopsies (Fig A) was positive in distal tubules only, similar to that seen in normal rat tissue. Tubular infiltrates in ACR were positive for T-SYK in 4/4 patients (B). In AMR (total n=12), total SYK, positive cells were identified in 5/10 cases with glomerulitis (C) and 7/10 cases of interstitium fibrosis (D).

Conclusions: We believe this is the first report that SYK is expressed in various types of renal allograft rejection in patients, and localises to pathological lesions (tubulitis, glomerulitis, peritubular capillaritis). SYK is also expressed and activated (i.e. phosphorylated) in a rat model of renal allograft rejection that responds to SYK inhibitor treatment. We therefore believe that clinical studies targeting SYK in allograft rejection are warranted.

FR-PO1047
Decreased Expression of Mitochondrial Energy Generation and Antioxidant Response Genes in One Year Protocol Biopsies Is Associated with Poor Allograft Outcome
Diana Zepeda-Orozco,1 Richard H. Scheuermann,2 1Pediatrics, Univ of Iowa Carver College of Medicine, Iowa City, IA; 2Informatics, J Craig Venter Institute, San Diego, CA.

Background: Progression of chronic histological damage associated with subclinical inflammation are factors associated with poor allograft survival. The role of non-immunological pathways in the activation of this chronic injury-repair response have not been assessed.

Methods: To identify non-immunological genes and pathways that might influence long-term allograft outcome, we analyzed a public microarray dataset that included low risk kidney transplant recipients without rejection episodes who underwent a 1-year protocol biopsy. Three patient/sample groups were defined based on their histological findings: normal histology (n=25), interstitial fibrosis alone (IF; n=24), and interstitial fibrosis with tubulitis (IFT; n=16). IF+1 was associated with lower death censored graft survival and lower renal function compared to the IF and normal histology groups. We performed data normalization, data filtering, and statistical testing with ANOVA on the gene expression microarrays to discover differentially expressed genes in the sample groups.

Results: Clustering and gene ontology (GO) enrichment analysis identified significant co-clustering of genes with similar functional properties. The analysis showed downregulation of mitochondrion (p=0.02E-17) and mitochondrial part (p=1.75E-11) genes in the IF+1 group compared to the other two groups, including genes involved in generation of precursor metabolites and energy, and response to oxidative stress, as the most significant biological processes.

Conclusions: Allografts with histological evidence of inflammation and interstitial fibrosis are associated with lower graft survival and poor renal function. Through gene expression analysis, we have found evidence that inadequate mitochondria function, and an inappropriate antioxidant response may be important non-immune factors involved in chronic allograft injury that could serve as novel targets for therapeutic intervention.

FR-PO1048
IgA Nephropathy Recurrence after Transplantation: Altered IgA Glycosylation and Its CD89 Receptor as Biomarkers of the Disease and Effectiveness of Steroid Pulse Therapy for Recurrence
Laureline Berthelot,1 Thomas Robert,1 Thierry Tabary,1 Vincent Vuiblet,2 Moustapha Drame,3 Philippe Rieu,3 Renato C. Monteiro,1 Fatouma Toure,2 Olivier Toupane.2 1INSERM U699, INSERM, Paris, France; 2CHU Reims, CHU, Reims, France.

Background: IgA nephropathy (IgAN) is a leading cause of end-stage renal disease and kidney transplantation. However, recurrence of the disease is frequent after transplantation. We investigated the efficacy of steroid treatment and predictive value of three markers for IgAN recurrence: galactose deficient (Gd) IgA1, IgA anti-IgA autoantibodies and IgA-soluble (s) CD89 complexes.

Methods: Kidney transplanted recipients treated with IV pulse steroids therapy for IgAN recurrence (R, n=11) were compared to those without recurrence (NR, n=13). Gd-IgA1 and IgA complexes containing IgG and sCD89 levels were determined in serum collected before and after transplantation.

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

603A
Results: Proteinuria was markedly reduced by steroids treatment in R group (p < 0.001). Before transplantation, serum levels of Gd-IgA1 were significantly higher in R group compared to NR group (p < 0.001). Both groups had enhanced values of IgA-cSCD89 complexes compared to healthy controls, but values were lower in R group compared to NR (p < 0.001). The receiver-operating-characteristic (ROC) curve showed predictive power of each biomarker for IgAN recurrence (p = 0.003; p = 0.0002; p = 0.0001). In the R group, disease recurrence was associated with decreased serum Gd-IgA1 and IgA-cSCD89 complexes while IgA-cSCD89 complexes were significantly increased. Treatment with steroids restored levels of all 3 markers back to pre-transplantation level.

Conclusions: Pulse IV steroid therapy was an efficient and safe option for treatment of Gd-IgA1 and IgA-cSCD89 complexes containing IgG or cSCD89 were found as biomarkers of the disease recurrence.

Funding: Government Support - Non-U.S.

FR-PO1049

Prognosis of Transplant Glomerulopathy with Complete versus Incomplete Criteria for Chronic Active Antibody-Mediated Rejection

Julie Lesage, Real Noel, Jean-guy Lachance, Isabelle Lapointe, Eric Wagner, Olivier Desy, Isabelle Houde, Sacha A. De Serres. Renal Div, CHUQ L'Hôtel-Dieu de Québec, Univ Laval, Quebec, Canada.

Background: Transplant glomerulopathy (TG) is currently included in the Banff classification as a criterion in the diagnosis of chronic active antibody-mediated rejection (CAMR). We aimed to compare TG score (cG) in recipients with complete (cCAMR) and incomplete (iCAMR) criteria for cCAMR.

Methods: From 2005 to 2012, 915 kidney transplantations were performed at Seoul National University Hospital. Among them, twenty-six (2.8%) patients were diagnosed as CAMR according to Banff '05 criteria. We reviewed the clinical and immunological findings during the time of diagnosis and CAMR. In addition, the responses to the anti-rejection therapy were classified according to the change of serum creatinine level, donor specific antibody (DSA) titer, and proteinuria amount.

Results: The increases of serum creatinine, DSA titer, and proteinuria were the main indications of the antibody-mediated biopsy. The median time from diagnosis of CAMR after kidney transplantation was 8.8 ± 5.8 years. The mean number of human leukocyte antigen (HLA) mismatch was 2.5 ± 1.5. Twenty-six patients showed a progressive decline of serum creatinine (Scr) and the presence of TG with incomplete criteria for cCAMR. We used Cox models adjusted for Scr, recipient gender and donor characteristics.

Conclusions: Median time post transplant was 189m. Compared to controls, patients with TG had a higher Scr (1.3±0.1 vs. 2.1±0.1) and a higher HLA-DR mismatch (0.5±0.1 vs. 0.7±0.1). 61 patients with TG reached the endpoint (p < 0.001). The proportion of patients with isolated TG (DSJ-D4-cG), TG but incomplete cCAAMBR (DSJ and/or cG), and cCAAMBR (DSJ+cG) were 59, 33 and 8% respectively, whereas their adjusted HR for the endpoint were 7.0, 9.7, and 18.5 (all p < 0.01). TG score (cg) was also associated with the endpoint (HR 1.8, 95% CI 1.4-2.3; p < 0.01). A higher proportion of patients with TG that had their maintenance immunosuppression reduced or withdrawn (15 vs. 30%, p < 0.01), mostly CNI (8 vs. 20%, p < 0.01).

Conclusions: The prognosis of TG with incomplete criteria for cCAMR, which represents a majority of cases, is dismal, however it is not considered in the current Banff cohort of TG patients in relation with C4d and DSA.

Funding: Government Support - Non-U.S.

FR-PO1050

Clinical Phenotypes of Chronic Antibody-Mediated Rejection after Kidney Transplantation

Sunhwa Lee, Ran-hui Cha, Jung Pyo Lee, Dong Ki Kim, Yon Su Kim, Haejung Lee. Dept of Internal Medicine, Seoul National University Hospital.

Background: Chronic antibody-mediated rejection (CAMR) is a significant challenge for long-term graft survival over the last decade. The prognosis of CAMR is poor, but the clinical and immunological phenotypes of CAMR remain unclear.

Methods: From 2005 to 2012, 915 kidney transplantations were performed at Seoul National University Hospital. Among them, twenty-six (2.8%) patients were diagnosed as CAMR according to Banff '05 criteria. We reviewed the clinical and immunological findings during the time of diagnosis and CAMR. In addition, the responses to the anti-rejection therapy were classified according to the change of serum creatinine level, donor specific antibody (DSA) titer, and proteinuria amount.

Results: The increases of serum creatinine, DSA titer, and proteinuria were the main indications of the antibody-mediated biopsy. The median time from diagnosis of CAMR after kidney transplantation was 8.8 ± 5.8 years. The mean number of human leukocyte antigen (HLA) mismatch was 2.5 ± 1.5. Twenty-six patients showed a progressive decline of estimated GFR of 1.6 ml/min/1.73m² over 6 months using simple regression analysis. Nine patients were non-responders, 6 patients were stable disease, and 8 patients were responders, respectively. Seven patients had reached to end stage renal disease in 24 months after biopsy.

Conclusions: Kidney transplant patients with biopsy findings concerning for AbMR and undetectable HLA alloantibodies should be screened for anti-AT1R-AA. An excellent response with plasmapheresis and phosphatase inhibitors might improve AbMR recurrence. Gd-IgA1 and IgA complexes containing IgG or sCD89 were found in serum samples of patients with 9 episodes of AbMR and no detectible anti-HLA alloantibodies at the time of rejection were retrospectively screened for the presence of AT1R-AA. A commercial ELISA assay was used for detection of antibodies. A result of >170 U/mL was considered positive based upon prior published data.

FR-PO1052

Peripheral Blood Mononuclear Cells (PBMCs) Phosphoproteome Analysis to Investigate Antibody-Mediated Chronic Rejection (AMCR)

Maria Teresa Rocchetti, G. Stallone, Paola Pontrelli, F. Rascio, Marco Fiorentino, Anna Zito, Anna Giustapapa, Loreto Gusaldo, Gi Giordano. Dept Emergency and Organ Transplantation, Univ of Bari, Bari, Italy; Dept of Medical and Surgical Sciences, Univ of Foggia, Foggia, Italy.

Background: AMCR represents one of the main causes of kidney transplant failure. Specific markers for an early diagnosis of AMCR are currently missing. In the attempt to find potential diagnostic markers and to elucidate the signaling pathways involved in AMCR pathogenesis, we analyzed the PBMCs phosphoproteome profile to identify cellular signaling networks differentially activated in AMCR patients.

Methods: PBMCs were harvested from 6 biopsy-proven AMCR according to Banff 2005 criteria. Six renal transplant recipients with normal graft function and histology (CTRL), and 6 healthy subjects (CTRL). Phosphoproteins were isolated by precipitation with lanthanum ions, separated by 2-D gel electrophoresis and stained by Sypro Red. Image Master Software was used to standardize the PBMCs phosphoproteome map and to list the differentially expressed protein spots among the 5 groups. MALDI-TOF-MS/MS analysis was used to identify the phosphoproteins.

Results: 2-D gel electrophoresis of PBMC detected 554±68 (mean±SD) protein spots (CV=26%) differentially expressed in CTRL, 41±119 protein spots (CV=35%) in AMCR and 475±75 protein spots (CV=20%) in CTRL. We recognized, by densitometric analysis, a protein signature of 10 protein spots, corresponding to 4 proteins, which discriminated AMCR patients from CTRL and sin-CTRL and 4 protein spots whose density was increased in all transplant recipients compared to CTRL. Finally, 5 protein spots, corresponding to 2 proteins, distinguished CTRL from AMCR.

Conclusions: Our preliminary results suggest that PBMC phosphoproteome might help to distinguish biopsy-proven AMCR patients from healthy subjects and stable renal transplant recipients. In addition, the differentially phosphorylated protein spots may indicate potential therapeutic targets for AMCR.

Funding: Government Support - Non-U.S.

FR-PO1053

Medical Complication after Acute Humoral Rejection Treatment


Nephrology, Pathology, and Transplantation, National Institute of Medical Sciences and Nutrition S2, Mexico City, DF, Mexico.

Background: Treatment for acute humoral rejection (AHR) includes removal of circulating HLA-antibodies (HLAabs) by plasmapheresis (PP), neutralization of HLAabs with IVlg, rituximab (RTX), and Bortezomib (Bort) intended to decrease HLAabs-producing plasma cells derived from B-cells, as well as use of rATG looking to control the

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

Underline represents presenting author/disclosure.

604A
cellular component (or interaction between T- and B-cells). Some of them potentially could increase the complication rates. This study compare the rate of complications between different treatment protocols.

Methods: Between May 08 and Apr 13, we prospectively recruited all 60 patients who had AHR. Each event was handled as a separate treatment with a total of 97 treatments cycles in 60 patients. The histological description was made according to modified Banff 97 classification. DS-HLAabs were determined by Luminex single antigen bead assay (One Lambda).

Results: We included 60 KTR. Mean age 33.2±11.9; male gender 70%; first transplant 85%; living donor 76.7%; induction therapy 56.7%; maintenance triple therapy with Cs 99.9%. The most used treatment schemes were PP +IVIG + RTX (36.7%), PP + IVIG + RTX + BORTE (35%), PF + IVIG + BORTE (6.7%), others (21.6%). A 41.7% received more than one treatment (2-7). A 95% of the patients used PP, and 55% received Borte. There were no differences in graft survival when Borte, RTX, or IVIG were added to PP. Also, receive more than one treatment cycle, or the time after KT did not showed difference. There was 30 complication in 26 treatments. The most frequent complication were infections (11 events), hematologic (10 events), neuropathy (4 events), metabolic (2 events), and other (3 events). There was no relationship between type of treatment and kind of complications.

Conclusions: Most of the complications were like we expected. Only few of them were severe. Intensification of treatment after AHR is safe.

Funding: Government Support - Non-U.S.

FR-PO1054

ABO Antibody Removal of Plasmapheresis (PP) with Intravenous Immunoglobulin (IVIG) before ABO-Incompatible (ABO1) Kidney Transplantation: Single Center Experience Jeongyoum Ahn, Dong Ryong Lee, Byung Chang Kim. Medicine, Maryknoll General Hospital, Busan Catholic Univ, Busan, Republic of Korea; Laboratory, Medicine, Maryknoll General Hospital, Busan Catholic Univ, Busan, Republic of Korea.

Background: ABO1 kidney transplantation is an inevitable option to overcome serious organ shortage. There are few data on success rates of ABO antibody removal or relating to patients in who antibody removal fails. The purpose of this study was to evaluate the likelihood of achieving transplantation depending on ABO antibody titer.

Methods: 55 patients were enrolled between 2007-2012. We perform ABO1 kidney transplantation using anti-CD20 antibody, tacrolimus and PP with IVIG. The median antibody titer was 1:64 (Range 4-4096). Transplantation was preceded when the ABO titer reached ≤ 1:8. To determine the likelihood of achieving transplantation, the number of PP required to proceed transplantation and baseline ABO1 titer were analyzed.

Results: All 55 patients(100%) successfully completed transplantation after 5.75±4.3 PP with IVIG. Three patients did not reach target ABO1 titer and their achieved ABO1 titer at the time of transplantation were 1:16. (Initial ABO1 titer were 1:256 in one patient, 1:2048 in one patient, and 1:1024 in one patient). The median follow-up duration was 18.1 month (Range 0.9-71.8). The mean age was 45.8±9.9 year and 65.6% were female. The median ABO1 titer was 2 (Range 1-64) at 1 month posttransplantation and 4 (Range 4-128) at the last follow-up, respectively. The number of PP to reach an ABO1 titer of ≤ 1:8 was significantly correlated with baseline ABO1 IgG titer (r=−0.829, P < 0.001).

Conclusions: All 55 patients successfully preformed ABO1 kidney transplantation without failure to achieve transplantation. Three patients even failed to reach target titer at the time of transplantation and all were successfully transplanted. Though optimal ABO1 titer at the time of transplantation remains debatable, we carefully need to tailor our protocol with target ABO1 titer of greater than or equal to1:16 at the time of transplantation to expand kidney donor pool.

FR-PO1055

Graft Survival after ABO Incompatible Renal Transplantation–A Metaanalysis of Available Evidence Bernhard M W Schmidt, Anette Mell, Daniel Kayser. Dept of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; Dept of Pediatric Nephrology, Hannover Medical School, Hannover, Germany.

Background: ABO incompatible (ABO1) renal transplantation (rTx) is increasingly used to overcome the organ shortage. Smaller studies evaluating the outcome of ABO1 rTx showed no difference in outcome compared to controls, but may have been underpowered. Our aim was to provide a broader data pool by meta-analyzing the available studies.

Methods: We identified studies by searching Medline and the Cochrane library. Additional studies were identified by review of cited literature. Primary efficacy endpoint was probability of 1-year graft survival. Random effects model was used. Subgroup analysis was performed for studies using rituximab or not, meta-regression analysis was used to evaluate the impact of continuous variables.

Results: From 536 articles 17 reports including 23 patient groups with ABO1 rTx could be used for data retrieval. Analysis of all 23 patient groups revealed significantly worse 1-year-graft survival in recipients of an ABO1 graft (OR 0.37, 95% CI 0.25-0.56, p<0.001) than in controls. The studies showed relevant heterogeneity (I²=62.3, Q test p<0.001). In studies using rituximab 1-year-graft survival was also worse in ABO1 rTx (OR 0.34, 95% CI 0.16-0.77, p<0.01). Within these studies we detected no heterogeneity (I²=0, Q test p=89). However, we detected signs of publication bias suggesting that studies showing worse outcome of ABO1 rTx have not been published.

Conclusions: Metaanalysis of the available evidence showed worse 1-year-survival for recipients of an ABO1 graft. This information should be acknowledged when informing patients about an ABO1 rTx. However, we should also acknowledge that in real life the right comparator is not ABO compatible living related donorship (as used in most studies) but waiting for a deceased donation for several years.

FR-PO1056

Immunoochemical Characterization of Light Chains in Posttransplant IgA Nephropathy Yasuhiro Otsuka, Asami Takeda, Shinichi Sueta, Keiji Horik, Daijo Inaguma, Yoshikiko Watarai, Kunio Morozumi. Kidney Center, Nagoya Daini Red Cross Hospital, Nagoya, Aichi, Japan.

Background: IgA nephropathy (IgAN) is a clinically and histologically diverse glomerular disease characterized by mesangial IgA deposits. The nature of the light chains in immunofluorescence (IF) studies in IgAN remains obscure, although there are a few reports that lambda light chains are found predominantly in the mesangial deposits in IgAN. In particular in posttransplant IgAN, some cases display poor prognosis, some cases can be diagnosed only by IgG deposits in the mesangial area, and the nature of the light chains is unknown.

Methods: In order to examine the immunoochemical characterization of light chains in posttransplant IgAN, direct IF studies using polyclonal rabbit anti-human kappa and lambda light chains were performed from consecutive 30 native renal biopsies of IgAN (native IgAN) and 18 cases of posttransplant IgAN, excluding Henoch-Schönlein Purpura.

Results: The age at the biopsy of native IgAN and posttransplant IgAN were 28.0±21.3 and 35.9±12.2, respectively. The diagnosis of posttransplant IgAN were made from 3 weeks to 15 years after transplantation. In native IgAN, both kappa and lambda light chains were detected in 57%. In 23% of native IgAN, both kappa and lambda light chains were detected in 11 of 18 cases, and 8 of 11 were strongly positive for lambda light chains. 2 of 30 native IgAN were negative for kappa and lambda light chains. The percentage of both kappa and lambda light chains negative cases were significantly higher in posttransplant IgAN (p<0.0091, Fisher’s exact test).

Conclusions: The nature of the light chains in posttransplant IgAN is not the same as the one in native IgAN. Our results suggest that the mechanism responsible for the development of IgAN is different from native IgAN and posttransplant IgAN.

FR-PO1057

Decreased Total Intestinal Inflammation with Higher Mycophenolate Mofetil Dose after Kidney Transplantation Karlo K. Mihovilovic, Petar Senjic, Bojana Maksimovic, Danica Galesic Ljubanovic, Renata Zunic, Bisera Palfi, Mladen Knock. Clinical Hospital Merkur, Zagreb, Croatia; Clinical Hospital Dubrava, Zagreb, Croatia; Clinical Hospital Zagreb, Zagreb, Croatia.

Background: We have recently found that higher average mycophenolate mofetil (MMF) dose in during first posttransplant year was associated with decreased progression of interstitial fibrosis and tubular atrophy during first posttransplant year in kidney transplant recipients. In the present study we sought to evaluate effect of MMF dose on total interstitial inflammation score at one year.

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

605A
Methods: This is a single-center retrospective study in which 67 kidney, or kidney-pancreas recipients with 12 month protocol biopsy were included. Patients with recurrence of glomerulonephritis and with BKV nephropathy were excluded from the analysis. Immunosuppression consisted of anti-IL2 induction, with tacrolimus or cyclosporine and MMF ± steroid maintenance. During 2007-2010 MMF was dosed in our center according to C0 monitoring, which led to its dose dispersion (1000-4000 mg/day). Total interstitial inflammation (ti score) and interstitial fibrosis (ci score) were determined according to Banff classification. Creatinine clearance (CrCl) was estimated by the Cockcroft-Gault formula.

Results: Recipients, were 44.75 ± 12.34 y/o, 65 percent of them were male. There were 20 living donor transplantations. At 12 months posttransplant mean MMF dose was 2205 ± 627 mg/dl, eCLCr 62.1 ± 16.4 ml/min, ci score 0.87 ± 0.78 and ti score 0.72 ± 0.88. Average MMF dose during first posttransplant year was 2238 ± 571 mg. There was positive correlation between 12 months ci and ti score (r = 0.716, p < 0.001). Both, ci (r = 0.401, p < 0.001) and ti score (r = 0.319, p < 0.01) were negatively correlated with MMF dose at 12 months. Similarly, there was a negative correlation of average MMF dose over first posttransplant year with ci (r = 0.337, p < 0.01) and ti score (r = 0.250, p < 0.05). MPA concentration (C0) at either 12 months, or 1 year average, as well as respective tacrolimus concentrations did not correlate with 12 month ci or ti scores.

Conclusions: Higher MMF dose during first year posttransplant may be associated with better kidney allograft histology and less inflammation.

FR-PO1058
Basiliximab versus Low Doses of Thymoglobulin as Induction Therapies in Kidney Transplant Recipients
Daniel Perez-Vega,1 Benjamin Gomez-Navarro,1 Enrique Rojas-Campos.2
1Dept of Nephrology and Organ Transplant Unit, Hospital de Especialidades, CMNO, IMSS, Guadalajara, Jalisco, Mexico; 2Medical Research Unit in Renal Diseases, Hospital de Especialidades, CMNO, IMSS, Guadalajara, Jalisco, Mexico.

Background: Induction therapies such as Basiliximab (BSX) and Thymoglobulin (rATG) are associated with lower incidence of acute rejection in kidney transplant recipients (KR) but there is still conflicting data regarding the outcomes of these agents specially comparing low dose schemes of rATG versus an Interleukin 2 receptor antagonist.

Methods: The aim of the study is to show the incidence of acute rejection (AR), adverse effects and the graft survival at 12 months with the use of two different induction therapies in a cohort of 225 KR that were prospectively analyzed in 2 groups according to the induction agent: group 1 with 125 KR that received BSX (20mg in day 0 and day 4), group 2 with 100 KR that received rATG in a low dose scheme (0.6 to 1.2mg/kg in days 0 to 4). The primary end point was the incidence of biopsy proven rejection and graft survival. The secondary end points were renal function, adverse effects and infections.

Conclusions: A deferred pre-emptive switch over from CNI to SRL safely improves renal function and Treg population at 6 months in living donor kidney transplant recipients.

FR-PO1060
Defered Pre-Emptive Switch from Calcineurin Inhibitor to Sirolimus Leads to Improvement in GFR and Expansion of T Regulatory Cell Population
Dinesh Bansal,1 Vivekanand Jha,1 Vinay Sakhuja,1 Mukut Minz,2 Ashok Kumar Yadav.1 1Nephrology, PGIMER, Chandigarh, India; 2Transplant Surgery, PGIMER, Chandigarh, India.

Background: Measures to prevent chronic calcineurin inhibitor (CNI) toxicity have included limiting exposure by switching to sirolimus (SRL). SRL may favorably influence T regulatory cell (Treg) population. This randomized controlled trial compares the effect of switching from CNI to SRL on GFR and Treg frequency.

Methods: In this prospective open label randomized trial, primary living donor kidney transplant recipients on CNI-based immunosuppression were randomized to continue CNI or switched to SRL 2 months after surgery; 29 were randomized to receive CNI and 31 to SRL.

Conclusions: In most women with allograft kidney, renal function was slightly improved during pregnancy and returned to previous level after delivery. To maintain therapeutic blood level, about 20–25% dose elevation of tacrolimus and cyclosporine should be considered.
FR-PO1061

Intensified Dosing of Mycophenolate in African American Renal Transplant Recipients Does Not Reduce Rejection or Graft Loss
Jillian Leigh Descourroux,1 David Hager,1 Glen E. Levenson,2 Arjang Djamali,2 Luis A. Fernandez,2 1Pharmacy, Univ of Wisconsin Hospital and Clinics, Madison, WI; 2Surgery, Univ of Wisconsin Hospital and Clinics, Madison, WI.

Background: Intensified mycophenolate dosing strategies have been proposed in African American (AA) renal transplant recipients to reduce rates of acute rejection, graft loss and to improve survival. This study evaluated the efficacy of intensified dosing of mycophenolate in a cohort of AA renal transplant recipients.

Methods: Adult AA renal allograft recipients (n=247) transplanted between 1/1/2002 - 12/31/2011 were divided as follows: group A (n=128) had a dose reduction in mycophenolate mofetil (MMF) to <3 g/day or mycophenolate sodium (MPS) to <2160 mg/day within 3 months post-transplant; group B (n=119) remained on ≥MMF 3 g/day or ≥MPS 2160 mg/day at 3 months post-transplant. The primary outcome was a composite of suspected rejection or treatment failure. Secondary endpoints included patient (PS) and graft survival (GS); death censored graft survival; graft function as measured by estimated glomerular filtration rate (eGFR) at 1 month, 6 months, 1, 3 and 5 years; and overall infection.

Results: Baseline characteristics did not vary between groups except the number of primary renal allografts was greater in group B (88.2% vs. 76.6%, p=0.03). A MMF or MPS dose reduction by 3 months post-transplant occurred in 51.8% of patients (n=128). No MMF or MPS dose reduction by 3 months post-transplant occurred in 51.8% of patients (n=128). No MMF or MPS dose reduction by 3 months post-transplant did not have improved efficacy or an increased risk of infectious complications. These results do not support the use of MMF >2000 mg/day or MPS >1440 mg/day.

FR-PO1062

Effect of Basiliximab Induction Therapy in Living Donor Renal Transplantation
Flávia Oliveira, Irene L. Noronha. Nephrology, Univ of Sao Paulo, Brazil.

Background: The beneficial effects of induction therapy with basiliximab in kidney transplantation with deceased donors has been extensively confirmed, but limited data are available for transplantation with living donors. The aim of this study was to analyze the impact of basiliximab in patients with HLA-haploidentical living donor kidney transplantation compared with no induction.

Methods: Primary kidney transplantation (n=74) receiving calcineurin inhibitor+mycophenolate+steroids were divided into 2 groups: basiliximab (n=34) and no induction (n=40). The primary endpoint was the occurrence of biopsy proven acute rejection (BPAR) at 1 year post-transplantation (post-Tx). Secondary endpoints included patient and graft survival at the 1st and 5th year, renal function and adverse events at 1 year post-Tx. Secondary endpoints included patient and graft survival at the 1st and 5th year, renal function and adverse events at 1 year post-Tx. Secondary endpoints included patient and graft survival at the 1st and 5th year, renal function and adverse events at 1 year post-Tx.

Conclusions: African American renal transplant recipients remaining on intensified dosing of mycophenolate at 3 months post-transplant did not have improved efficacy or an increased risk of infectious complications. These results do not support the use of MMF >2000 mg/day or MPS >1440 mg/day.

FR-PO1063

Predictors of Diabetes after Kidney Transplant
Maria P. Martinez Cantarin,1 Scott W. Keith,2 Bonita E. Falkner.1 1Medicine-Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA; 2Pharmacology, Thomas Jefferson Univ, Philadelphia, PA.

Background: New Onset Diabetes After Kidney Transplantation (NODAT) is a highly prevalent complication after solid organ transplantation and is associated with worse transplant outcomes including graft loss and patient death. The aim of this study was to determine if an inflammatory phenotype is associated with development of diabetes post-transplantation.

Methods: End stage kidney disease patients that did not have diabetes were recruited from Thomas Jefferson University Transplant program before kidney transplantation. Participant’s plasma was obtained pre-kidney transplantation and at three to six months post-transplantation. Inflammatory and anti-inflammatory cytokines including IL-8, IL-6, TNF alpha, CRP, MCP-1, total adiponectin and high molecular weight (HMW) adiponectin were assayed by ELISA. Participants were followed prospectively for 1 year and monitored for development of NODAT. Unadjusted comparisons of the distributions of variables between study groups were made by the Kruskal-Wallis test or the Fisher’s exact test. Logistic regression was used to determine a model of the risk of NODAT.

Results: Of the 32 participants enrolled in the study, 11 developed NODAT using ADA criteria. Participants that develop NODAT had the same median age, BMI and proportion of male/females than participants that did not develop NODAT. Transplant patients that develop NODAT had lower total adiponectin, lower HMW to adiponectin ratio and higher TNF alpha levels pre-transplant. After transplant, inflammatory cytokines (IL-8, CRP and HGF) increased in both groups but transplant patients that develop NODAT maintained higher IL-6, IL-8 and CRP and lower HMW to adiponectin ratio. The odds of NODAT were significantly increased by almost 5-fold for each half-unit increase in log TNF-α (OR = 4.90, p = 0.04) pretransplant after adjusting for age in years (OR = 1.10, p = 0.07).

Conclusions: Our data suggest that a phenotype of increased inflammation with lower adiponectin levels pre-transplant could be associated with the development of diabetes after kidney transplant and that TNF alpha may be a predictor of NODAT.

Funding: Private Foundation Support

FR-PO1064

Low Vitamin D and Adverse Allograft Outcomes in Kidney Transplant Recipients
Yoshitsu Ohi,1 Takayuki Hamano,2 Naoaishigehuichamaru,1 Kodo Tomo,3 Nishikho Fujii,1 Kota Matsu,1 Hiroaki Rakugi,1 Shiro Takahara,1 Yoshitaka Isashita,1 Yoshihara Tsukahara.1 1Dept of Geriatric Medicine & Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Dept of Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 3Dept of Advanced Technology for Transplantation, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

Background: Low vitamin D is highly prevalent complication after solid organ transplantation and is associated with worse transplant outcomes. Vitamin D has potential immunomodulatory effects.

Methods: In a prospective cohort of 264 ambulatory KTx recipients, we measured the baseline 25-hydroxyvitamin D (25D) levels and examined its association with (i) annual decline in estimated glomerular filtration rate (eGFR), (ii) the composite event of a 50% increase in serum creatinine, end-stage renal disease, or death; and (iii) rejection episodes, with intravenous methylprednisolone ≥250 mg (IV-MP) as the index.

Results: Multivariate cubic spline analysis showed that the serum 25D levels had an almost linear relationship with annual eGFR decline. With vitamin D deficiency (≥20 ng/mL) as the reference, inadequacy (≥12 and <20 ng/mL) and deficiency (<12 ng/mL) showed a significant dose-dependent association with a higher risk of the composite event and IV-MP as the multivariate Cox regression analyses. These findings were confirmed in the propensity-matched cohort independent of 30 potential confounders. Further, time after KTx was a significant effect modifier for the association of serum 25D levels with annual eGFR change and IV-MP. Stratified analyses showed pronounced relationships in patients with <10 years since KTx (1.04 [95% CI, 0.26–1.83] mL/min/1.73 m² per 10 ng/mL of serum 25D levels in the analysis for annual eGFR decline), but no significant associations in patients with ≥10 years since KTx.

Conclusions: Low vitamin D predicts adverse allograft outcomes, and vitamin D supplementation early after KTx may improve patient outcome.

Funding: Private Foundation Support

FR-PO1065

Correlation of Kidney Transplant Referral with Transplant Rates at the Dialysis Facility Level
Rachel E. Patzer,1 M. Ahinee Amamoo,2 Jenna Krisher,2 1Emory Transplant Center, Atlanta, GA; 2Southeastern Kidney Council, Raleigh, NC; 3Georgia Regents, Augusta, GA; 4Piedmont Transplant Institute, Atlanta, GA.

Background: Variability in dialysis facility-level kidney transplant (KTx) rates have been reported, but little is known about whether KTx referral rates vary by facilities and the extent to which referral rates are correlated with transplant rates.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Methods: Through the Southeastern KTx Coalition of End Stage Renal Disease Network 6, we collected data on all patient referrals to the 3 adult Ktx centers in Georgia (GA) from 2008-2011 and calculated crude referral rates and standardized referral ratios (SRR) -- the number of observed divided by the number of expected Ktx referrals -- for each GA dialysis facility using a 2-stage Cox model. Pearson correlation coefficients (r) were calculated to examine correlations between referral and transplant rates, and the SRR and the standardized transplant ratio (STR).

Results: 276 dialysis facilities referred 7,180 ESRD patients for transplant in GA from 2008-2011. The median age was 52 years (IQR: 41, 61), 56.6% were male, and 68.5% were African American. The median annual KTx referral rate at the dialysis facility level was 16.6% (IQR: 9.7%, 22.2%) over 4 years. We found a weak correlation between the SRR and STR (r=0.16, p=0.0175).

Figure. Standardized Referral Ratios and Standardized Transplant Ratios among Dialysis Facilities in Georgia (2008-2011)

There was a moderate correlation between crude referral and transplant rates (r = 0.25, p=0.0001) that was higher among facilities with 25+ patients (r=0.33, p<0.0001).

Conclusions: Crude referral rates and SRR are correlated with KTx rates. Quality improvement interventions targeting facilities with lower than expected KTx referrals may improve patient access to KTx. SRR may be used to help launch a surveillance system throughout ESRD Network 6 to regularly measure KTx referral.

Funding: Other NIH Support - National Institute on Minority Health and Health Disparities

FR-PO1066

Renin Gene Mutation Causing Anemia and Kidney Injury in Childhood
Faris O. Hashim,1 Anthony J. Bleyer,2 Stanislav Knouch,3 Richard E. Neiberger.1
1Pediatric Nephrology, Univ of Florida, Gainesville, FL; 2Internal Medicine-Nephrology, Wake Forest School of Medicine, Winston-Salem, NC; 3Institute of Inherited Metabolic Disorders, Charles Univ, Prague, Czech Republic.

Background: REN mutations produce rare but treatable conditions. There have been only five reported cases of mutations in the REN gene encoding renin causing chronic kidney disease (CKD) [1, 2]. Here we report a new family with this condition.

Methods: A 5 year old girl presented for evaluation of a hemoglobin of 8.8 g/dl and a serum creatinine (Cr) level of 0.5 mg/dl (eGFR 86 ml/min/1.73m²). The patient’s mother had undergone a kidney biopsy showing medullary cystic kidney disease. On physical examination, blood pressure was 87/56, height 101 cm (10th percentile) and weight 14.3 kg (3rd percentile). Her examination was unremarkable. Urinalysis was normal. The serum uric acid (SUA) was 9.2 mg/dl (normal for age <6 mg/dl) with a 24 h urate excretion of 125 mg/day (normal <175 mg/day) and fractional urate excretion 6.5 % (normal 18±5 %).

Conclusions: A renal ultrasound showed normal size kidneys. A mutational analysis of the REN gene revealed three different amino-acid changes. One was a novel stop codon (p.E189X), which decreased her UAC to 7.4 mg/dl. The mother developed acute kidney injury at 17 years after running in a race. A kidney biopsy revealed medullary cystic kidney disease. She had minimal proteinuria and a SUA concentration of 11 mg/dl. Her eGFR was 38ml/min (Cr 2 mg/dl) at age 32 years.

Conclusions: This child presented with a classic case of a REN mutation, anemia, mild hyperkalemia, mild hypertension, and CKD. The acute kidney injury that occurred in her mother has also been noted to occur in patients with this condition. Recognition of REN Gene Mutation allows prompt intervention to treat anemia, hyperkalemia, hyperuricemia, and avoid acute kidney injury.


FR-PO1067

Implications of an Unusual Diagnosis: Uromodulin-Associated Kidney Disease
Jonathan A. Bolanos,1 Anthony J. Bleyer,2 Christina M. Yuan,1 John Stephen Thurlov.1 1Wake Forest Natl Medical Center, Bethesda, MD; 2Wake Forest Univ School of Medicine, Winston Salem, NC.

Background: Uromodulin-Associated Kidney Disease (UAKD), synonymous with medullary cystic kidney disease type 2 and familial juvenile hyperuricemic nephropathy, is a rare autosomal dominant interstitial kidney disease caused by mutations in the UMOD gene encoding uromodulin (Tamm-Horsfall protein). These mutations result in defective assembly and subsequent accumulation of mutated uromodulin in tubular cells, leading to cell atrophy and death.

Methods: A 35 y/o white male presented for transplant evaluation. He had suffered from slowly progressive chronic kidney disease (CKD) for over a decade and had a 4 year history of recurrent gout. His father and paternal uncle had gout in their 30s, followed years later by ESRD attributed to glomerulonephritis. His paternal grandfather died in his 30s from an uncertain cause. Urinalysis was bland with no proteinuria or hematuria, and renal imaging was unremarkable. Mutational analysis of exons 4 and 5 of the UMOD gene (Athena Diagnostics) by PCR amplification identified a missense mutation resulting in a substitution of tyrosine for cysteine at codon 148, a common mutation associated with UAKD. Due to this finding, family members were contacted, and three living family members have since been diagnosed and others are undergoing evaluation.

Conclusions: The diagnosis of UAKD requires a careful family history in patients with a bland urine sediment, gout, and slowly progressive kidney disease. Correct diagnosis of an individual often leads to diagnosis for many family members. As in the current case, UMOD analysis can then be performed in potential living-related kidney donors to improve safety and quality of donation. Genetic counseling, gout treatment, and CKD management, including renal transplant evaluation, are the cornerstones of therapy for UAKD. The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Department of the Army, the Department of the Navy, the Department of Defense, nor the US Government.

FR-PO1068

Tri-Allelic Inheritance of NPHS1 Gene in Infantile-Onset Steroid-Resistant Nephrotic Syndrome: A Case Report
Yusuke Kumagai,1 Hiroaki Uda,1 Koichi Nakashima,2 Norishige Yoshikawa,2 Ryota Kurayama,1 Kunimasa Yan,2 Akira Ashida,4 Daisuke Yamamoto,5 Michio Nagata,2 Rika Fujimaru.1 1Pediatrics, Osaka City General Hospital, Osaka, Japan; 2Pediatrics, Wakayama Medical Univ, Wakayama, Japan; 3Pediatrics, Kyorin Univ School of Medicine, Tokyo, Japan; 4Pediatrics, Osaka Medical College, Osaka, Japan; 5Biomedical Computational Computing, Osaka Medical College, Osaka, Japan.

Background: Recently, NPHS1 mutations have been identified as a cause of steroid-resistant nephrotic syndrome (SRNS) in all age groups and milder courses of the disease. We report a case of infantile-onset SRNS associated with a severe mutation and two mild variants, which resulted in the tri-allelic hit of the NPHS1 gene.

Methods: A girl was diagnosed with SRNS at 9 months of age. A renal biopsy showed glomerulomnophrropy and severe interstitial fibrosis without focal glomerulosclerosis. Electron microscopy revealed effacement and fusion of podocyte foot processes. In immunohistochemistry, the expression of nephrin protein had partially decreased, while podocin showed along the glomerular capillary wall. Genetic analysis of the NPHS1 gene revealed three different amino-acid changes. One was a novel stop codon (p.E189X), and the others (p.P206T and p.R800C) had previously been reported on either missense variants or polymorphisms. No mutation of NPHS2 was detected. Mutation screening of two consanguineous healthy parents revealed that the E189X and R800C were paternal origin and that the P206T was maternal which was predicted to be a disease-causing mutation.

Conclusions: Based on our molecular model analysis, the R800C substitution also could be classified as a mild missense variant, probably leading to conformational changes in nephrin structure. After a year of follow-up, she had a mild clinical course because of the disappearance of edema but persistent proteinuria with administration of an angiotensin receptor blocker.

FR-PO1069

Very Early Onset of Alport Syndrome in a Two Year Old Lithuanian Boy with Additional Polymorphisms in Nphrin- and Podocin-Genes
Jenny Kruegel,1 Matthias Kettwig,2 Hermann-Josef Groene,3 Mato P. Nagel,4 Hildegard F. Zappel,1 Oliver Gross. 1Pediatrics, Univ Medicine Goettingen, Goettingen, Germany; 2Pediatrics, Univ Medicine Goettingen, Goettingen, Germany; 3Cellular & Molecular Pathology, German Cancer Research Center, Heidelberg, Germany; 4Nephrology & Metabolic Medicine Goettingen, Goettingen, Germany.

Background: Some patients with familial benign hematuria develop early onset of renal failure despite a “benign” heterozygous mutation in type IV collagen genes (COL4A3/4/5). According to our hypothesis, polymorphisms in other genes of the glomerular filtration barrier can aggravate the clinical course of glomerular diseases such as Alport syndrome.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Methods: A two year old boy with macrohematuria and 1.2 g/gCr in proteinuria was referred to our clinic for further evaluation. His non-consanguinous parents originate from Lithuania and had no history of renal diseases. Renal biopsy revealed ultrastructural changes typical for Alport syndrome. However, referred to the patient’s age, an unusual severe splitting and thickening of the glomerular basement membrane (GBM) with prominent focal segmental glomerular sclerosis was found. Additional defects in podocyte genes were suspected. The diagnosis of X-chromosomal Alport syndrome was confirmed by sequencing. Direct sequencing of NPHS1 (Nphs1) and NPHS2 (Podocin) resulted in additional Nphs1- and Nphs2-polymorphisms. Interestingly, the COL4A5 mutation and Nphs2 polymorphism were de novo in the boy, with a heterozygous Nphs1 polymorphism in the father. Ramipril therapy was started and proteinuria gradually dropped within 12 months below 0.5g/gCr.

Conclusions: In conclusion, Podocin-polymorphisms can aggravate heterozygous COL4A5 mutations – as described previously in patients with familial benign hematuria. In our patient, polymorphisms of Nphrin and Podocin might exacerbate Alport-pathogenesis. This points towards a possible synergistic role of genes coding for GBM- and slit-ditragm-proteins in the pathogenesis of glomerular kidney diseases. The podocyte-interaction between GBM and slit diaphragm is currently investigated by our group using a COL4A5-/- Nphs2-/-;014 mouse model.

FR-PO1070
Diagnostic Difficulty in Alport Syndrome Jennifer H. Adam, Katrina M. Wood, John Andrew Sayer. 1,2 Dept of Renal Medicine, Freeman Hospital, Newcastle upon Tyne, Tyne and Wear, United Kingdom; 3Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, Tyne and Wear, United Kingdom.

Background: Alport syndrome is an inherited disease that causes progressive glomerular damage, often in association with sensorineural deafness. The histological diagnosis of Alport syndrome can present a challenge as features on light microscopy can be non-specific and ultrastructural lesions may not be apparent until later in life.

Methods: Family 1 A 26 year old man presented with hypertension, haematuria, proteinuria and sensorineural deafness. His renal biopsy revealed light microscopy features consistent with FSGS. Electron microscopy (EM) revealed pathognomonic splitting of the glomerular basement membrane suggesting Alport syndrome. His mother had undergone a renal transplant eleven years previously. A review of her native renal biopsy revealed mesangial proliferative changes on light microscopy. There were no glomeruli in EM or IMF specimens. These mesangial changes on light microscopy had, over time, been misdiagnosed as a result of a failed attempt to induce renal allograft rejection. In later life the proband developed CKD. Had his mother’s initial diagnosis been accurate, his renal biopsy could have avoided a familial difficulty.

Family 2 A 47 year old woman presented with haematuria, proteinuria and abnormal renal function. Her renal biopsy showed mild mesangial proliferative changes. EM of glomeruli was not available. She also had high frequency hearing loss and a family history of renal disease. Genetic analysis confirmed that the proband and two of her daughters with microscopic haematuria were heterozygous for a pathogenic mutation in COL4A5 known to be associated with autosomal dominant Alport syndrome.

Conclusions: These cases demonstrate that a diagnosis of Alport syndrome can elude nephrologists in patients with non-specific histological changes on light microscopy, particularly when EM is not available. It also highlights the important role of molecular genetics in confirming a diagnosis of Alport syndrome. We stress the importance of eliciting a family history of renal and extra-renal disease in all patients.

FR-PO1071
Early Bilateral Nephrectomy as Rescue Therapy for Autosomal Recessive Polycystic Kidney Disease with Progressive Massive Nephromegaly in Early Infancy Tamara Mallett, Emma O’Hagan, Karl McKeever. Dept of Paediatric Nephrology, Royal Belfast Hospital for Sick Children, Belfast, Co Antrim, United Kingdom.

Background: The management of neonatal Autosomal Recessive Polycystic Kidney Disease (ARPKD) complicated by severe pulmonary insufficiency presents complex clinical challenges. Where massive nephromegaly exists, early bilateral nephrectomy, supportive peritoneal dialysis (PD) and early aggressive nutrition can improve survival. Consensus is lacking as to the optimal timing and indeed role of nephrectomy, with decision making driven by the patient’s clinical condition and expertise of centre. We report an infant with ARPKD requiring PD and survival at 9 months following early bilateral nephrectomy.

Methods: A male infant diagnosed antenatally with ARPKD and third trimester oligohydramnios, was born at term with pulmonary insufficiency requiring high pressure ventilation. He had massive bilateral nephromegaly with renal insufficiency and hypertension. A PD catheter was inserted on day 15 and dialysis commenced in view of progressive renal impairment, oliguria and respiratory failure. Unilateral nephrectomy was performed at 2 months of age in view of massive nephromegaly, high frequency oscillatory ventilator-dependence and failure to tolerate enteral nutrition. Recovery was complicated by respiratory compromise secondary to increasing nephromegaly. Contralateral nephrectomy was performed 11 days later allowing withdrawal of ventilatory support and establishment of enteral nutrition and PD. The infant is now 9 months old on nocturnal PD, complicated by a solitary episode of bacterial peritonitis. He has no respiratory support and growth is optimised by nasogastric feeding. Development is moderately delayed and there is evidence of early hepatic involvement.

Conclusions: Early bilateral nephrectomy should be considered as a potential rescue therapy for infants with ARPKD where progressive massive nephromegaly results in ventilator-dependent pulmonary insufficiency and failure to establish enteral nutrition.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
FR-PO1074

Incompatible Renal Transplantation Can Improve HLA-Matching in Children

Anjali B. Navak1 Robert B. Ettinger1 Gerald S. Lipshtiz2 Eileen W. Tsai1 1Pediatric Nephrology, Mattel Children’s Hospital, UCLA, Los Angeles, CA; 2Pediatric Radiology, UCLA, Los Angeles, CA; 3Dept of Surgery, UCLA, Los Angeles, CA.

Background: It is important for pediatric (Ped) patients (pt) to get expedited kidney (Kid) transplants (Tx) to resolve uremic symptoms and grow. Also, due to long projected life-years, it is optimal for them to get well-matched Tx to minimize the chances of long-term sensitization. Such sensitization has been reported to make second Tx difficult in these pts. In North America ped Kid transplants are largely dependent upon the use of deceased donor organs making it challenging to identify timely well matched Tx. One solution is to utilize ABO incompatible (ABOi) Txs and, if necessary, paired donation.

Methods: In the past year, we adopted this approach for 3 pts. (age 2-13 yrs) who got transplanted across the ABO barrier with Tx’s well matched for HLA A, B, DR and DQ.

<table>
<thead>
<tr>
<th>Table 1. Donor and Patient HLA Typing</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>Patient 1</td>
</tr>
<tr>
<td>Patient 2</td>
</tr>
<tr>
<td>Patient 3</td>
</tr>
<tr>
<td>Couple 1</td>
</tr>
<tr>
<td>Couple 2</td>
</tr>
<tr>
<td>Couple 3</td>
</tr>
</tbody>
</table>

Conclusions: Pts received pre-Tx immunomodulation (anti-CD20 antibody, intravenous immunoglobulin, and plasmapheresis) until an acceptable isografting (IG) titer < 1:8 was reached at Tx. IG titers were monitored, and postoperative plasmapheresis was initiated if titers increased. We utilized standard immunosuppression with anti-thymocyte globulin induction, prednisone, MMF, and tacrolimus. All grafts functioned well 3-12 mos post-Tx, without development of DSAs. Particularly notable was a 13 yo male with > 90% CPRA due to a previous failed transplant, and had been waiting on the deceased donor list for 2 years. He received an ABOi paired exchange Tx donor with 5/6 HLA match; the Tx has an eGFR of >90mL/min/1.73 m2 at 1 yr post Tx. Both pt and renal allograft survival to date is 100%.

Conclusions: These results highlight the safety and efficacy of ABOi Txs in Ped Kid Txs. Combining the paired exchange program with ABOi Txs can improve HLA matching, minimize wait times, and enhance allograft survival.

FR-PO1075

Perinephric Fluid Collection in a Girl with Dandy Walker Malformation: Mystery Revealed

David M. Shafrazi1 Rajesh Raina1 Katherine MacRae Dell1 Jonathan Ross2 1Dept of Pediatrics, Nephrology, Univ Hospitals, Rainbow Babies and Children’s Hospital, Cleveland, OH; 2Dept of Pediatric Surgery, Univ Hospitals, Rainbow Babies and Children’s Hospital, Cleveland, OH.

Background: Renal lymphangiectasia, a developmental malformation of the renal lymphatics, is a rarely reported clinical entity. Hematuria, flank pain and abdominal pain are usually the presenting symptoms. It is described in the limited literature as “self-resolving”. It typically resolves without intervention. Several medical treatments, including those used in our patient, have been described in case reports in the literature. However, none were successful in this case. Whether surgical intervention resulted in resolution or was coincidental is unknown.

Funding: Private Foundation Support

FR-PO1076

Successful Treatment for Short Stature in a Pubertal Kidney Transplant Recipient Using a Combination of Gonadotropin Releasing Hormone Agonist and Growth Hormone

Hideki Matsumura1 Akihiko Shirasu1 Hyogo Nakaura1 Akira Ashida1 Motooshi Hattori2 Hiroshi Tama1 1Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan; 2Pediatric Nephrology, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Despite various developments in the management of children with CKD, including the use of recombinant human growth hormone (rhGH), achieving an adequate final body height remains a challenge for such children, especially around the time of puberty. Here, we report a pubertal kidney transplant recipient with short stature who was treated with a combination of gonadotropin releasing hormone analog (GnRHa) and rhGH.

Methods: We treated an 18-year-old girl with ESRD due to Senior-Loken syndrome. Peritoneal dialysis had been started at the age of 8 years. Her height standard deviation score (SDS) had deteriorated, becoming -3.5 at the age of 12 years 5 months, and we started rhGH therapy. Although her height velocity improved from 0.5 cm/year to 6 cm/year within one year after starting rhGH therapy, her height SDS did not improve. At the start of rhGH therapy, the patient had been at Tanner stage I; therefore, we decided to add GnRHa therapy in order to prolong the pre-pubertal growth phase and obtain catch-up growth. At the age of 13 years 9 months, 4 months after initiation of the combined therapy, the patient underwent living-donor kidney transplantation. Immunosuppressive agents included cyclosporine, mycophenolate mofetil, and methylprednisolone. The methylprednisolone was reduced quickly to 0.3 mg/kg/day at 4 weeks after transplantation, and to 4 mg on alternate days from 4 months. At the age of 15 years 8 months, her height SDS had improved to -2.3, and we terminated the GnRHa therapy. At the age of 16 years 6 months, the patient had her first menstrual period, and as her height SDS had reached -2.1, we completed the rhGH therapy. Finally, by the age of 18 years, her height SDS had improved to -1.8. Since then, her transplanted kidney function has been stable and her menstruation cycles have been regular.

Conclusions: Combination therapy with rhGH and GnRHa may be safe and effective option for the treatment of short stature in pubertal kidney transplant recipients.

FR-PO1077

A Novel Biphasic Dialytic Strategy for the Treatment of Neonatal Hyperammonemia

Mark Hanodel1 Sonal Avsare1 Eileen W. Tsai1 Joshua Zaritsky2 1Pediatrics, UCLA, Los Angeles, CA; 2Dept of Pediatrics, UCLA, Los Angeles, CA.

Background: Neonates with inborn errors of metabolism often develop hyperammonemia which, if not corrected quickly, may result in poor neurologic outcomes. As pharmacologic therapy cannot rapidly lower ammonia levels, dialysis is frequently required. Both intermittent hemodialysis (IHD) and standard-dose continuous renal replacement therapy (CRRT) are effective; however, IHD may be followed by post-dialytic ammonia rebound, and standard-dose CRRT may not effect a rapid enough decrease in ammonia levels.

Methods: We present two cases of IEM-associated neonatal hyperammonemia. The first patient, eventually diagnosed with citrullinemia, presented with lethargy on the fourth day of life. The second patient, eventually diagnosed with methylmalonic acidemia, presented with poor feeding and abnormal newborn screening results on the fourth day of life. Both patients were found to be hyperammonemic (peak ammonia levels 841 umol/L and 1830 umol/L, respectively). For both patients, we employed a biphasic dialytic treatment strategy, initially using dialysis parameters closer to those of IHD (blood flow rate 20-30 mL/min and dialysate flow rate 5000 mL/hr) to rapidly decrease ammonia levels to <400 umol/L, then transitioning to treatment parameters closer to those of standard CRRT (blood flow rate 30 mL/min and dialysate flow rate 500 mL/hr, approximately 4000 mL/hr/1.73m2) to maintain ammonia levels <200 umol/L without rebound.

Conclusions: These cases provide an example of a novel biphasic dialytic treatment strategy for neonatal hyperammonemia, effecting rapid ammonia reduction without rebound, employing a seamless transition between two dialytic modalities without equipment changes.
Methods: A 55-year-old male presented with 6 months of malaise, night sweats and weight loss. He had bilateral cervical and axillary lymphadenopathy. His white blood cell count (WBC) was 5600/mm³, with an absolute eosinophil count of 265/mm³. The serum creatinine was 1.9 mg/dL and the urinalysis showed 1+ albuminuria, without WBC or red blood cells. A CT scan revealed multiple enlarged mesenteric and retroperitoneal lymph nodes. There was diffuse enlargement of both kidneys with bilateral hydronephrosis and perinephric inflammatory changes. There was thickening of both renal pelvises and proximal ureters with involvement of the periureteral fat. A kidney biopsy showed chronic and active tubulointerstitial nephritis with eosinophils and involvement of the outer renal cortex and extrarenal fibroadipose tissue. The glomeruli were normal. Bone marrow biopsy was normocellular with eosinophilia. Immunophenotyping did not show a B-cell clone or aberrant T-cell population. There was no evidence of eosinophilic leukemia. He was diagnosed with IHES and treated with 40 mg prednisone daily. His symptoms resolved in 1 week. After 3 weeks, his AEC was 0 cells/mm³ and the creatinine decreased to 1.2 mg/dL. Six months later, a renal ultrasound revealed mild residual dilatation of the right kidney collecting system, and complete resolution of the left-sided hydronephrosis.

Conclusions: IHES should be considered in patients presenting with AKI and unexplained eosinophilia. Renal involvement is rarely described in IHES. Our case highlights a novel renal manifestation of IHES: obstructive AKI due to periureteral and perirenal eosinophilic infiltration and lymphadenopathy. The obstruction and AKI resolved with prednisone.

FR-PO1078
What Looks like Fabry Disease, May Not Be Fabry! Reem Daloul, Francis Dumler, Ping L. Zhang. William Beaumont Hospital, Royal Oak, MI.

Background: Fabry disease is a rare x-linked lysosomal storage disorder caused by deficiency of lysosomal hydrolyase alpha-galactosidase A (alpha-Gal A). This results in the accumulation of globotriaosylceramide within the lysosomes of different cell types with eventual organ dysfunction. Renal involvement is characterized by proteinuria and progressive renal failure.

Methods: We report a 38 year old previously healthy African American male who presented with intermittent gross hematuria. The patient was otherwise asymptomatic. Family history was strongly positive for chronic kidney disease in both parents, sister, maternal and paternal grandmothers. Urinalysis showed >3 blood, 8 RBCs, 4 WBCs and no protein. Creatinine and eGFR were 1.02 mg/dL and 99 mL/min/1.73m². Urine protein/creatinine ratio was 0.1. Abdominal CT, renal ultrasound, and cystoscopy were all normal. No protein. Creatinine and eGFR were 1.02 mg/dL and 99 mL/min/1.73m². Urine protein/creatinine ratio was 0.1. Abdominal CT, renal ultrasound, and cystoscopy were all normal. No protein.

Conclusions: The pathological findings are consistent with LECT2-type amyloid. Immunohistochemistry was the usual method used for typing renal amyloid in more than 90% of cases. In the last decade, at least 12 cases of LECT2-type renal amyloidosis have been reported and described as negative for κ/λ light-chains, AA protein, fibrinogen and transthyretin. However, our experience in this case raises concern that in some cases, LECT2-type renal amyloid may react with partial antiserum. LC MS/MS is crucial in such cases for accurate diagnosis.

FR-PO1079
Acute Kidney Injury with Hydronephrosis, Eosinophilic Tubulointerstitial Nephritis and Extracapsular Perirenal Eosinophil Infiltrates. A Rare Presentation of Idiopathic Hypersesinophilic Syndrome Marat Abdullin, Kiran M. Goll, Jonathan Freeman, Syed S. Ali, Jonathan Bayuk, Benjamin J. Freda. 1Medicine, Baystate Medical Center; 2Pathology, Baystate Medical Center.

Background: We describe a patient with Acute Kidney Injury (AKI), hydronephrosis and eosinophilia. To our knowledge, this is the first reported case of Idiopathic Hypersesinophilic Syndrome (IHES) with renal involvement characterized by both obstruction and renal parenchymal injury.

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

611A
FR-PO1082

Using Fresh Frozen Plasma with Therapeutic Plasma Exchange in a Patient with Acquired C1 Esterase Inhibitor Deficiency Without Triggering Angioedema


Background: Acquired C1 esterase inhibitor deficiency (acquired angioedema [AAE]) is a rare syndrome affecting the skin, gastrointestinal (GI) and respiratory tracts. The syndrome’s acquired form appears after 40 years of age and is associated with lymphoproliferative B cell disorders. In acute attacks, lack of C1 esterase leads to uninhibited bradykinin generation, causing angioedema presenting as cutaneous swelling, severe GI symptoms (colic, nausea, and vomiting) and severe laryngeal edema. The acute attack is unaffected by conventional treatments for allergic angioedema (steroids, epinephrine). First line pharmacologic therapies are seldom readily available. Plasma, with natural C1 esterase inhibitor, has been used for acute attacks but there are concerns that plasma could potentially trigger or worsen angioedema through bradykinin substrate replenishment.

We present a case of a patient with AAE who developed thrombotic thrombocytopenic purpura (TTP), successfully treated with a series of therapeutic plasma exchange (TPE) using fresh frozen plasma (FFP).

Methods: A 39 year old female with B cell lymphoproliferative disease and AAE had malaise and headache with a platelet count of 20,000 k/uL, LDH 701 U/L, reticulocyte count 2.7%, haptoglobin <15 mg/dl and 10-15 schistocytes per high power field. TTP was suspected as the underlying disease process and emergent TPE was ordered. Aware of a potential connection from a fatal reaction to fresh frozen plasma (FFP) use, Eapen (kallikrein inhibitor in AAE) was used through bradykinin substrate replenishment.

We present a case of a patient with AAE who developed thrombotic thrombocytopenic purpura (TTP), successfully treated with a series of therapeutic plasma exchange (TPE) using fresh frozen plasma (FFP).
hyperplastic cells present within Bowman’s Space. Electron microscopy demonstrated definite segmental sclerosis with ultrastructural analysis confirming the segmental sclerosis with collapsed glomerular capillary loops accompanied by hyalinosis in the subendothelial regions. There was also fairly prominent podocyte foot process effacement present. No definitive electron dense “immune-type” deposits were identified.

Conclusions: To our knowledge we are presenting the first documented case of CLL induced membranous nephropathy with clinical and biopsy proven resolution after Rituximab treatment. This case demonstrates the potential clinical utility of Rituximab as monotherapy for CLL induced membranous nephropathy.

FR-PO1088

Use of Adrenocorticotropic Hormone in Managing Proteinuria and Hypoaalbuminemia Associated with Focal Segmental Glomerulosclerosis Leading to End Stage Renal Disease

Pallavi D. Shirsat, Sabeen Y. Habib.

Dept of Pediatrics, LSU Health Shreveport, Shreveport, LA.

Background: 14 year old African American female with history of End stage renal disease, moderate interstitial fibrosis and glomerular sclerosis (Figure B).

Methods: Patient responded to ACTH gel and showed significant improvement in her serum albumin level. Serum albumin improved from 0.5 g/dl at the beginning of treatment to 3.7 g/dl over a period of 6 months. She did not have any significant adverse effects except for cushingoid facies. She is now off Acahr with sustained normal albumin level.

Conclusions: ACTH therapy has shown to benefit patients with Idiopathic Membranous Nephropathy in a study conducted in Europe by Ponticelli et al and few observational retrospective studies conducted in the United States. Based on the encouraging results, we decided to use it in our ESRD patient, who has biopsy proven FSGS with proteinuria resistant to conventional treatment with corticosteroids and tacrolimus. After starting ACTH therapy, patient showed significant improvement in her serum albumin level; without having any serious adverse effects. The mechanism of action of ACTH remains unclear at this time; the proposed theories is may work at the melanocortin receptor in podocytes to reduce proteinuria, or by stimulating endogenous cortisol secretion. ACTH therapy may be a promising treatment for patients with nephrotic syndrome resistant to conventional therapies like corticosteroids and immune suppression. Results available from the limited studies using ACTH therapy are encouraging. Further studies in this area using large sample size and long term follow up are warranted.

FR-PO1089

Unusual Cause of Renal Vein Thrombosis

Mohammad Sharifi,1 Navin Jaipaul,2 Seyed-ali Sadjadi. 3

Nephrology, Loma Linda Univ Medical Center, Loma Linda, CA; 3Nephrology, Veterans Affairs Loma Linda Healthcare System, Loma Linda, CA.

Background: Renal vein thrombosis (RVT) has numerous etiologies; such as, nephrotic syndrome, pregnancy, hypercoagulable state, oral contraceptive pills use, steroids therapy, trauma, and kidney transplant. We present a case of an elderly gentleman who developed RVT after laser lithotripsy for obstructive nephrolithiasis.

Methods: A 76-year-old male, known to have hypertension, coronary artery disease, stroke and dyslipidemia presented with left flank pain, hematuria and left renal angle tenderness, was found to have left ureteric stone with hydronephrosis which was diagnosed by abdomen computed tomography (CT) scan. He underwent left ureteroscopic laser lithotripsy with stent placement. Pain and acute kidney injury improved and he was discharged home. A few days later, he pulled the string of the stent and he was able to remove it. Then two days after, he started to complain of left flank pain. Laboratory evaluation showed Creatinine decreased compared to discharge value. Abdominal CT scan was repeated and showed new filling defect in the left renal vein consistent with RVT.

Conclusions: Laser lithotripsy is not a recognized etiology for RVT. In this case, common causes were ruled out and the proximity of the procedure to his presentation made RVT likely induced by laser lithotripsy, which could be explained by edema and pressure induced by instrumentation of the ureter or by pressure induced when he self-retracted the stent or combination of both. This case could be an eye opener for unknown etiology of RVT or possibly underdiagnosed etiology of flank pain post laser lithotripsy.

FR-PO1090

Novel Mutations in CLDN16 Gene in a Belgian Patient with Hypomagnesemia, Hypercalcuria and Nephrocalcinosis

Pauline Erpicum,1 Laurent E. Weeckers,1 Emilie Castermans,2 Vincent Bourx,3 Jean-marie H. Krzesinski,1 Francois Jouret.1

Nephrology, ULg CHU, Liege; 2Genetics, ULg CHU, Liege.

Background: Hypomagnesemia, hypercalcuria and nephrocalcinosis (HHN) is a rare autosomal recessive tubular disorder characterized by urinary losses of Mg2+ and Ca2+. HHN leads to end-stage renal disease (ESRD) in early adulthood. HHN is genetically heterogeneous, with mutations in CLDN16 or CLDN19 genes.

Methods: At the age of 19, our patient presented with a loss of consciousness secondary to dehydration. His medical history included dehydration at birth and GFR decline estimated at 8.2 ml/min per 1.73m2/year. The patient met the criteria for accelerated loss of renal function, 5 years post KTx.

Results: Patient responded to ACTH gel and showed significant improvement in her serum albumin level. Serum albumin improved from 0.5 g/dl at the beginning of treatment to 3.7 g/dl over a period of 6 months. She did not have any significant adverse effects except for cushingoid facies. She is now off Acahr with sustained normal albumin level.

Conclusions: ACTH therapy has shown to benefit patients with Idiopathic Membranous Nephropathy in a study conducted in Europe by Ponticelli et al and few observational retrospective studies conducted in the United States. Based on the encouraging results, we decided to use it in our ESRD patient, who has biopsy proven FSGS with proteinuria resistant to conventional treatment with corticosteroids and tacrolimus. After starting ACTH therapy, patient showed significant improvement in her serum albumin level; without having any serious adverse effects. The mechanism of action of ACTH remains unclear at this time; the proposed theories is may work at the melanocortin receptor in podocytes to reduce proteinuria, or by stimulating endogenous cortisol secretion. ACTH therapy may be a promising treatment for patients with nephrotic syndrome resistant to conventional therapies like corticosteroids and immune suppression. Results available from the limited studies using ACTH therapy are encouraging. Further studies in this area using large sample size and long term follow up are warranted.

Funding: Pharmaceutical Company Support - Questcor Pharmaceuticals

He was started on anticoagulation. Extensive work up showed no evidence of glomerular disease, malignancy or thrombophilia. At 3-month follow up, the pain has subsided and a repeat CT scan showed resolution of the thrombosis.

Conclusions: Laser lithotripsy is not a recognized etiology for RVT. In this case, common causes were ruled out and the proximity of the procedure to his presentation made RVT likely induced by laser lithotripsy, which could be explained by edema and pressure induced by instrumentation of the ureter or by pressure induced when he self-retracted the stent or combination of both. This case could be an eye opener for unknown etiology of RVT or possibly underdiagnosed etiology of flank pain post laser lithotripsy.

FR-PO1100

Novel Mutations in CLDN16 Gene in a Belgian Patient with Hypomagnesemia, Hypercalcuria and Nephrocalcinosis

Pauline Erpicum,1 Laurent E. Weeckers,1 Emilie Castermans,2 Vincent Bourx,3 Jean-marie H. Krzesinski,1 Francois Jouret.1

Nephrology, ULg CHU, Liege; 2Genetics, ULg CHU, Liege.

Background: Hypomagnesemia, hypercalcuria and nephrocalcinosis (HHN) is a rare autosomal recessive tubular disorder characterized by urinary losses of Mg2+ and Ca2+. HHN leads to end-stage renal disease (ESRD) in early adulthood. HHN is genetically heterogeneous, with mutations in CLDN16 or CLDN19 genes.

Methods: At the age of 19, our patient presented with a loss of consciousness secondary to dehydration. His medical history included dehydration at birth and GFR decline estimated at 8.2 ml/min per 1.73m2/year. The patient met the criteria for accelerated loss of renal function, 5 years post KTx.

Results: Patient responded to ACTH gel and showed significant improvement in her serum albumin level. Serum albumin improved from 0.5 g/dl at the beginning of treatment to 3.7 g/dl over a period of 6 months. She did not have any significant adverse effects except for cushingoid facies. She is now off Acahr with sustained normal albumin level.

Conclusions: ACTH therapy has shown to benefit patients with Idiopathic Membranous Nephropathy in a study conducted in Europe by Ponticelli et al and few observational retrospective studies conducted in the United States. Based on the encouraging results, we decided to use it in our ESRD patient, who has biopsy proven FSGS with proteinuria resistant to conventional treatment with corticosteroids and tacrolimus. After starting ACTH therapy, patient showed significant improvement in her serum albumin level; without having any serious adverse effects. The mechanism of action of ACTH remains unclear at this time; the proposed theories is may work at the melanocortin receptor in podocytes to reduce proteinuria, or by stimulating endogenous cortisol secretion. ACTH therapy may be a promising treatment for patients with nephrotic syndrome resistant to conventional therapies like corticosteroids and immune suppression. Results available from the limited studies using ACTH therapy are encouraging. Further studies in this area using large sample size and long term follow up are warranted.

Funding: Pharmaceutical Company Support - Questcor Pharmaceuticals

He was started on anticoagulation. Extensive work up showed no evidence of glomerular disease, malignancy or thrombophilia. At 3-month follow up, the pain has subsided and a repeat CT scan showed resolution of the thrombosis.

Conclusions: Laser lithotripsy is not a recognized etiology for RVT. In this case, common causes were ruled out and the proximity of the procedure to his presentation made RVT likely induced by laser lithotripsy, which could be explained by edema and pressure induced by instrumentation of the ureter or by pressure induced when he self-retracted the stent or combination of both. This case could be an eye opener for unknown etiology of RVT or possibly underdiagnosed etiology of flank pain post laser lithotripsy.

FR-PO1100
apparent compound heterozygosity includes one nonsense mutation truncating the protein in the first extracellular domain and one intronic mutation of a highly conserved nucleotide close to exon 2 donor splice site. Their impact on claudin 16 expression, function and distribution remains to be determined.

**Funding:** Clinical Revenue Support

**FR-PO1091**

Renal Cell Carcinoma Associated with Xp 11.2 Translocation in Autosomal Dominant Polycystic Kidney Disease

Hyeok Huh,1 Hayne C. Park,1 Yongjin Yi,1 Miyeun Han,1 Young-Hwan Hwang,2 Curie Ahn.1

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary cystic disease. The prevalence of renal cell carcinoma (RCC) has been reported to be higher in ADPKD patients with advanced renal failure. Xp11.2 translocation RCC is related to translocation of several genes involving the transcription factor E3 (TFE3) gene. Xp11.2 translocation RCC have an aggressive clinical course with tendency to spread to perirenal lymph nodes in adults. This is the first case report of Xp11.2 translocation RCC in an ADPKD patient.

**Results:** A 38-year-old woman was diagnosed of ADPKD in 1996. She had multiple cysts in kidney and liver. 10 x 1 cm sized cystic lesion with inner septation and well-enhancing solid portion was incidentally detected in her right kidney upper pole on 2004. The cystic mass was followed up by biennial abdominal CT or ultrasonography and found to be stable without change in morphology or size until January 2011. Then, the size of cystic mass began to increase from 10 x 11 to 10 x 12 cm, and lymph node enlargement was newly found in the retrocardiac and aorticaval areas. Cyst aspiration and cytologic examination did not show malignant cells. After 6 months, the size of cystic mass further increased to 10.7 x 12.7 cm. In October 2011, we decided to perform diagnostic and therapeutic right radical nephrectomy. Microscopic examination of the right kidney revealed RCC containing clear cell components with strong TFE3 expression. The FISH confirmed the diagnosis of Xp 11.2 translocation by showing break-apart signal in TFE3 gene. Shortly after the diagnosis, multiple metastatic lesions were detected in lung and she has been treated by systemic chemotherapy.

**Conclusions:** In general, Xp 11.2 translocation RCC is reported to appear in the childhood and shows female preponderance. It accounts for approximately 5% to 20% of RCCs in pediatric patients, but is much less common in adults RCCs (1.6%-5%). This case suggests that Xp 11.2 translocation RCC change the clinical manifestation of renal mass dynamically in ADPKD patients.

**FR-PO1092**

Ezetimibe, Hyperoxaluria and Nephrolithiasis

Ivan E. Porter, William E. Haley.

**Background:** Excessive urinary excretion of oxalate can manifest as recurrent urolithiasis, nephrocalcinosis and progression to ESRD. This is described in primary hyperoxaluria and also with the use of lipase inhibitor orlistat. I present two cases of hyperoxaluria associated with the use of ezetimibe, a selective cholesterol absorption inhibitor.

**Methods:** Case1: 74-year-old Caucasian female was evaluated for renal insufficiency. She had no history of kidney stones, but hyperlipidemia, intolerant of statins, treated with ezetimibe starting about 10 years prior. Her urinalysis was unremarkable and 24 hr urine showed supersaturation of calcium oxalate and U oxalate of 0.47 mmol/spec. Renal US showed normal renal parenchyma. Case2: 53-year-old male presented with hyperoxaluria and calcium oxalate stone formation. He was on ezetimibe for 10 years. He has developed hypercalcemia with serum Ca (12.8 mg/dL) and CRP levels, while his serum PTH and PTHrP levels were normal. His serum calcium level (26 mg/L) was much higher than the average value in hemodialysis patients. Computed tomography showed enlargement of the systemic lymph nodes. A lymph node biopsy showed massive proliferation of histiocytes with emperipolesis in the dilated sinuses. The final diagnosis was “Rosai-Dorfman disease”. Interestingly, an immunohistochemical analysis of the affected lymph nodes disclosed many histiocytes (Rosai-Dorfman cells) positive for 1a-hydroxylase, provided evidence for the extra-renal overproduction of calcitriol. Oral prednisolone therapy attenuated inflammation and decreased the serum creatinine level (9 mg/dL), followed by the normalization of hypercalcemia and hyperparathyroidism.

**Conclusions:** These cases raise the possibility of a role of ezetimibe in hyperoxaluria and calcium oxalate stone formation. Previous studies suggest that the use of lipase inhibitors is associated with an increase in urinary oxalate along with a decrease in urine calcium and urine magnesium. Fat and bile acids react with calcium in the gut preventing binding with free oxalate, raising intestinal oxalate and thus urinary excretion of oxalate and a predisposition to calcium oxalate stones. This same association has been described with the selective cholesterol absorption inhibitor ezetimibe. Based on the mechanism of action of ezetimibe and the findings of a relationship between stone formation and the use of orlistat, ezetimibe use should be considered in the evaluation and management of patients with nephrolithiasis.

**FR-PO1093**

Use of Cinacalcet for Treatment of Hypercalcaemia of Malignancy Refractory to Conventional Therapies

Sean R. Campbell,1 Carlos D. Flombaum,2 Ilya Glezereman.1,2

**Background:** Hypercalcaemia of malignancy (HCM) occurs either due to tumor bone invasion causing increased osteoclastic activity or in humoral HCM due to tumor secreted parathyroid hormone related peptide (PTHrP) direct effect on the bone. Initial treatment of hypercalcaemia of malignancy includes intravenous hydration, IV bisphosphonates and denosumab. Cinacalcet is a calcimimetic agent that binds tissue calcium sensing receptor (CaSR). It has been used to treat hyperparathyroidism and parathyroid carcinoma. We present a case of a patient with HCM, which was resistant to standard therapy but responded to cinacalcet.

**Methods:** The patient was a 66 years old male with history of metastatic renal cell carcinoma. He had developed hypercalcaemia with serum Ca (sCa) of 11.4 (8.5-10.5) mg/dl and was started on bisphosphonates and hydration. CT scan of the pelvis was significant for ileal lytic lesions, PTH was 10 (12-88) pg/dl and PTHrP 114 (14-27) pg/dl. Due to ongoing hypercalcemia two doses of denosumab (120mg) were given with no response. After 4 months of worsening hypercalcaemia patient was hospitalized with sCa level of 14.2 mg/dl. He was started on cinacalcet 30mg daily and at discharge sCa was 11.0 mg/dl. One week later sCa was 11.4 mg/dl and cinacalcet was increased to 60 mg daily. Ten weeks after initiation of cinacalcet sCa was 10.1 mg/dl and PTHrP level was 159 pg/ml.

**Conclusions:** CaSR is expressed in many tissues including bone, intestine, renal tubules and in malignant tissue secreting PTHrP. Cinacalcet may act by binding CaSR and lowering PTHrP level, increasing calcitriol, decreasing intestinal calcium absorption and decreasing calcium efflux from bone. Recently cinacalcet was used in a patient with non small cell lung cancer and humoral HCM resulting in lowering of sCa and PTHrP levels. In our patient the PTHrP levels did not decrease and cinacalcet therapeutic effect was likely mediated via its effect on non-malignant tissues. Cinacalcet is a well-tolerated drug with a low side effect profile which warrants further investigation as treatment of HCM.

**FR-PO1094**

Hypercalcemia Induced by Ectopic Overproduction of Calcitriol in a Hemodialysis Patient with Rosai-Dorfman Disease

Yamada,1,2 Masanori Tokumoto,2 Kazuhiko Tsuruya,1 Takanari Kitazono.1

**Background:** Hypercalcemia is usually associated with the excessive use of Ca-containing Pi-binders or VDRA in dialysis patients. Extra-renal overproduction of calcitriol occasionally leads to hypercalcemia. We report the case of a hemodialysis patient with Rosai-Dorfman disease, who developed hypercalcemia as a result of the ectopic overproduction of calcitriol.

**Methods:** A 65-year-old male receiving hemodialysis for 33 years was admitted because of declining consciousness and fever. His laboratory data showed an increase in his corrected serum Ca (12.8 mg/dL) and CRP levels, while his serum PTH and PTHrP levels were normal. His serum calcium level (26 mg/L) was much higher than the average value in hemodialysis patients. Computed tomography showed enlargement of the systemic lymph nodes. A lymph node biopsy showed massive proliferation of histiocytes with emperipolesis in the dilated sinuses. The final diagnosis was “Rosai-Dorfman disease”. Interestingly, an immunohistochemical analysis of the affected lymph nodes disclosed many histiocytes (Rosai-Dorfman cells) positive for 1a-hydroxylase, provided evidence for the extra-renal overproduction of calcitriol. Oral prednisolone therapy attenuated inflammation and decreased the serum creatinine level (9 mg/dL), followed by the normalization of hypercalcemia (8.6 mg/dL) and consciousness, and also a remission of the lymph node swelling.

**Conclusions:** Rosai-Dorfman disease is a benign lymphoproliferative disorder characterized by the massive proliferation of histiocytes with emperipolesis in the dilated sinuses of lymph nodes (Rosai J et al. Arch Pathol 1969). The etiology is unknown, but an association with immunological disorders and the effectiveness of corticosteroid therapy are assumed. Hypercalcemia induced by Rosai-Dorfman disease has been rarely reported. This case is worth reporting, because we have demonstrated that the ectopic overproduction of calcitriol in the lymph node led to hypercalcemia.

**FR-PO1095**

Proteomics in Guanine-Nucleoside Induced Nephrotoxicity: A Pseudomatrix Stone

Faheemuddin A. Ahmed,1,2 Ann M. Kolbach,1 Samuel R. Cohen,2 Neil S. Mandel,1 Jeffrey Wesson,1,2

**Background:** A number of drugs, including Guanine-Nucleoside, have been reported to cause kidney stones, but there are no proteomic reports on these stones. We present a case that was referred for evaluation of matrix stones, which turned out to be a guanine-related kidney stone with a matrix-like component.

**Methods:** A 30 year-old Caucasian woman with no medical history presented at age 27 with renal colic and was found to have acute kidney injury. Work-up revealed bilateral nephrolithiasis with hydropnephrosis and had subsequent stent placement. Urine sediment analysis was reported as 100% mucin and no other known stone material. Her symptoms resolved and creatinine returned to baseline. Her medications included potassium citrate

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

Underline represents presenting author/disclosure.
and allopurinol. Her OTC medications included mucinex and claritin for allergy symptoms. The patient was referred to our clinic and enrolled in our IRB approved study. Laboratory evaluation showed normal blood tests. Her urorisk panel revealed low urine volume, low citrate, high sodium, high oxalate, high uric acid and pH 5.5. The patient experienced bilateral flank pain similar to prior episodes and collected a urine sample that showed three discrete phases: urine, mucus strand and sediment. Microscopy of the urine sediment showed spherical, birefringent crystals. FTIR analysis of the sediment revealed 40% guaifenesin and 60% protein. The sediment was fractionated into the drug and protein isolate using ultrafiltration. Standard gel electrophoresis performed on the urine proteins as compared to the sediment proteins revealed increased concentrations of Tamm Horsfall glycoprotein, transferrin and osteopontin and decreased concentrations of albumin and zinc alpha 2 glycoprotein. These findings were further confirmed with mass spectroscopy.

Conclusions: Drug-induced kidney stones can mimic matrix stones and can be misdiagnosed with insufficient or inaccurate stone analysis. The guaifenesin associated proteome was found to be different from that reported in the literature for both calcium and matrix stones.

Funding: NIDDK Support

FR-PO1096
Calciphylaxis Presenting as Progressive Gangrene of the Digits and Penis
Vasili Peey, Sharad Virmani, Ali Nayer. Div of Nephrology and Hypertension, Univ of Miami, Miami, FL.

Background: Calciphylaxis, known as calcic uremic arteriolopathy, is characterized by slowly progressive necrosis of skin and subcutaneous tissue secondary to calcification and thrombosis of small- and medium-sized arteries. It manifests most commonly in middle-aged individuals with renal disease involving their abdomen, legs, and breasts. The digits and penis are rarely affected.

Methods: A 49-year-old woman presented with gangrene of the fingers and penis. Past medical history included diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, peripheral vascular disease, and end-stage renal disease on hemodialysis for 5 years. Physical examination revealed dry gangrene of the fingers (A, B), penis, and scrotum. Dusky red discoloration of right lateral great toe was also noted (C). Serum concentration of albumin was 1.7 g/dL, calcium 7.7 mg/dL, phosphorus 5.0 mg/dL, and parathyroid hormone 162 pg/mL. Laboratory tests revealed no cryoglobulins, cold agglutinins, cryofibrinogen, lupus anticoagulant or Prothrombin G20210A mutation. Antibodies directed against cardiolipin, beta 2 glycoprotein I, myeloperoxidase, proteinase 3, platelet factor 4, nuclear antigens, hepatitis B and C were negative. Serum concentrations of antithrombin, protein S, protein C and complement C3 and C4 were normal. Gangrene of the affected areas worsened (D-F) during work-up. Radiographs of hands and feet revealed vascular calcification (G-J). Skin biopsy revealed calcified subcutaneous small blood vessels consistent with calciphylaxis (Von Kossa stain) (K). Microthrombi were noted in subcutaneous small blood vessels (L, M).

The diagnosis of calciphylaxis was confirmed with a biopsy of the thigh showing medial calcification in small blood vessels.

Conclusions: Calciphylaxis is a disease caused by arteriolar calcification leading to tissue ischemia and necrosis. The mortality rate approaches 50% at one year. Most patients with calciphylaxis have ESRD or kidney transplant. Additional risk factors include hyperparathyroidism, an elevated calcium-phosphate product, female sex, diabetes, obesity, warfarin use, and chronic inflammation. Classic skin lesions are livedo reticularis and necrotic ulcers, though skeletal muscle myopathy has been described in the absence of cutaneous findings. Imaging modalities that aid in the diagnosis are mammography and bone scintigraphy. Catching the diagnosis at an early stage, prior to skin ulceration, confer a greater chance of treatment response. Thus, in patients with ESRD, calciphylaxis should be considered in the differential diagnosis for myopathy, and a reasonable non-invasive diagnostic modality is bone scintigraphy.

FR-PO1098
Pre-Uremic Calciphylaxis
Sharad Virmani, Loay H. Salman, Ali Nayer. Div of Nephrology and Hypertension, Univ of Miami Miller School of Medicine, Miami, FL.

Background: Calciphylaxis, also known as calcic uremic arteriolopathy, is a life-threatening disorder characterized by calcification and thrombosis of small- and medium-sized arteries resulting in ischemic necrosis of skin and subcutaneous tissue. The pathogenesis is incompletely understood. Primarily diagnosed in dialysis patients, calciphylaxis is rarely diagnosed in patients with CKD in the pre-uremic phase.

Methods: A 72-year-old obese Caucasian woman with CKD presented with worsening left lower leg pain and purplish skin discoloration with ulcerations on the heel and dorsal foot. Past medical history was significant for long-standing diabetes mellitus, hypertension, peripheral vascular disease, secondary hyperparathyroidism, and deep vein thrombosis. Physical exam revealed a 10-cm calf ulcer and a violaceous eschar of the heel (Figure1). Significant tenderness to palpation was present in the left upper thigh, calf and foot. Serum creatinine was 3.1mg/dL, calcium of 7.9mg/dL, phosphorous of 6.6mg/dL, and albumin of 1.7g/dL. Angiography revealed occluded left superficial femoral artery, popliteal artery and distal tibial artery. A left below-the-knee amputation was performed. Gross examination revealed calciphylaxis within adipose tissue and severe calcific atherosclerosis (Figure1). Histologic examination disclosed calciphylaxis among large and small vasculature with Van Kossa staining.

Conclusions: This case illustrates a striking presentation of a rare and life-threatening disorder. Similarly presenting conditions like antiphospholipid syndrome, cryoglobulinemia, Waldenstrom’s macroglobulinemia, thrombophelia, and scleroderma were excluded.
CONCLUSIONS: We highlight calciphylaxis in a patient with chronic kidney disease before starting dialysis. When affecting distal limbs, calciphylaxis can clinically resemble atherosclerotic peripheral vascular disease. This case also emphasizes that calciphylaxis and peripheral vascular disease share many risk factors and can coexist in the same patient. This case increases the awareness to a disorder that could be disguised as peripheral vascular disease.

FR-PO1099
Successful Treatment of Recurrent Calciphylaxis Using Sodium Thiosulfate in a Patient with Normal Renal Function
Ankur Sharma, Burl R. Don.
Div. of Nephrology, Univ of California, Davis, Sacramento, CA.

Background: Calciphylaxis (CPX), also known as calcific uremic arteriolopathy, is a clinical condition of accelerated dermal arterial medial calcification resulting in severe cutaneous ulcerations and eschar formation. It is seen generally in patients with advanced chronic kidney disease (CKD) and carries a poor prognosis. Sodium thiosulfate (STS) has been used with varying degrees of success in the treatment of CPX in patients with CKD, but its use for patients with recurrent CPX and normal renal function has not been described.

Methods: A 53 year old woman with alcoholic liver disease and normal renal function was admitted to the hospital with preliminary diagnosis of severe bilateral lower extremity cellulitis refractory to outpatient antibiotics and cutaneous thigh ulcers. She underwent debridement of the non healing ulcers and a subsequent skin biopsy noted vascular calcification consistent with CPX. The patient had normal creatinine, calcium, phosphorus, parathyroid hormone, 25-OH and 1,25-OH vitamin D blood levels. Treatment with IV STS, 25 g thrice weekly was initiated and after two months of therapy, there was dramatic improvement of the ulcers and reduction of the cutaneous inflammation. The STS was discontinued, but after one month. She had a relapse with recurrent violaceous inflammation resulting in severe ulceration in her thighs. Additional lab work noted normal FGF-23, complement, PTH related peptide, protein S, protein C blood levels and a negative rheumatologic panel. STS was restarted and she had marked improvement in her cutaneous lesions within 1 month.

Conclusions: CPX in the setting of normal renal function is unusual and has been described in association with primary hyperparathyroidism, chronic liver disease, Crohn's disease, warfarin use, systemic steroids and malignancy. The use of STS in the treatment of CPX and normal renal function has been noted, but there are no randomized trials assessing its efficacy. This case establishes that STS is effective therapy for CPX inasmuch as discontinuation of STS resulted in relapse and retreatment resulted in remission. STS is an effective therapy for recurrent CPX.

FR-PO1100
Secondary Hyperparathyroidism in Association with Combined Use of Proton Pump Inhibitors and Intravenous Magnesium
Sami Safadi, Qi Qian
Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: The interplay between magnesium and calcium is complex and crucially influences calcium homeostasis. We describe a unique case of secondary hyperparathyroidism associated with combined use of PPI and IV magnesium.

Methods: 49-year old woman with ulcerative colitis that required total colectomy and ileostomy was diagnosed with severe magnesium deficiency. Her initial magnesium level was near 0 mg/dL. Oral magnesium was started, but due to intolerance, it was switched to IV magnesium sulfate. The dose was titrated up to 4 grams of magnesium sulfate twice weekly. This was continued for almost a year, but her blood magnesium level remained low between 1.0 to 1.2 mg/dL. She remained quite weak and unable to work. The patient was then referred to our clinic. Her examination revealed a magnesium IV pump imbedded subcutaneously in the mid-abdomen, and a colostomy bag in the right lower quadrant. Labs revealed a creatinine of 0.7 mg/dL (ref. 0.6-1.1), Calcium of 10.7 mg/dL (ref. 8.9-10.1), and magnesium of 1.5 mg/dL (ref. 1.7-2.5). PTH was 105 pg/ml (ref. 15-65). A parathyroid scan showed two foci of increased sestamibi radiotracer uptake suspicious for adenomas. Her urine calcium excretion was normal. The patient’s IV magnesium was stopped, and she was converted to an oral magnesium regimen. Oral PPI was discontinued as it likely had interfered with magnesium absorption from the GI tract. Her magnesium normalized to 1.7 mg/dL. Her PTH normalized as well (as per her local MD records) and a repeat scan one year later showed stable appearance.

Conclusions: We present here an unusual case of severe hypomagnesemia that’s likely caused by oral PPI intake, and secondary hyperparathyroidism likely triggered by repeat IV magnesium. We hypothesize that severe hypomagnesemia diminishes PTH secretion. However, episodic IV magnesium infusions release the block on PTH secretion. Repeated parathyroid stimulation by high magnesium levels results in secondary hyperparathyroidism. This case cautions us to avoid using chronic IV magnesium as a treatment for total body magnesium depletion as it would not restore magnesium homeostasis, and can induce abnormalities in the PTH-Ca axis.

FR-PO1101
Normocalcemic Hyperparathyroidism Presenting with Multiple Brown Tumors Mimicking Malignancy in a Kidney Transplant Recipient
Shuang Ying Bao,1 Alan Mark Weinstein,1 Sheron Latcha,1,2 Ilya Glezerman,1,2
1Dept of Nephrology and Hypertension, Weil Cornell Medical College, New York, NY; 2Dept of Nephrology, Memorial Sloan-Kettering Cancer Center, New York, NY.

Background: Although secondary hyperparathyroidism is common in dialysis patients, it resolves after renal transplantation in parallel with improvement in renal function. Some patients develop tertiary hyperparathyroidism and hypercalcemia which persists even after the transplantation. We present a case of normocalcemic hyperparathyroidism in a transplant patient.

Methods: Case Description: 36 years old female patient with history of renal transplant in 2005 presented with left arm pain. Plain X-ray showed 7 cm area of lytic bone lesion. PET scan showed multiple bone lesions involving cervical and lumbar spine, femoral neck, iliac and clavicle bone. Patient underwent fixation of the left humerus and right hip hemiarthroplasty. Bone biopsy showed giant cell rich lesion consistent with brown tumor. Primary hyperparathyroidism (PTH) was 1947 pg/ml (12-88), serum creatinine 1.5 mg/dL (0.6-1.3), ionized calcium 4.7 mg/dl (4.8-5.3), Phos 2.9 mg/dl (2.4-4.7). Review of labs showed that patient’s calcium and phosphate levels have been normal since the transplantation. No data prior to the transplantation was available for review. Thyroid ultrasound and parathyroid nuclear scan revealed possible left parathyroid adenoma.

Conclusions: Brown tumor is a rare manifestation of tertiary hyperparathyroidism in kidney transplant recipients and is associated with hypercalcemia. Our case shows that the calcium level may be normal in that setting. It is prudent to obtain baseline PTH level in all transplant patients to screen for hyperparathyroidism.

FR-PO1102
Brown Tumor: A Serious Complication of an Old Disease
Rodrigo Ambiand Wanderley, Márcia Avéline, Jose Edevanilson Guerios, Ana Paula Guerios.
Nephrology Div, IMIP, Recife, Pernambuco, Brazil.

Background: Brown Tumor (BT) is a serious consequence of secondary hyperparathyroidism (SHPT). The majority of cases report the maxilla and mandible as the principal sites of occurrence. Symptoms result from considerable dimensions of the tumor and its localization. When BT involves the face and has progressive growth, it may cause severe deformities, discomfort, and alteration of the masticatory apparatus.

Methods: The objective of this study was to describe the case of a patient with BT in the face provoked by severe SHPT. Case: Patient of 32 years, male and on hemodialysis for 10 years. He has developed in six months a tumor located in the fast growing region of the face, affecting the palate. The lesion expanded so severely that destroyed the entire base of the nose, prevented the closure of the mouth and dramatically reduced the space between the palate and tongue. As a result, the patient presented with difficulty breathing and swallowing and also reported intense and generalized bone pain, muscle weakness, loss of height, and weight loss. Patient reported unsuccessful attempts SHPT treatment with calcitriol and sevelamer. Laboratory tests evidenced iPTH 2527pg/mL, calcium 8.1 mg/dL, phosphorus 4.0 mg/dL, alkaline phosphatase 2024 IU/L, 25OH vitamin D 58.9 pg/ml and hemoglobin 5.2 g/ct. The CT scan demonstrated change in bone volume and texture, highlighting a greater impairment of mandible and maxillary bones, identifying numerous erosions, deformities, discomfort, and alteration of the masticatory apparatus.

Conclusions: BT represent a serious presentation of cystic fibrosis osteitis caused by SHPT. Although benign, can grow aggressively, causing destructive lesions and morbidity. Surgical PTX is the most adequate therapeutic approach in patients with unsatisfactory response to medical treatment.
**FR-PO1103**

**Multiple Bone Lesions in Cinacalcet Era. A Case Report**
Natacha Rodrigues,1 Estela Nogueira,1 Maria Alice Gonçalves Fortes,1 Tiago Rodrigues,2 Antonio Gomes da Costa,1 Andre L. Weigert,1 Sofia C.A. Jorge,1 Nephrology, CHLN, Portugal; 2Radiology, CHLN, Portugal.

**Background:** Chronic Kidney Disease (CKD) commonly evolves with disturbances in mineral and bone metabolism, currently defined as Chronic Kidney Disease - mineral and bone disorder (CKD-MBD). Although, management strategies have changed and progressed along the years, our knowledge is still sparse and consensus in treatment has not been achieved. Severe complications of high turnover bone disease have been significantly reduced after the emergence of calcimimetic agents. Nevertheless, sporadic cases of brown tumors in patients with controlled hyperparathyroidism have been reported in the literature. They result from increased osteoclast activity and if left untreated can have disastrous consequences.

**Methods:** The authors describe a case of a 42-years-old female, undergoing hemodialysis in the last 13 years, that developed a scull lesion that was submitted to surgery and several weeks later was admitted in the hospital with severe low back pain with radiation to the left limb. CT scan revealed several lytic lesions in the jaw, dorsal vertebral, right acetabulum, pubis and ilium (with extraosseous component of 7,5 cm) and full body X ray demonstrated lesions in the right metacarpal bones.

A biopsy of the iliac bone was compatible with brown tumor. Retrospectively, PTH levels in the last 6 months were 300 to 600 ng/l, under treatment with vitamin D analogs and cinacalcet. The gravity of this case, with multiple bone lesions, severe pain and possible neurologic impairment lead to the decision to parathyroidectomy. Following the surgery and cinacalcet. The gravity of this case, with multiple bone lesions, severe pain and possible neurologic impairment lead to the decision to parathyroidectomy. Following the surgery and cinacalcet.

**Conclusions:** Treatment generally requires parathyroidectomy. Approaching a CKD patient with bone lesions even if PTH levels appear fairly controlled.

![Image](image_url)

**FR-PO1104**

**The Formation Process of “White Kidney” in a Patient with Late Onset Primary Hyperoxaluria Type I**

**Background:** Primary hyperoxaluria type I (PHO-I) is a peroxisome disease in which glyoxlate metabolism is congenitally impaired. A characteristic whole kidney calcification called “white kidney” is seen in its advanced stage, while its formation process remains obscure.

**Methods:** A 62-year-old man with no particular personal or family medical histories visited Niigata University Medical and Dental Hospital complaining of fatigue. Although he had received regular medical check up every year, kidney dysfunction was not detected. Fever persisted for 1 week, and thereafter his appetite decreased for 2 months untill his visit. Although he had received regular medical check up every year, kidney dysfunction was not detected. Fever persisted for 1 week, and thereafter his appetite decreased for 2 months untill his visit. He had received regular medical check up every year, kidney dysfunction was not detected.

**Conclusions:** A biopsy of the iliac bone was compatible with brown tumor. Retrospectively, PTH levels in the last 6 months were 300 to 600 ng/l, under treatment with vitamin D analogs and cinacalcet. The gravity of this case, with multiple bone lesions, severe pain and possible neurologic impairment lead to the decision to parathyroidectomy. Following the surgery and cinacalcet. The gravity of this case, with multiple bone lesions, severe pain and possible neurologic impairment lead to the decision to parathyroidectomy. Following the surgery and cinacalcet.

![Image](image_url)

**FR-PO1105**

**Peritoneal Dialysis Peritonitis Associated with Beta Cap Adapters: Quality Improvement Project**
Pavan Devlapally, Sudhir R. Thaduri, Dumitru Rotaru. Dept of Nephrology, Univ Arkansas for Medical Sciences, Little Rock.

**Background:** Puncture holes and catheter disconnection of the PD catheter is an uncommon occurrence.

**Methods:** Between Dec 2012 and Apr 2013 we identified 7 patients in our Davita PD clinic with puncture holes at the junction of PD catheter and the proximal end of the Beta cap adapter. 1 patient also had an episode of disconnection of the transfer set from the distal end of the adapter. As a consequence PD peritonitis occurred in 2 patients associated with puncture hole events and in the patient with the disconnection. 2 patients needed hospitalization and 1 attended the ER. One of the catheters was removed due to relapsed PD peritonitis.

**Results:** A similar experience with catheter holes associated with beta cap adapters was reported in 2012. These authors felt that these events were related to a recent change in the design of the proximal end of adapter from a rounded edge to a sharper edge. We also found an FDA class II recall in 2011 and an ECRI alert in 2012 both reporting a reduction in thread engagement which may lead to a risk of separation of transfer set from the distal end of the adapters.

**Conclusions:** We undertook a QI project with goals to decrease the risk of PD peritonitis, to improve quality of patient care in our clinic and increase the awareness of this complication. We reported our findings to the UHC Patient Safety Net, DaVita Dialysis management, company representative and at our QA Faculty Meeting. Based on the experience with the titanium adapter in our VA PD clinic and also from previous literature reports we decided to use the titanium adapters for all new and existing PD catheters in our clinic.

**FR-PO1106**

**Continuous Renal Replacement Therapy (CRRT) in Times of Calcium Shortage, Do We Have Options?**
Nitin Relia, Yusra R. Cheema, Rupal Mehta, Cybele Ghossein. Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.

**Background:** The use of citrate as regional anticoagulation in patients on continuous renal replacement therapy (CRRT) requires IV calcium to maintain therapeutic systemic ionized calcium levels. The shortage of IV calcium has limited the use of citrate. We present a case of a patient on CRRT managed with the use of citrate and only commercially available calcium containing replacement solution.

**Methods:** The patient is an 80 year old male admitted to the Surgical Intensive Care Unit for repair of a leaking abdominal aortic aneurysm. Postoperatively, he developed Acute Kidney Injury (AKI) necessitating CRRT. Continuous Veno Venous Hemofiltration (CVVH) was initiated on Prismaflex machine using a HF 1400 filter but was limited by multiple cloting episodes. Citrate, in the form of Acid Citrate Dextrose (ACD), was initiated as an anticoagulant at a rate of 300 ml/hr pre-filter and rates adjusted in units of 10 ml/hr to target circuit ionized calcium of 0.25-0.35 mmol/L. The blood flow rate was set at 200 ml/hr and post-filter replacement solution containing 3.5 mEq/L of calcium chloride was started at a rate of 2L/hr giving a total of 3.5 mmol of calcium/hr.

**Conclusions:** Most cases of late onset PHO-I have clinical episodes that would cause acute kidney injury before its onset. The cortico-medullary border is the most sensitive area of acute kidney injury related ischemia. We concluded that calcium oxalate crystals are initially deposited in the damaged tubular lumen, then calcified deposits extend into the upstream direction, and finally form white kidney.

![Image](image_url)

**Figure 1**

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral: PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Figure 1 shows the trends of ionized calcium of the patient and circuit over the next 11 days. The post filter replacement fluid was adjusted increased at marked time points (arrows in figure 1) to achieve near therapeutic serum ionized calcium levels (0.9-1.0 mmol/L). CVVH was able to run for next 11 days without further episodes of clotting.

Conclusions: We present a protocol for the use of citrate for anti coagulation in CRRT without the need of separate IV calcium drip but with the use of calcium containing replacement fluid.

FR-PO1107

Peritoneal Fibrosis Caused by Short-Term Peritoneal Dialysis

Leslie J. Padmos, 1 Niraj Patel, 1 Maxwell L. Smith, 2 Leslie F. Thomas. 1Internal Medicine Residency, Mayo Clinic Arizona, Phoenix, AZ; 2Div of Laboratory Medicine & Pathology, Mayo Clinic Arizona, Scottsdale, AZ; 3Div of Nephrology & Hypertension, Mayo Clinic Arizona, Phoenix, AZ.

Background: Complex changes to the peritoneum have been described in patients treated with peritoneal dialysis (PD). A rare complication of PD is encapsulating peritoneal sclerosis (EPS), which may lead to bowel obstruction due to a progressive fibrosis of peritoneal tissue. Previously described cases of EPS typically occurred after years of treatment with PD.

Methods: A 40-year-old woman with a three month history of PD use was hospitalized with a one month history of progressive anorexia, nausea, vomiting, and epigastric pain. The patient was found to have resolving esophagitis on endoscopy and discharged. She was hospitalized one month later with a similar presentation and PD was stopped. Six months later, she was hospitalized with severe malnutrition. She demonstrated ascites which eventually was attributed to her severe hypoproteinemia. Tube feeds were attempted, but they were not tolerated. A small bowl follow-thru was normal. Trials of anti-emetics and proton pump inhibitors were unsuccessful. After 30 days of multiple studies and therapeutic interventions, an exploratory laparoscopy was performed. The appearance of the organs and peritoneum was normal. Peritoneal biopsy showed marked fibrohistiocytic thickening with scattered hemosiderin laden macrophages and reactive mesothelial cells. IgG staining was negative. Overall, the histologic changes were strikingly similar to those found in EPS.

The patient was treated with prednisone 50 mg daily for 12 weeks and tapered off over the next 12 weeks with a prolonged improvement in symptoms.

Conclusions: Symptomatic peritoneal fibrosis is typically associated with PD after several years of therapy. We now demonstrate similar changes in a patient who received PD for four months. Glucocorticoid therapy led to a swift resolution of her symptoms, which had previously been resistant to multiple other treatments.

FR-PO1108

Initiation of Peritoneal Dialysis in a Patient with Liver Disease and Refractory Ascites

Satyam Arora, Oleg Grapp, Alden Michael Doyle. Dept of Medicine, Div of Nephrology, Drexel Univ College of Medicine, Philadelphia, PA.

Background: Patients with end-stage liver disease (ESLD) complicated by refractory ascites often have concomitant ESKD. The dialysis modality of choice has been diffusion-based dialysis, such as haemodialysis, but slow continuous UF may be more appropriate in ESLD. Peritoneal dialysis (PD) for four months. Glucocorticoid therapy led to a swift resolution of her symptoms, which had previously been resistant to multiple other treatments.

Methods: A 40-year-old woman with a three month history of PD use was hospitalized with a one month history of progressive anorexia, nausea, vomiting, and epigastric pain. The patient was found to have resolving esophagitis on endoscopy and discharged. She was hospitalized one month later with a similar presentation and PD was stopped. Six months later, she was hospitalized with severe malnutrition. She demonstrated ascites which eventually was attributed to her severe hypoproteinemia. Tube feeds were attempted, but they were not tolerated. A small bowl follow-thru was normal. Trials of anti-emetics and proton pump inhibitors were unsuccessful. After 30 days of multiple studies and therapeutic interventions, an exploratory laparoscopy was performed. The appearance of the organs and peritoneum was normal. Peritoneal biopsy showed marked fibrohistiocytic thickening with scattered hemosiderin laden macrophages and reactive mesothelial cells. IgG staining was negative. Overall, the histologic changes were strikingly similar to those found in EPS.

The patient was treated with prednisone 50 mg daily for 12 weeks and tapered off over the next 12 weeks with a prolonged improvement in symptoms.

Conclusions: Symptomatic peritoneal fibrosis is typically associated with PD after several years of therapy. We now demonstrate similar changes in a patient who received PD for four months. Glucocorticoid therapy led to a swift resolution of her symptoms, which had previously been resistant to multiple other treatments.

FR-PO1110

Hemodialysis in a Patient with Eisenmenger’s Syndrome

Akinwande A. Akinfolakin, 1 Anitra W. Romhli, 2 Dirk M. Hentschel, 3 Finnian R. McAusland. 1Renal Div, Brigham & Women’s Hospital; 2Dept of Cardiology, Children’s Hospital, Boston.

Background: Adults with cyanotic congenital heart disease (CCHD) present a unique set of challenges for hemodialysis. We present a patient with unrepaired patent ductus arteriosus (PDA), hypoplastic right lung and resultant Eisenmenger’s syndrome referred for dialysis initiation.

Methods: A 49yo woman with CCHD and Eisenmenger’s syndrome experienced progressive proteinuric kidney disease, presumed secondary to chronic glomerulosclerosis. Her baseline O2 saturations displayed differential cyanosis, with upper extremities in the low 90’s and lower extremities in the 70-80’s. A left radial arterial catheter was inserted and continuous veno-venous hemofiltration was created months prior without change in symptoms. Significant laboratory values included a creatinine of 4.7 mg/dL, albumin of 2.3 g/dL and hemoglobin of 23.4 g/dL. At the end of her first session (Qb 200mL/min, Qd 300mL/min, F160 membrane, no UF) she experienced increasing dyspnea and a decline in upper extremity O2 sats, requiring initiation of non-invasive support. These changes were felt to be due to a hemodialysis-induced decline in systemic vascular resistance, resulting in increased right-to-left shunting and decline in systemic oxygenation. Her subsequent treatments were notable for high transmural pressures, thought to be due to hyperviscosity requiring clotted filters and thus auto-phlebotomized to a hemoglobin of 20.1 g/dL. These concerns necessitated manipulations in the dialysis prescription: 1) saline infusion pre-filter with UF post-filter in an effort to dilute blood and prevent clotting; 2) slower titration in Qb, Qd and session length; 3) heparin to minimize filter clotting; 4) close attention to hemoglobin goals (iron repletion as needed; avoidance of EPO where possible; but higher target hemoglobin in setting of chronic erythrocytosis).

Conclusions: Hemodialysis in patients with CCHD presents several challenges. Close attention must be paid to volume status, hemodynamics, target hemoglobin, residual renal function and nutritional status. In our case we successfully manipulated the hemodialysis prescription to minimize hemodynamic perturbations and clotting.

FR-PO1111

Treatment of Life Threatening Hyperkalemia with Peritoneal Dialysis—A Slower but Effective Option

D.A. Roseman, Jasvinder S. Bhatia. Renal Section, Boston Univ Medical Center, Boston, MA.

Background: Life threatening hyperkalemia is an uncommon scenario in maintenance peritoneal dialysis (PD) and because potassium clearance rates are significantly lower in PD compared to hemodialysis (HD), its use for this condition is generally discouraged. There is limited data regarding the use of PD for patients at imminent risk of death due to hyperkalemia.

Methods: A 48 year old man with history of hypertension, anuria and ESRD on automated peritoneal dialysis for five years presented directly to the emergency department (ED) with two days of weakness and non-productive cough after returning from a two week Caribbean vacation. The patient had discontinued dialysis for one week prior to presentation due to a perceived lack of sterility in the PD unit and fear of infection. On presentation, the patient was conversant, hypertensive, tachycardic, and hypoxic. His respiratory rate was progressively increased with associated leghema requiring non-invasive mechanical ventilation. An EKG showed sinus tachycardia with loss of P-waves and early peaked T-waves that quickly deteriorated into a wide complex tachycardia. Laboratory values showed Na 140 mmol/L, K 8.1 mmol/L, Cl 103 mmol/L, CO2 13.2 mmol/L, BUN 179 mg/dL, serum creatinine 31 mg/dL. The patient was treated with rapid bolus of calcium gluconate, insulin, dextrose, sodium bicarbonate, and albuterol. A manual PD exchange was initiated in the ED and the patient was transferred to the intensive care unit where he subsequently underwent manual 2 liter exchanges every 2 hours. After 10 hours serum potassium decreased to 6.6 mmol/L and by hours was 5.4 mmol/L with no concerning events on telemetry. Exchanges were then extended to every 4 hours. The patient was discharged 3 days after admission with complete resolution of hyperkalemia.

Conclusions: This case illustrates that PD, when combined with standard medical therapy, can be an effective treatment modality for life-threatening hyperkalemia if initiated quickly by experienced staff. The slower potassium clearance rates of PD compared to HD should not limit its consideration. This may be particularly relevant for patients with indwelling PD catheters and centers with limited or delayed resources.

FR-PO1112

Severe Mycobacterium Fortuitum Infection due to Inappropriate Exit-Site Care by Using Mountain Spring Water in a Patient Undergoing Continuous Ambulatory Peritoneal Dialysis

Yasuhiro Yoshimura, 1 Yoshihazu Miyasato, 2 Masataka Adachi, 2 Yasuyuki Fujii, 2 Naoki Shirahashi, 2 Kenichiro Kitanuma. 1Dept of Nephrology, Arao Municipal Hospital, Arao, Japan; 2Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.

Background: Exit-site infections are common complications among peritoneal dialysis (PD) patients. Nontuberculous mycobacterium (NTM) species which are usually derived from environmental sources account for less than 1% of exit-site infections. These organisms are more resistant to the antimicrobial agents that are typically used as an initial therapy for the exit-site infections and they often cause the loss of PD catheter and the interruption of PD. Here, we report a case of severe Mycobacterium fortuitum exit-site infection due to the inappropriate exit-site care by using mountain spring water.

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

168A
Methods: A 54-year-old woman with end-stage kidney disease due to IgA nephropathy had been treated with continuous ambulatory peritoneal dialysis (CAPD) for 3 years when she presented with purulent discharge from the exit-site. Although we introduced the standard exit-site care procedure by using normal saline as a cleaning solution, she had been using mountain spring water for 1 year. M. fortuitum grew on the culture of the purulent discharge. Acid-fast staining of the mountain spring water revealed acid-fast bacilli (AFB) and 16S rRNA sequencing confirmed the causative organism. She was treated with oral levofloxacin and clarithromycin. However, since the exit-site infection was not improved during the 6 weeks course of therapy, her PD catheter was removed and her dialysis modality was switched to hemodialysis.

Conclusions: Diagnosis of NTM species should be considered in PD patients with exit-site infections that are refractory to initial antimicrobial therapy. To our knowledge, this is the first report demonstrating that mountain spring water was responsible for the source of M. fortuitum exit-site infection. Routine evaluation and repeated education of the exit-site care would have prevented the M. fortuitum exit-site infection and the additional catheter surgery.

FR-POI112
A Case Report of Staphylococcus aureus Non-Valvular Endocarditis in a Chronic Hemodialysis Patient Jennifer C. Rodrigues,1 Paul E. Barre,2 Richard Fraser,2 Ahsan Alam.1 1Div of Nephrology, McGill Univ, Montreal, Canada; 2Pathology, McGill Univ, Montreal, Canada.

Background: Staphylococcus aureus bacteremia is a common infectious complication of central venous catheter (CVC) access. Non-valvular endocarditis occurs infrequently and may be an under recognized issue in hemodialysis. Here we present a case of right papillary muscle endocarditis diagnosed at autopsy in a hemodialysis patient treated for S. aureus sepsis.

Methods: A 54-year-old man was on chronic hemodialysis via a tunneled CVC. His ESRD was from reflux nephropathy and he had a failed kidney transplant. He was also known for congestive heart failure, chronic obstructive pulmonary disease, and bilateral below knee amputations secondary to throbosangiitis obliterans. He presented with progressive dyspnea, cough, nausea, vomitting, and diarrhea. He presented with a fever of 101.3°F, bibilarial crakles, and an elevated jugular venous pressure. He did not have any stigmata of endocarditis. His CVC had been changed three months prior. His chest x-ray showed mild pulmonary edema, and thus was treated with moxi, inhaled bronchodilators, intravenous steroids, and additional dialysis treatments. Due to a lack of improvement within 48 hours, broad-spectrum antibiotics (piperacillin-tazobactam and vancomycin) were initiated. Blood cultures returned positive for S. aureus in four of four bottles. The patient complained of chest pain, developed dyspnea and hypoxemia that deteriorated rapidly culminating in. Resuscitation was unsuccessful and he expired. Postmortem examination showed extensive PE.

Conclusions: Access thrombosis is frequently associated with subclinical PE that is usually inconsequential but occasionally it may be fatal. In cases of access clotting with extension to the central vein, it is advisable to forego the existing access and use a central vein catheter or a new access to dialyze the patient.

FR-POI115
Transplant Nephrectomy due to Persistent Bacteremia Maryam Sharif-Hassanabad, Alfred C. Cottrell. Nephrology, Loma Linda Univ Medical Center, Loma Linda, CA.

Background: Bacteremia after kidney transplant is a significant cause of morbidity and mortality. Here we report a complicated case of early post-transplant infection.

Methods: A 57 years old female with history of diabetes, hypertension, breast cancer and end stage renal disease on hemodialysis for 11 years was admitted for deceased donor renal transplant. She received Cefazolin as surgical prophylaxis. During the surgery, urinary bladder was found to be small with friable mucosa, making implantation of ureter difficult. On post-op day 3 she developed fever and all cultures grew multidrug resistant Enterobacter Aerogenes(sensitive to Imipenem). Despite Meropenem, the patient complained of chest pain, developed dyspnea and hypoxemia that deteriorated rapidly culminating in. Resuscitation was unsuccessful and he expired. Postmortem examination showed extensive PE.

Conclusions: Access thrombosis is frequently associated with subclinical PE that is usually inconsequential but occasionally it may be fatal. In cases of access clotting with extension to the central vein, it is advisable to forego the existing access and use a central vein catheter or a new access to dialyze the patient.
The fully functional kidney was removed to allow vascular repair of the large mycotic aneurysm as there was no safe way to salvage the transplant organ. The likely initial source of infection was the fragile bladder colonized with organisms resistant to Cefazolin. Early bacteremia at the time of transplant, failure of initial antibiotics to cover the organism and immunosuppression led to the aneurysm. 

**Conclusions:** Anuric patients can have low level bladder infections and may harbor organisms with multidrug resistance. In certain instances intraoperative flushing of the bladder with extended spectrum antibiotics or perioperative use of a broad spectrum antibiotic to cover resistant bacteria may be prudent.

---

**FR-PO1116**

**Acute Right Sided Heart Failure as a Complication of AVG Creation in a Dialysis Patient**


**Nephrology Div, Univ of Wisconsin, Madison, WI.**

**Background:** Heart failure is an important source of mortality in dialysis patients.

Predisposing factors that might contribute to pump failure in dialysis patients include high output hemodynamics due to dialysis access including arteriovenous fistulae (AVF) and grafts (AVG).

In this case report, we describe a dialysis patient presenting with right-sided heart failure and high output cardiac failure precipitated by AVG creation.

**Methods:** Case Description: A 68 year old male dialysis patient with history of hypertension, cardiomyopathy and orthotopic heart transplant presented with new onset hypotension and tachycardia. Few days prior to presentation, he had a new axillary artery catheterization. At the time of presentation, he had a new pericardial effusion.

**Conclusions:** To our knowledge, this is the first reported case of high cardiac output failure in a patient with AVG with axillary-axillary anastomosis. The exact prevalence of high output failure in dialysis population is unknown; however several factors are associated with an increased risk of fistula-induced high-output cardiac failure. These include location of the dialysis access (proximalmore than distal), male sex, high blood flow through the fistula.

The patient’s hemodynamics improved significantly with bedside manual occlusion of his AVG. AVG fistulogram and ligation of the AVG was done by Interventional Nephrology team. The patient’s hemodynamic profile improved significantly and he was discharged with normal vital signs.

---

**FR-PO1117**

**Dialysate Temperature Adjustment as an Effective Treatment for Baroreflex Failure Syndrome in Hemodialysis Patient**

Natsumi Tanabe, Koki Takane, Yudo Tanno, Keitaro Yokoyama, Izumi Yamamoto, Ichiro Okhido, Takashi Yokoo. 

**Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.**

**Background:** Baroreflex failure syndrome is a rare disorder which causes labile blood pressure, headache, flushing, diaphoresis and emotional lability.

It is caused by history of trauma or radiotherapy around neck, bilateral carotid-body tumor or section of glossopharyngeal nerve. We report a case of a hemodialysis patient with labile blood pressure during hemodialysis because of his baroreflex failure syndrome.

**Methods:** We report a case of a 68-year-old CKD5 patient who had difficulties of hemodialysis treatment because of severe fluctuations in blood pressure with hypertensive attacks or hypotensive episodes which caused him a severe discomfort. His dialysis treatment was started in 2010 and since that time baroreflex failure syndrome has been suspected because of his clinical manifestations and history of radiotherapy around his neck for his cancer of tongue in 1994. Baroreflex failure syndrome is diagnosed by cold stressor test.

**Conclusions:** In our case, environmental stimulation such as temperature change modified the patients fluctuating blood pressure. Change of dialysate temperature could be an option for controlling the unstable blood pressure due to baroreflex failure syndrome.

---

**FR-PO1118**

**A Rare Case of Upper Gastrointestinal Bleeding in a Hemodialysis Patient**

Deepak K. Nandikanti, Saba Farooq, Elvira Gosmanova. 

**Nephrology, Univ of Tennessee Health Science Center, Memphis, TN.**

**Background:** Upper esophageal varices (UEV), a rare cause of upper gastrointestinal bleeding (UGIB), typically occurs with superior ven a cava (SVC) obstruction. Here we describe a hemodialysis (HD) patient with UEV resulting from right innominate vein (RIV) occlusion with a patent SVC, complicated by UGIB.

**Methods:** 31-year old male with ESRD on HD via right (R) brachiocephalic AV fistula (AVF) presented with hematemesis and tarry stools for 2 days. He also reported progressive worsening of R upper extremity (RUE), neck and facial swelling. Prior to AVF placement in 2011, he had bilateral internal jugular (IJ) tunneled catheters, but no arm swelling. On exam, BP was 88/40 mmHg, Facial swelling, nasal congestion, and a hoarse voice were present. RUE had pitting edema. AVF had a normal thrill. Multiple collateral veins were noted on R side of the neck and upper chest. His hemoglobin was 9.1 g/dL (2 weeks prior it was 11.6 g/dL) and stool hemoccult positive. EGD showed distal RUE but no active bleeding. CT stenosis showed severe UEV obstruction with extensive CT stenosis of R pneumonia. Left RUE collateral, bilateral IJ narrowing but no evidence of intrathoracic masses. SVC appeared patent. RUE venogram confirmed the severe RUE occlusion that was not amenable to recanalization. Facial and arm swelling, nasal congestion and mild stridor were concerning for SVC-like syndrome, related to RIV stenosis in combination with RUE AVF. The patient coming from AVF was likely overwhelming venous return from the RUE and the head, causing blood shunting into right thyroid vein that in turn, led to the development of UEV and UGIB. Since RV could not be recanalized, the AVF was ligated and the patient was switched to peritoneal dialysis. Complete resolution of stridor, facial, and RUE swelling occurred within 10 day of AVF ligation. No further episodes of UEV were noted.

**Conclusions:** Development of arm and facial swelling after AVF construction warrants evaluation for central vein stenosis, which untreated can lead to development of UEV. UEV are usually asymptomatic, but can lead to life threatening UGIB. Repair of the stenosis or AVF ligation leads to resolution of both SVC syndrome and UEV.

---

**FR-PO1119**

**Pulmonary Nocardiosis and Pneumocystis Jiroveci Pneumonia: Dual Opportunistic Lung Infection in a Kidney Transplant Recipient**

Ekmol Tantisattamo, Ashfar Chami, Stephen O. Pastan. 

**Renal Div, Dept of Medicine, Emory Univ School of Medicine, Atlanta, GA.**

**Background:** Pulmonary infections are a common complication after kidney transplantation. We report a case of a kidney transplant recipient who presented with a mixed pulmonary infection with both Nocardia pseudobrasiliensis and Pneumocystis jirovecii.

**Methods:** Case Description: A 60-year-old man with history of ESRD received a deceased donor renal transplant and was treated with tacrolimus, mycophenolate mofetil and prednisone. He presented 1 year post transplantation with a week six history of fever, night sweats and a 14 kg weight loss. For three weeks he complained of dyspnea and fatigue. Serum creatinine was elevated to 11mg/dL. Chest x-ray was unremarkable; however, a chest CT scan revealed a 2.8x2.6 cm right lower lobe mass. Initially, he was empirically treated for a fungal infection with amphotericin B and posaconazole. He underwent bronchoscopy with transbronchial biopsies, but pathology revealed no evidence of malignancy and tissue culture was negative for bacteria and legioella. Acid fast bacilli and fungal smear were also negative. As he continued having fevers and hypoxemia, video-assisted thoracoscopic surgery (VATS) with biopsy was performed and frozen section revealed evidence of granulomatous disease. Gram stain suggested Nocardia spp. and trimethoprim/sulphamethoxazole was started. Finally, tissue culture grew Nocardia pseudobrasiliensis and pathology revealed Pneumocystis jirovecii by GMS stain. He responded well to treatment with trimethoprim/sulphamethoxazole, tacrolimus and mycophenolate mofetil doses were reduced during the hospitalization, and renal function resolved to his baseline.

**Conclusions:** Bacterial infection is the most common cause of pneumonia in kidney transplant recipients, although opportunistic infections are also commonly seen. Immunosuppressed patients are also at risk for infection with multiple organisms. Early use of invasive diagnostic measures, such as bronchoscopy or VATS, should be pursued for patients who present with nonspecific symptoms and who do not respond to initial empiric treatment.

---

**FR-PO1120**

**Eculizumab in the Treatment of De Novo Post-Transplant Thrombotic Microangiopathy**

Federico Calaf, Juan M. Gonzalez, Wadi N. Sukri. 

**Dept of Internal Medicine, The Methodist Hospital, Houston, TX.**

**Background:** Eculizumab is an anti C5 monoclonal antibody currently approved for the treatment of Paroxysmal Nocturnal Hemoglobinuria and atypical Hemolytic Uremic Syndrome. Experimental data suggests complement activation is involved in Anti Phospholipid Syndrome (APS) pathogenesis, yet the mechanism remains unclear. We add eculizumab as a salvage therapy for treatment of acute de novo allograft thrombotic microangiopathy. Our case suggests that activation of the complement cascade plays a crucial role in graft thrombosis, even though currently there is no complement target therapy approved for APS.

**Methods:** A 42 y/o Caucasian male with history of End Stage Renal disease secondary to Anti Phospholipid Syndrome (APS) and SLE nephritis on hemodialysis for 10 months presented to the hospital with severe chest pain and shortness of breath. Chest CT scan revealed a large left pleural effusion with associated pulmonary infiltrates. After discussion with the patient, we decided to proceed with the treatment of serious chest pain and shortness of breath with heparin and eculizumab. After a successful trial, the patient was sent to the ICU to continue anticoagulation with eculizumab and prednisone. He presented 1 year post transplantation with a six week history of fever, night sweats and a 14 kg weight loss. For three weeks he complained of dyspnea and fatigue. Serum creatinine was elevated to 11mg/dL. Chest x-ray was unremarkable; however, a chest CT scan revealed a 2.8x2.6 cm right lower lobe mass. Initially, he was empirically treated for a fungal infection with amphotericin B and posaconazole. He underwent bronchoscopy with transbronchial biopsies, but pathology revealed no evidence of malignancy and tissue culture was negative for bacteria and legioella. Acid fast bacilli and fungal smear were also negative. As he continued having fevers and hypoxemia, video-assisted thoracoscopic surgery (VATS) with biopsy was performed and frozen section revealed evidence of granulomatous disease. Gram stain suggested Nocardia spp. and trimethoprim/sulphamethoxazole was started. Finally, tissue culture grew Nocardia pseudobrasiliensis and pathology revealed Pneumocystis jirovecii by GMS stain. He responded well to treatment with trimethoprim/sulphamethoxazole, tacrolimus and mycophenolate mofetil doses were reduced during the hospitalization, and renal function resolved to his baseline.

**Conclusions:** Bacterial infection is the most common cause of pneumonia in kidney transplant recipients, although opportunistic infections are also commonly seen. Immunosuppressed patients are also at risk for infection with multiple organisms. Early use of invasive diagnostic measures, such as bronchoscopy or VATS, should be pursued for patients who present with nonspecific symptoms and who do not respond to initial empiric treatment.
antithymocyte globulin, solumedrol, and mycophenolate. Due to the lack of improvement in renal function, a renal allograft percutaneous biopsy was performed three days post-operatively. The biopsy showed chronic tubulointerstitial nephritis with interstitial fibrosis, focal vascular thrombosis and endothelial injury. The c4d stainings were negative. No signs of hemolytic anemia or thrombocytopenia were evident and haptoglobin remained normal. Laboratory data showed a weakly positive antinuclear antibody, elevated antinuclear and ANA antibodies and undetectable double stranded DNA. C3 and C4 complement levels were low, but had been within normal levels prior to surgery. An ADAM 13 activity level was unremarkable. On post-operative day 4, eculizumab 900mg IV-weekly infusion was added to his immune suppression regimen. After three weeks, eculizumab was increased to 1200mgIV every other week for five additional doses. The serum creatinine improved from 6.7mg/dl before eculizumab to 3.4mg/dl at the end of the treatment. A repeat kidney biopsy showed tubular atrophy and interstitial fibrosis but no features of acute thrombotic microangiopathy. Seven months after his last eculizumab treatment his serum creatinine is 2.5mg/dl.

FR-PO1121

Eculizumab for Treatment of Acute Antibody Mediated Rejection Manmeet Brar, Youshally Humayun, Jasminna Craci, Kenneth E. Kokko, Steven Wagner. Internal Medicine Nephrology, Univ of Mississippi Medical Center; Jackson, MS.

Background: Antibody mediated rejection (AMR) complicates about 5% of all kidney transplants. AMR is relatively refractory to therapy and leads to reduced graft survival. Current therapy is often insufficient. Here we present a patient who was successfully treated for AMR with Eculizumab, an inhibitor of the terminal complement cascade.

Methods: A 24 year old male with a failed living related donor kidney transplant 6 years ago received a deceased donor SCD transplant with thymoglobulin induction. Post-operative day 4, c4d was 16% class I and 70% class II, with negative FAs. He received a single 900mg dose of Eculizumab. Urine output decreased and creatinine increased to 1.6. He was readmitted after one week with anuria and a creatinine of 5.1. A repeat kidney biopsy showed diffuse 3+ C4d staining and diffuse peritubular capillaritis with luminal neutrophils, consistent with Banff grade II acute antibody mediated rejection (AMR). Donor specific antibodies were detected to A29 (1:16), B45 (1:16), DR4 (1:64), and DR15 (1:64). In addition to solu-medrol, two sessions of plasma exchange, and 4 doses of rituximab were given. Over 10 days, his serum creatinine dropped to 1.4mg/dl. Repeat kidney biopsy showed tubular atrophy and interstitial fibrosis but no features of acute thrombotic microangiopathy. Seven months after his last eculizumab treatment his serum creatinine is 2.5mg/dl.

FR-PO1122

Alemtuzumab for the Treatment of Acute Humoral Renal Allograft Rejection Mohit Agarwal, Jasminna Craci, Kenneth E. Kokko, Steven Wagner. Internal Medicine Nephrology, Univ of Mississippi Medical Center; Jackson, MS.

Background: Alemtuzumab is a recombinant DNA-derived humanized, rat immunglobulin G1 (IgG1) monoclonal antibody directed against CD52, a cell surface glycoprotein expressed at high levels by T and B lymphocytes. It was originally approved as Campath® in 2001 for B-cell chronic lymphocytic leukemia (B-CLL) but was subsequently withdrawn in 2012 for relaunch as Lemtrada® for the management of Multiple Sclerosis. It has also found use in kidney transplantation and is increasingly being utilized for induction therapy and for the management of acute cellular rejection (ACR). We report the 1st case series of its use in the management of acute humoral rejection (AHR).

Methods: We retrospectively evaluated the efficacy of Alemtuzumab in three patients with biopsy confirmed acute humoral rejection of renal allografts. Two patients also had prominent acute cellular rejection. All patients were on triple maintenance immunosuppression with prednisone, tacrolimus and mycophenolate and were treated with Alemtuzumab 30 mg IV in conjunction with three day course of high dose IV methylprednisolone. Alemtuzumab exhibited depletion of peripheral lymphocytes. One of the patients with mixed cellular and humoral rejections, one patient (Grade AHR-II, ACR-IA) had a drop in serum creatinine (sCr) from 3.3 to 1.8 in two weeks and the other patient (Grade AHR-III, ACR-IA) had a sudden rise in sCr from 2.1 to 2.4 next day followed by a progressive fall to 1.8 over the next week. The third patient had predominantly humoral rejection (Grade AHR-II, ACR-Questionable) with coexisting transplant glomerulitis and chronic transplant glomerulopathy. She exhibited minimal initial response followed by a progressive sustained rise in sCr from 1.8 to 4.8. A repeat biopsy three and half month later was suggestive of chronic transplant glomerulopathy. For the above, though, this time accompanied by calcineurin inhibitors acute tubular toxicity.

Conclusions: Alemtuzumab destroys mature lymphocytes expressing CD52. Our experience suggests that it can be a viable treatment option in the management of acute humoral rejection (AHR) of renal allografts.

FR-PO1123

Sirolimus-Induced Diffuse Alveolar Hemorrhage in a Kidney Transplant Recipient Manpreet Singh, Sandeep Ghaai, Moshe Shashar, Steven C. Borkan, Jean M. Francis. Renal Section, Boston Univ School of Medicine, Boston, MA.

Background: Sirolimus, a mammalian target of rapamycin inhibitor, is commonly used in solid organ transplant recipients. Diffuse alveolar hemorrhage related to sirolimus has been reported in 9 cases in the literature. The case herein describes an additional kidney transplant recipient who developed diffuse alveolar hemorrhage while on sirolimus.

Methods: We describe a 36 year-old Ethiopian female with a past medical history significant for end stage renal disease secondary to uncontrolled hypertension and treated latent tuberculosis. She underwent a cadaveric renal transplant 10 months prior to admission to our hospital. She received tacrolimus, prednisone and mycophenolate for 4 months. She developed severe immune suppression 9 months after kidney transplantation, sirolimus was substituted for tacrolimus due to calcineurin inhibitors toxicity. 4 weeks after the switch, she presented to our hospital with productive cough, fever and hemoptysis. Although clinically stable on admission, 24 hours later, the patient acutely decompensated and required ventilator support. Computed Tomography of her thorax demonstrated bilateral multifocal infiltrates. Bronchoscopy confirmed the presence of diffuse alveolar hemorrhage. Extensive workup was negative for infectious, autoimmune or neoplastic processes.

Conclusion: Sirolimus induced diffuse alveolar hemorrhage was the likely etiology. Sirolimus was discontinued on admission and high-dose steroids were administered. The patient developed severe kidney graft failure secondary to acute tubular necrosis that was confirmed by allograft biopsy. She improved clinically on high dose steroids and was successfully weaned off the ventilator, but continued to require dialysis after discharge.

Conclusions: We describe a case of sirolimus induced diffuse alveolar hemorrhage in a kidney transplant recipient. Extensive workup to rule out other etiologies, early withdrawal of sirolimus and high dose steroids seem to be effective in the treatment of this near fatal complication. This case substantiates the need for close monitoring of pulmonary symptoms while taking Sirolimus.

FR-PO1124

Back to Square One: Graft Irradiation for the Treatment of Kidney Transplant Rejection Paramveer Singh Saluja, Marwan M. Abu Minhasr, Ann Kathleen N. Gamilla-Crudo, Pradeep V. Kadambi. Internal Medicine, UTMB, Galveston, TX.

Background: Kidney transplant is the preferred option to treat end stage kidney disease (ESKD). Allograft rejection continues to be a major cause of transplant failure in spite of ongoing advancement in immunosuppression (IS). We are presenting a case series of patients who underwent local graft irradiation (RT) for acute allograft rejection refractory to conventional therapies.

Methods: A 40 year old male with ESKD due to Membranous Nephropathy received a kidney transplant in 2005. His clinical course within the first year was complicated by 2 episodes of acute cellular rejection (ACR) that led to loss of allograft function, necessitating nephrectomy. He received a second kidney transplant in 2009 with an initial baseline creatinine of 1.9 mg/dl. Three years after transplant, he developed ACR (Banff 2b) and humoral rejection, and was treated with IVIG, anti-thymocyte globulin (ATG), and steroids. His allograft function continued to worsen (peak creatinine of 4.6 mg/dl) and repeat biopsy 3 weeks later revealed persistent resistant Banff 2b ACR. Since he had high residual rejection, he was treated with 4 doses of RT combined with IS. Over 1 month following treatment, his creatinine improved to 1.9 mg/dl. A 50 year old male with ESKD due to DM type 1 received a SPP kidney transplant (CV D+/R-) in 2012 with new creatinine level of 1.2 mg/dl. Six months after transplant, he developed ACR (Banff 2b) and humoral rejection, and was treated with IVIG, anti-thymocyte globulin (ATG), and steroids. His allograft function continued to worsen (peak creatinine of 6.9 mg/dl). After 3 months, he was treated with 3 doses of RT combined with IS. Over 3 months following treatment, his creatinine improved to 1.9 mg/dl.

Conclusions: Based on our experience and available literature, patients who have acute rejection refractory to IS or those who have concomitant infection, local radiation of the allograft would be a viable adjunct to the overall management.

FR-PO1125

Pulmonary Phaeohyphomycosis Caused by Phaeoacremonium and Dactylaria Constricta in a Renal Transplant Recipient: Successful Treatment with Posaconazole Saivaralaex Monaganti, Carlos Q. Santos, Daniel C. Brennan. Internal Medicine, Washington Univ School of Medicine, St. Louis, MO.

Background: Phaeoacremonium and Dactylaria are dematiaceous fungi. Over 70 genera and 150 species cause human and animal disease. They are widely distributed in soil, wood and decomposing plant debris and characterized by melanin or melanin-containing hyphal cells. Phaeoacremonium is a collective term for cutaneous, subcutaneous and systemic disease caused by dematiaceous fungi. It is most frequently an opportunistic infection in immunosuppressed patients, and has been rarely reported to affect organ transplant recipients. The overall mortality rate with skin, soft-tissue or joint infection is 25% and 57% with systemic disease. To our knowledge, this is the first case of pulmonary infection by multiple dematiaceous fungi and only the third reported case of lung infection caused by Phaeoacremonium.

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

Underline represents presenting author/disclosure.

621A
Methods: A 49 year old white female, 6 years post renal transplantation, presented to the transplant clinic with a history of worsening dyspnea, cough and fatigue over 6 months after failure to respond to several courses of antibiotics prescribed by her primary physician. Physical exam was unremarkable. CT of the chest revealed nodular opacities in the right upper lobe. Culture of a fine needle aspiration yielded Pseudomonas aeruginosa. Culture of BAL, yielded Daclactria constricta and a few Mycobacterium avium-intracellulare. The patient was started on posaconazole 200 mg PO QD and her tacrolimus dose was reduced. A repeat CT after 1 month showed improvement. Posaconazole was changed to 400 mg PO BID for 4 months with complete resolution.

Conclusions: There is no standard antifungal regimen for Daclactria or Pseudomonas aeruginosa reported in the literature. Posaconazole is the most recently approved triazole with an extended spectrum of activity. Posaconazole was chosen over other azoles because it is well tolerated, has a favorable side effect profile, and low potential of drug interactions with only a moderate interaction with tacrolimus compared to other azoles. Our patient responded well to treatment with no relapse of symptoms during 2.5 years of follow up.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO1126
The Story of Having Subclavian Venous Catheter and the AV Fistula on Same Side

Background: The use of subclavian veins (SCV) as hemodialysis vascular access is not recommended. Patients who had SCV catheter in the past can present with a problem years later.

Methods: This is the story of a 33 years old man who was initiated on hemodialysis (HD) in the year 2000 through right internal jugular vein (IJV) non-cuffed catheter, for his ESRD due to CTID. Soon, he had left wrist native AV fistula (AVF) and the right IJV catheter was removed after 4 weeks. The left AVF had spontaneous closure after 3 months following an episode of post HD hypotension. He had right SCV non-cuffed HD catheter as right IJV could not be cannulated. He agreed for a second AVF at right wrist, 8 months later. This fistula matured well and his right SCV catheter was removed after 9 months. In 2005, he developed right upper limb (UL) swelling and was diagnosed to have right SCV stenosis. He underwent right SC venoplasty with stenting and the AVF worked well till 2009, when he underwent cadaver renal transplantation. The AVF was not used since 2009. He developed swelling of right UL over past 1 year.

He was detected to have fracture of right SCV stent with obstruction. He underwent stent plasty with new covered stent in the SCV. 1 month later, his swelling disappeared, and his right wrist AVF was surgically ligated. Hand returned to near normal shape.

Conclusions: SCV HD catheters are associated with high risk of central venous stenosis and hence it is recommended not to use SCV for HD catheters. This patient had a SCV in the era when such recommendation did not exist. Also, stenting of central vein stenosis is not preferred at present. This patient had a stent in the right SCV at a time when it was the usual practice. The stent fractured and led to severe venous congestion of right UL which could have resulted in the loss of right UL.

FR-PO1127
De Novo Renal Cell Carcinoma in Renal Graft 22 Years Following Cadaveric Transplantation with Atypical Presentation of Refractory Metabolic Acidosis
Zaid Brikanji, Kavita Pal, Raafat Farag Makary, Andrea Pocanariu. 1Div of Nephrology and Hypertension, Dept of Medicine, Univ of Florida, Jacksonville, Jacksonville, FL, 2Dept of Medicine, Univ of Florida, Jacksonville, Jacksonville, FL, 3Pathology and Laboratory Medicine, Univ of Florida, Jacksonville, Jacksonville, FL.

Background: Post-Transplant graft Renal Cell Carcinoma (RCC) has rarely been reported. The longest post-transplant time at the diagnosis of graft RCC reported has been 13 years.

Methods: We present the case of a fifty-two year old African American female who received a cadaveric right kidney transplantations in 1990 secondary to End State Renal Disease (ESRD) from Systemic Lupus Erythematosus (SLE). She had stable chronic allograft dysfunction and was being maintained on Cyclosporine, Mycophenolate Mofetil , in addition to Prednisone. Regular follow up revealed no complaints of gross hematuria or flank pain. Ultrasonography, performed due to refractory metabolic acidosis, revealed a 4.5 cm heterogenous hypoechoic lesion within the midportion of the transplanted allograft with increased vascularity. MRI confirmed the presence of a highly suspicious mass for renal cell carcinoma with no distant metastases. A renal allograft biopsy revealed renal cell carcinoma (RCC), conventional clear cell type. The patient subsequently underwent successful Radical Transplant Nephrectomy and was placed on Hemodialysis.

Conclusions: This case demonstrates a rare presentation of allograft RCC 22 years following transplantation with refractory metabolic acidosis. It also highlights the importance of regular close follow up with ultrasonography and the need for more clear guidelines for post-transplant ultrasonographic follow up, especially in cases of long post-transplant period.

FR-PO1128
Polyomavirus-Associated Nephropathy: Not Just BK-Virus
Sandra Barrow, Juan M. Gonzalez, Wadi N. Suki. Internal Medicine/ Nephrology, Methodist Hospital, Houston, TX.

Background: Over the past decade, polyomavirus associated nephropathy (PVAN) emerged as a major cause of allograft dysfunction and graft loss. The vast majority of PVAN is associated with BK virus infection but this case illustrates that other polyomaviridae need to be considered in the differential diagnosis.

Methods: A 61 year old man with end stage renal disease received a living nonrelated donor transplant in 2004. He had stable renal allograft function with serum creatinine ranging from 1.9 - 2.5 mg/dl. He received maintenance immunosuppressive therapy with prednisone, mycophenolate mofetil and tacrolimus. Eight years after transplantation, his serum creatinine increased to 3.5 mg/dl. Kidney biopsy was performed. Light microscopy revealed several foci of tubular lymphocytic infiltration along with viral nuclear changes. Calibrochôme® Anti-SV40 T Antigen stain was strongly positive suggesting a diagnosis of BK virus-associated nephropathy. Surprisingly, BK viral loads measured by PCR assay in the biopsy material remained undetectable, whereas a positive Anti-SV40 T Antigen stain may also represent the presence of other human polyomaviruses. Therefore, urinary and serologic samples were analyzed for JC virus (JCV) and PCR assays revealed markedly elevated urinary levels as well as JCV viremia. A diagnosis of JC virus associated nephropathy was established and reduction of immunosuppression was initiated. Additionally, the patient received intravenous immunoglobulin injections two weeks. Treatment is currently in progress and creatinine levels have remained stable.

Conclusions: BKV, JCV and the monkey virus SV40 belong to the family of polyomaviridae. They share 69-75% of their DNA sequences and immunohistochemical staining using Calibrochôme® Anti-SV40 T Antigen does not distinguish between them. JCV associated nephropathy is an exceptionally rare cause of PVAN. Therapy primarily targets a reduction of immunosuppression but successful treatment with immunoglobulins, cidofovir and leflunomide have been reported. Since timely treatment of PVAN is crucial it is important to recognize that a positive Anti-SV40 T Antigen stain in the absence of BKV viremia may represent JCV associated nephropathy.

FR-PO1129
Intrarenal Urothelial Carcinoma Staining Positive for BKV Years after Resolution of BKV Nephropathy
Patricia M. Myers-Gurevich, Darshana Madhandia, Steven Salvatore, Jun B. Lee, Surya V. Seshan. Nephrology and Hypertension, New York Presbyterian Hospital - Weill Cornell, New York, NY.

Background: Reactivation of BKV is common in renal allograft recipients, placing them at risk for nephropathy and graft loss. Recent literature suggests BKV infection may be associated with certain malignancies. We report a case of intra-graft malignant urothelial carcinoma (UC) associated with positive staining for BKV presenting years after resolution of BK viremia/nephropathy.

Methods: A 53 year old sensitized woman received a living unrelated renal transplant following pre-transplant immunomodulation for a positive donor flow cytometry crossmatch. Post-transplant, baseline creatinine (crt) was 1.5mg/dl. At 6 months, her crt rose to 2.2mg/dl in the setting of high BK viremia. Renal allograft biopsy was positive for BKV associated nephropathy. Immunosuppression was reduced, and repeat was negative for BKV. 7 months later BK viremia cleared and crt normalized. 5 years post-transplant, the patient still free of BK viremia, developed de novo DSA to DR53. Immunosuppression was intensified. 7 years post-transplant, the patient was admitted for gastrointestinal symptoms and rising crt. She underwent a repeat renal biopsy which revealed intratubular UC in situ associated with positive BKV and p53 stain. The benign tubules were negative for BKV. Subsequent transplant nephrectomy revealed microinvasive high grade UC, extensively involving renal tubules, with multifocal lymphatic invasion.

Conclusions: Immunosuppression places transplant recipients at higher risk for malignancy. The incidence of UC in this population is low (2%). Most UC arises in the native bladder, rarely ureter, and is very rarely restricted to the allograft. Although there is a known association with BK virus infection and urothelial malignancy, intrarenal UC staining positive for BKV has not been reported. The positive BKV stain within the tumor nuclei may signify incorporation of BKV DNA transcripts into the genome of neoplastic cells. With negative C4d staining and no evidence of antibody mediated rejection, the rising DSA could be an indirect sign of local immune activation to control tumor growth.

FR-PO1130
Fever of Unknown Origin in a Renal Transplant Patient
Karl Pembarg, Grant Springman, Joseph Kremer, Blake Nestok. The Christ Hospital, Cincinnati, OH.

Background: PTLD is a complication following organ transplantation that occurs in 1%-2% of patients post-transplant. Current research has concluded that the degree of immunosuppression along with positive EBV serotype leads to triggering of monocyte activation of B cells resulting in lymphoma.

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

Underline represents presenting author/disclosure.
Fever and Pancretopathy in Kidney Transplant Recipient-Malignancy Is Always a Possibility Jie Cui, Francesca Cardarelli, Vanesa Bijol, Martina M. McGrath. Nephrology Dept, Brigham and Women’s Hospital, Boston, MA.

Background: Single or multi-lineage cytopenia is very common in renal transplant patients. While infection and immunosuppression are the most common causes of pancytopenia in transplant recipients, it is crucial to maintain a high suspicion of other relevant etiologies including thrombotic microangiopathy, graft-versus-host disease, autoimmunity and malignancy.

Methods: A 33-year-old male with a history of ESRD due to diabetic nephropathy received a deceased donor renal allograft in 2007, and presented with a one week history of nausea, vomiting and right lower quadrant abdominal pain. Physical examination revealed a temperature of 37.2°C, BP of 139/69 mmHg and HR of 121 beats/min. His abdominal examination revealed right lower quadrant tenderness over the allograft. Urinalysis was positive for leukocyte esterase and >182 WBC/hpf. He received empiric piperacillin/tazobactam on admission. Over the next 24 hours, the patient developed septic shock with acute respiratory failure requiring intubation and norepinephrine. His urine and blood cultures grew klebsiella pneumoniae. A noncontrast CT scan of the abdomen and pelvis showed heterogeneous gas containing collection in the allograft. Transplant kidney nephrectomy was performed. The gross pathology revealed an acutely inflamed, friable, necrotic, gas filled kidney with extensive hemorrhage with yellow exudates. Microscopic examination revealed acute severe pyelonephritis with abscesses. He postoperatively completed two weeks of antibiotic therapy and was discharged home in stable condition.

Conclusions: EPN is an acute, severe, necrotizing bacterial or fungal infection of the renal parenchyma, collecting system or perinephric tissue. The grade of severity of EPN guides therapy and Al-Geizawi et al have classified EPN of the renal allograft into 3 stages that is determined by the extent of gas collection. Our patient with multi-organ failure and uncontrolled sepsis not responding to medical management falls into the severest category (stage 3) of his classification. Our patient underwent emergent nephrectomy and rapidly improved thereafter. Recognition of the severity of EPN guides therapy.

FR-PO1132

Iron Metabolism and Rapamycin (Sirolimus)-Induced Microcytic Anemia in Renal Transplant Patients Shivani Upadhyaw, Joshua Zaritsky, Tomas Ganz. UCLA.

Background: Sirolimus is a macrocytic antibiotic, which binds to the FK binding protein and modulates the activity of mTOR (mammalian target of rapamycin). This drug is widely used for preventing rejection of solid organ transplants and graft vs host disease following bone marrow transplantation. A unique feature of sirolimus is that it also induces profound microcytosis, which is poorly understood. Previous studies in renal transplant patients have demonstrated that oral iron supplementation in patients who received sirolimus did not improve their microcytic anemia. However, anemia improved once patients discontinued sirolimus.

Methods: First a retrospective chart review of pediatric renal transplant patients was done to determine the prevalence and characteristics of sirolimus-induced anemia. Then a prospective study was designed to evaluate functional iron deficiency in pediatric patients who were not anemic but had increased serum ferritin and transferrin saturation.

Conclusions: The pathologies seen in the transfusion biopsy duplicated the findings of the native disease in this patient. The disease recurred approximately three years after transplant, which is much more rapid than expected in the case of recurrent diabatic nodular glomerulosclerosis. We believe this to be the first case of recurrent idiopathic glomerulosclerosis post-kidney transplantation. It establishes that the condition can redevelop and that the lag time for recurrence may be shorter than that seen with diabatic nodular glomerulosclerosis.

Funding: Clinical Revenue Support

FR-PO1134

Recurrent Idiopathic Nodular Glomerulosclerosis after Kidney Transplantation Mamoun Elsir Bashir,1 Irfan Warraich,2 Melvin E. Laski.1 1Internal Medicine, Texas Tech Univ Health Sciences Center; Lubbock, TX; 2Pathology, Texas Tech Univ Health Sciences Center; Lubbock, TX.

Background: Idiopathic nodular glomerulosclerosis is a rare condition that closely resembles diabetic nodular glomerulosclerosis but occurs in non-diabetic individuals. It differs from the nodular glomerulosclerosis that develops in fibriiliary diseases and membranoproliferative glomerulonephritis by the absence of fibrils or tubular structures on electron microscopy and negative immunofluorescence respectively. The cause of idiopathic glomerulosclerosis remains unknown but it has been associated with tobacco use in some studies.

Methods: Patient is 64 year old non-diabetic, non-smoking Caucasian male with history of well controlled hypertension who developed end stage renal disease secondary to idiopathic nodular glomerulosclerosis diagnosed by renal biopsy. The biopsy tissue revealed typical nodular glomerulosclerosis and was negative for amyloid material, and negative for fibrils or other deposits on electron microscopy. The patient underwent deceased donor kidney transplant and did well in regard to his renal transplant with creatinine between 1.0 and 1.5 mg/dl and no significant proteinuria. Two years later worsening allograft renal function (creatinine 1.6 mg/dl) and progressive proteinuria (up to 4 gm/dl) were noted. Subsequent transplant biopsy diagnosed recurrent idiopathic nodular glomerulosclerosis, and also was negative for amyloid or other fibriillary structures. There was no sign of humoral or cell mediated rejection. The patient remained non-diabetic throughout the pre- and post-transplant course.

Results: .

Conclusions: The pathology seen in the transplant biopsy duplicated the findings of the native disease in this patient. The disease recurred approximately three years after transplant, which is much more rapid than expected in the case of recurrent diabatic nodular glomerulosclerosis. We believe this to be the first case of recurrent idiopathic glomerulosclerosis post-kidney transplantation. It establishes that the condition can redevelop and that the lag time for recurrence may be shorter than that seen with diabatic nodular glomerulosclerosis.
and adult patients with solid organ transplants treated with sirolimus. The study design includes evaluation of serum iron, total iron binding capacity, serum hepcidin, ferritin, mean corpuscular hemoglobin concentration, reticulocyte count and CRP prior to initiation of sirolimus therapy and at four time points post initiation of therapy.

Results: The retrospective chart review of 21 renal transplant patients (10 pediatric, 11 adult) was completed. The hemoglobin and MCV were compared one month prior to the start of sirolimus and 6 months after. MCV was decreased in sirolimus-treated patients compared to baseline (0.0001, paired t-test). We currently have enrolled 5 pediatric patients in the prospective study showing microcytosis and iron deficiency after the start of sirolimus. The hepcidin appropriately responded to iron deficiency showing decreasing levels from baseline to 2 months after the start of sirolimus. However, they continue to remain iron deficient. Ferritin also is low in these patients.

Conclusions: Hepcidin does have appropriate response to iron deficiency in patients on sirolimus. Therefore, sirolimus must work downstream of the hepcidin pathway. There is evidence to suggest that sirolimus does affect the iron pathway, however, it is not through hepcidin.

FR-PO1135

Treatment of Post-Transplant Immunosuppression Resistant Focal Segmental Glomerulosclerosis with Adrenocorticotropic Gel

Patrick P. McHugh, Muhammad Ahmad Mujtaba, Tim E. Taber, Muhammad S. Yaqub, Asif A. Sharifuddin.
Nephrology/Transplant, Medicine, Indiana Univ, Indianapolis, IN.

Background: Post-transplant recurrence of focal segmental glomerulosclerosis (FSGS) is associated with poor outcomes and early graft failure. Adrenocorticotropic Hormone (ACTH) has shown efficacy in some cases of native kidney nephrotic syndrome including FSGS. Its actions include reducing oxidative stress and diminishing podocyte apoptosis and podocyte loss through binding to melanocortin receptors. We report a case of immunosuppression resistant FSGS after transplant treated with ACTH with resultant decrease in proteinuria.

Methods: A 60-year-old white female with a history of FSGS since 2003 (chronic kidney disease stage 5) underwent pre-dialysis living related kidney transplant. She was induced with Thymoglobulin®, early corticosteroid (4-day) withdrawal, and was maintained on tacrolimus and mycophenolate mofetil. Her serum creatinine (Cr) at postoperative week 16 was 0.9 mg/dL. On POD11 she was readmitted with Cr of 3.1 mg/dL and worsening proteinuria. Biopsy showed no evidence of rejection and negative immunofluorescence staining, but electron microscopy showed widespread podocyte effacement consistent with recurrent FSGS. Plasma exchange and high dose steroids were given. Conventional antiproteinuric treatments included ACEi/ARB and statin, plus those shown below.

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

Underline represents presenting author/disclosure.

624A

FR-PO1137

Pregnancy or Uremia? - A Case of Pregnancy Symptoms Mimicking Uremia in a Woman with Advanced Chronic Kidney Disease (CKD)

Antionios Tzmaloukas, 2 David Buchwald, 1 Amarpreet S. Sandhu.
1Div of Nephrology, Dept of Internal Medicine, Univ of New Mexico Health Science Center, Albuquerque, NM; 2Div of Nephrology, Dept of Internal Medicine, VA Hospital Albuquerque, Albuquerque, NM.

Background: Pregnancy is rare in women undergoing renal replacement therapy (RRT) and may lead to maternal and fetal complications. Due to negligible rates of conception, early pregnancy symptoms can be confused with uremic symptoms in patients with CKD stage V. We present a case that illustrates the diagnostic and management challenges created by pregnancy in women on peritoneal dialysis (PD).

Methods: A 25-year-old-woman with CKD stage V (CrCl < 15 mL/min) due to autosomal dominant polycystic kidney disease developed nausea, vomiting, and anorexia. A PD catheter was placed for presumed uremic symptoms. Two weeks after placement of the PD catheter, she presented with persistent nausea, vomiting, and abdominal cramps. CT showed ascending colitis, scattered free intra-abdominal fluid, polycystic kidneys, and no mention of uterus. She was diagnosed with gastroenteritis. Serum ß-HCG, obtained 2 weeks later, was positive. US revealed a 20-week pregnancy. At 24 weeks of gestation, PD prescription was changed. Fluid volume was decreased to 1.5 L and exchanges increased to 5 cycles. Dialysis adequacy was maintained with Kt/V urea of 0.35 and Kt/V BUN of 50 mg/dl throughout the pregnancy. She received increased doses of iron and epoetin. Labor was induced after she developed abdominal discomfort during infusion of the dialysate at 38 weeks. She delivered a healthy baby boy. During labor PD was continued with a decreased fill volume dwell time. Regular PD prescription was resumed 12 hours after delivery.

Conclusions: A combination of low expectation of pregnancy as well as gastrointestinal symptoms resulted in a delayed diagnosis of pregnancy in this case. The CT scan did not show the pregnancy, probably because of the early stage. Coordinated care between a nephrologist, obstetrician, and midwife is essential for better outcomes. Women on PD require special care towards the end of pregnancy.

FR-PO1138

Panci Immune ANCA Associated Vasculitis De Novo in Pregnancy

Hasan Riaz, 1 Qurram-ul-Ain Shamim, 1 Raafat Farag Makary, 2 Leighton R. James, 1 Andreae Poonmaru, 1 1Dept of Medicine, Div of Nephrology, Univ of Florida College of Medicine, Jacksonville, FL; 2Dept of Pathology, Univ of Florida College of Medicine, Jacksonville, FL.

Background: Antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis (AAV) is infrequently seen in women of childbearing age. Pregnancies occurring in active disease have a documented unfavorable outcome for both the mother and the child. There is a dearth of literature on the de novo occurrence of AAV in pregnancy and on the best approach to management.

Methods: We present a case of a young woman who was admitted to hospital with hyperemesis gravidarum, volume depletion and acute kidney injury (plasma creatinine 4.46 mg/dL). Urinalysis demonstrated hematuria, pyuria and urination sedimentation showed leukocytes, erythrocytes and no casts. Despite adequate volume repletion, the patient became increasing oliguric with further deterioration in renal functional parameters. Serologic testing revealed elevated c-ANCA titer and kidney biopsy was consistent with pan-nuclear immune crescentic glomerulonephritis. Despite steroids, intravenous immunoglobulin (5x at 400mg/kg) and plasma exchange (1.5 plasma volumes every other day for 7 days) the patient required hemodialysis. Following pregnancy termination, intravenous cyclophosphamide therapy (1mg/m² once a month) was initiated. After two months, renal function recovered and hemodialysis was discontinued. She continues on tapering prednisone and monthly cyclophosphamide (1 mg/m²) without relapse.

Conclusions: This case highlights the challenges related to management of pregnant patients with new onset Pan-antic-immune ANCA positive, rapidly progressive glomerulonephritis (ANCA-associated glomerulonephritis (ANCA-GN)). Given the limited guidelines, management of affected individuals requires multi-disciplinary teams that have developed skills in managing pregnant patients with rare autoimmune disorders.
FR-PO1139

De Novo Collapsing Glomerulopathy Associated with Pregnancy
Ederson Vidal Moura,1 Carla Queiroz Neves,1 Alline S. A. Oliveira,1 Camila Barbosa L. Oliveira,1 Luis H.B.C. Sette,1 Gisele Vajgel Fernandes,1 Filipe Carrilho,1 Lucila Maria Valente.1 1Nefrologia, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil; 2Nefrologia, UFPE, Recife, Pernambuco, Brazil.

Background: Collapsing glomerulopathy (CG) was initially described as idiopathic or related to HIV. Currently is associated to other clinical conditions such as: autoimmune diseases, drugs, infections and trombotic microangiopathy. In renal allografts, CG may be recurrent or rarely de novo.

Methods: A 39 years old female patient diagnosed with SLE in 1993 developed ESRD. She underwent hemodialysis for 7 years and kidney transplant (deceased donor) in 2001. During follow-up serum creatinine (Scr) levels remained around 1.0 mg/dL. She had IgG+ for CMV and HTLV since pre-transplant period, without clinical evidence of infection. Immunosuppressive drugs were prednisone, FK and azathioprin. In march 2013, during the 27th week of pregnancy, she developed proteinuria (3.19 g/24 h), edema, dyslipidemia, hypertension and worsening Scr, without symptoms of lupus flare or infection. Pregnancy was interrupted and blood pressure levels improved, but both renal function (Scr 2.3) and proteinuria (11.4 g/24 h) worsened. Renal biopsy, performed a month after pregnancy interruption, revealing: 9 glomeruli, 4 presenting with collapse of glomerular capillaries consistent with CG. Moderate chronic transplant nephropathy and arteriolar hyaline deposits were also found. Immunofluorescence revealed traces of IgG in glomeruli. During follow-up the patient showed stabilization of renal function (Scr 2.0), lower proteinuria (2.5 g/24 h) and a proper blood pressure control.

Conclusions: CG is associated with multiple trigger factors including hemodynamic disturbance and endothelial lesion. In this case report, no other factor such as: HTLV, CMV or Parvovirus B19 activity were found in histologic and sorologic investigation. Histological findings were absent for endotheliosis, however the biopsy was performed lately enough for regression of the lesions. The association with pregnancy was performed since it was the most obvious precipitating factor for the onset of nephrotic syndrome and renal allotraft dysfunction.

FR-PO1140

Post-Partum Hypopituitarism Presenting with Symptomatic Hyponatremia
Richa A. Pandey, Quynh N. Lam, Didier Portilla. Div of Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR.

Background: Post partum anterior pituitary insufficiency from pituitary necrosis is rare and can manifest as SIADH causing hyponatremia.

Methods: 29 year old Egyptian lady presented with acute onset dizzines 7 days post-vaginal delivery of a term pregnancy, complicated by profuse vaginal bleeding. Pregnancy was interrupted and blood pressure levels improved, but both renal function (Scr 2.3) and proteinuria (11.4 g/24 h) worsened. Renal biopsy, performed a month after pregnancy interruption, revealing: 9 glomeruli, 4 presenting with collapse of glomerular capillaries consistent with CG. Moderate chronic transplant nephropathy and arteriolar hyaline deposits were also found. Immunofluorescence revealed traces of IgG in glomeruli. During follow-up the patient showed stabilization of renal function (Scr 2.0), lower proteinuria (2.5 g/24 h) and a proper blood pressure control.

Conclusions: CG is associated with multiple trigger factors including hemodynamic disturbance and endothelial lesion. In this case report, no other factor such as: HTLV, CMV or Parvovirus B19 activity were found in histologic and sorologic investigation. Histological findings were absent for endotheliosis, however the biopsy was performed lately enough for regression of the lesions. The association with pregnancy was performed since it was the most obvious precipitating factor for the onset of nephrotic syndrome and renal allotraft dysfunction.

FR-PO1141

Hypertension and Hyponatremia during Pregnancy with Complete Aldosterone Suppression
Louis R. Spiegel, Anna Mathew, Alessandro Bellucci. Div of Kidney Diseases & Hypertension, Hofstra North Shore - LI School of Medicine, Great Neck, NY.

Background: Common causes of hypertension during pregnancy include pre-existing hypertension, gestational hypertension, and pre eclampsia. If hyponatremia and metabolic alkalosis are present then disorders of the renin-angiotensin-aldosterone system must be considered. We present a case of a woman with hypertension and hyponatremia during the third trimester of her first pregnancy, likely due to a rare gain-of-function mutation of the mineralocorticoid receptor.

Methods: A 21 year old female with no prior medical history was admitted to the hospital from her obstetrician’s office at 32 weeks of gestation with hypertension to 170/100. Upon hospitalization serum potassium was 2.2 mEq/L and serum bicarbonate was 27mEq/L. She denied history of hypertension, or intake of licorice. Workup for secondary hypertension, including 24 hour urine for cortisol and catecholamines, plasma metanephrines and serum TSH, was negative. Transstubular potassium gradient (TTKG) was elevated indicating renal potassium wasting. She had no edema and 24 hour urine protein was 180 mg/day. Plasma renin activity was 0.97 ng/mL/hr and plasma aldosterone was suppressed to <1 ng/dL. Frequent intravenous and oral potassium supplementation normalized the serum potassium. Adequate blood pressure control was obtained via up-titration of oral labetalol.

Conclusions: We present a unique case of de novo onset hypertension and hyponatremia during the third trimester of pregnancy. Suppressed levels of aldosterone and elevated TTKG are most consistent with a rare gain-of-function mutation of the mineralocorticoid receptor (Geller’s syndrome), causing progesterone to act as an agonist. High levels of progesterone result in hypertension during the second or third trimester. Follow-up genetic testing for this autosomal dominant point mutation of the mineralocorticoid receptor will be conducted to confirm the diagnosis.
SA-PO001

Design of a Bioartificial Renal Cell System (BRECS) for Mass Production
H.D. Humes,1 C. Pino,1 T. DeLandsheer,1 A. Westover,1 D. Buffington,1
1Innovative BioTherapies; 2Univ of Michigan.

Background: The bioartificial renal epithelial cell system (BRECS), is a cell-based device to treat acute kidney injury. This technology is based on a Phase I/II clinically proven cell-therapy approach, previously demonstrated by our group: renal assist device (RAD). To enable widespread implementation of cell therapy, the BRECS was designed to be cryopreserved as a complete device, cryoystored, cryoshipped to an end-use site, thawed as a complete device, and employed in a therapeutic extracorporeal hemofiltration circuit. This strategy overcomes the storage and distribution issues that have been previous barriers to cell therapy.

Methods: Following computer aided design (CAD) to simulate flow through the device, prototype BRECS were produced by stereolithography (SLA-BRECS) and tested to determine the design to be mass-produced by injection molding (IM-BRECS). Cell viability and functionality were assessed by lactate production, oxygen consumption rate (OCR) and glutathione degradation over extended culture periods up to 2 months. ZO-1 (epithelial tight junctions), AT-1 (central cilia) and brush border enzymes were evident on SLA-BRECS and IM-BRECS were assessed by metabolic function after thaw, and viability stains upon study termination.

Results: The SLA-BRECS design with the best cell performance was chosen to be manufactured by injection molding. The resulting IM-BRECS design was palm-size, had a fill volume of ~10 mL, and exhibited near plug-flow conditions without major stagnation points or areas of recirculation. This design was capable of supporting ~1 x 10^10 cells, with a mean OCR of ~200 mmol/min, lactate production of ~700 μmol/day, and glutathione degradation of ~800 nmol/hr over extended culture periods up to 2 months.

Conclusions: IM-BRECS can be mass-produced for potential use in AKI and related indications which have been preliminarily assessed in pre-clinical large animal models. This innovative, tissue engineered device overcomes many of the hurdles to clinical implementation of cell therapy.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO002

Comparison of Kidney Injury between Two Stage Revision Arthroplasty with Antibiotic Loaded Spacers and Other Revision Orthopaedic Procedures
Arpita Bhalla,1 Manmadathu Ran,2 1Dept of Orthopaedics, Tufts Medical Center, Boston, MA; 2Dy of Nephrology, Tufts Medical Center, Boston, MA.

Background: Two-stage revision arthroplasty using antibiotic loaded spacers (ALS) is the standard of care for prosthetic joint infections (PJI). Although systemic toxicity of ALS is the standard of care for PJI, compared to other revisions and is accentuated by comorbidities. This innovative, tissue engineered device overcomes many of the hurdles to clinical implementation of cell therapy.

Methods: Following computer aided design (CAD) to simulate flow through the device, prototype BRECS were produced by stereolithography (SLA-BRECS) and tested to determine the design to be mass-produced by injection molding (IM-BRECS). Cell viability and functionality were assessed by lactate production, oxygen consumption rate (OCR) and glutathione degradation over extended culture periods up to 2 months. ZO-1 (epithelial tight junctions), AT-1 (central cilia) and brush border enzymes were evident on SLA-BRECS and IM-BRECS were assessed by metabolic function after thaw, and viability stains upon study termination.

Results: The SLA-BRECS design with the best cell performance was chosen to be manufactured by injection molding. The resulting IM-BRECS design was palm-size, had a fill volume of ~10 mL, and exhibited near plug-flow conditions without major stagnation points or areas of recirculation. This design was capable of supporting ~1 x 10^10 cells, with a mean OCR of ~200 mmol/min, lactate production of ~700 μmol/day, and glutathione degradation of ~800 nmol/hr over extended culture periods up to 2 months.

Conclusions: IM-BRECS can be mass-produced for potential use in AKI and related indications which have been preliminarily assessed in pre-clinical large animal models. This innovative, tissue engineered device overcomes many of the hurdles to clinical implementation of cell therapy.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO004

Early Goal-Directed Therapy in the Management of Type 1 Hepatorenal Syndrome: A Combined Retrospective and Pilot Study
Zhiwei Zhang,1 Geetha S. Maddukuri,2 1Nephrology, VA Loma Linda Healthcare System and Loma Linda Univ, Yorba Linda, CA; 2Nephrology, St. Louis Univ, St. Louis, MO.

Background: Appreciation of the central role for arterial vasodilatation in the pathogenesis of hepatorenal syndrome (HRS) has led to routine use of vasoconstrictors in combination with albumin as a medical therapy for HRS. Various vasoconstrictors have been explored but the optimal approach for such therapies has not yet been established. The aim of current study was to examine the role of early goal-directed therapy (EGDT) in the management of type 1 HRS, a condition associated with very poor prognosis.

Methods: A total of 59 patients with type 1 HRS who received a combination therapy of vasoconstrictors and albumin were enrolled into a retrospective cohort study. Subjects having a sustained increase of more than 10 mmHg in mean arterial pressure (MAP) by day 3 after initiation of therapy were categorized as EGDT and the rest as controls. In addition, five patients were enrolled into a prospective pilot study in which a titration protocol of vasoconstrictors was utilized to achieve EGDT.

Results: Patients in the EGDT group achieved significantly higher incidence of treatment success or total response, less requirement of dialysis and more incidence of liver transplantation. More importantly, EGDT is associated with better short-term and long-term overall survival as well as transplant-free survival. The effectiveness of such an approach was further confirmed in the pilot study.

Conclusions: Management of HRS with EGDT is associated with favorable clinical outcomes. Targeting an early and sustained increase in MAP is clinically feasible and physiologically sound, although the optimal target has yet to be determined by prospective studies.

Funding: Veterans Affairs Support

SA-PO005

Body Composition Monitor in Contrast-Induced AKI: A New Tool for an Old Enemy
Paolo Lentini,1 Luca Zanolii,2 Stefania Rastelli,2 Massimo de Cal,1 Anna Basso,1 Andrea Contestabile,1 Valentina Pellanda,1 Roberto Dell’Aquia,1 1Nephrology, San Bassiano Hospital, Bassano del Grappa (VI), Italy; 2Internal Medicine, Catania, Italy.

Background: Most radiological procedures require administration of contrast media. Contrast-induced acute kidney injury (CI-AKI) is the third cause of hospital acquired AKI. Extracellular volume expansion reduced contrast-induced tubulo-toxic effects. We aimed to test if control of hydration by bioimpedance is useful to reduce incidence of CI-AKI.

Methods: 50 patients undergoing contrast medium infusion of 100-150 ml of iopamidol for abdominal or thoracic computer tomography were enrolled into a retrospective cohort study. Subjects having a sustained increase of more than 10 mmHg in mean arterial pressure (MAP) by day 3 after initiation of therapy were categorized as EGDT and the rest as controls. In addition, five patients were enrolled into a prospective pilot study in which a titration protocol of vasoconstrictors was utilized to achieve EGDT.

Results: Patients in the EGDT group achieved significantly higher incidence of treatment success or total response, less requirement of dialysis and more incidence of liver transplantation. More importantly, EGDT is associated with better short-term and long-term overall survival as well as transplant-free survival. The effectiveness of such an approach was further confirmed in the pilot study.

Conclusions: Management of HRS with EGDT is associated with favorable clinical outcomes. Targeting an early and sustained increase in MAP is clinically feasible and physiologically sound, although the optimal target has yet to be determined by prospective studies.

Funding: Veterans Affairs Support

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

Underline represents presenting author/disclosure.

626A
bicarbonate and N-acetyl-cysteine twice a day. In the bioimpedance-based protocol, a mild over-hydration (within ±1 and ±3) was obtained the day of the procedure and the next 3 days. Bioimpedance was performed daily with Body Composition Monitor (BCM - Fresenius Medical Care®) to evaluate the hydration status. Laboratory and clinical examination were performed daily after the procedure for 3 days. CI-AKI was defined as a rise in sCr of 0.5 mg/dL 48 hrs after a radiological procedure.

Results: 49 patients were enrolled (36:14:4Y:GFR66±13mL/min/1.73m²). 29 patients were included in the bioimpedance-based protocol and 20 patients in standard protocol for hydration. For a comparable age, sCr and GFR at baseline, incidence of AKI was significantly lower in bioimpedance-based than in standard protocol (14% vs 40%, respectively; P=0.04). In multivariate analysis adjusted for age, the bioimpedance-based protocol (OR 0.17 if performed; 95%CI 0.03-0.99; P<0.05) and high baseline GFR (OR 0.92 for 1 mL/min/1.73 mL increase; 95%CI 0.87-0.98; P=0.005) reduced the risk of CI-AKI.

Conclusions: The bioimpedance-based control of hydration is useful to reduce CI-AKI incidence in patients undergoing abdominal or thoracic computer tomography.

SA-PO006
Acute Creatinine Improvement after CT with and without Intra venous Iodinated Contrast Use Masahiko Nagahama,1 Goki Eriguchi,2 Keita Hirano,1 Fumika Taki,1 Takuya Fujimura,1 Kenicho Koi ta thashi,2 Kumiko Shimasaki,1 Yasuhiro Komatsu.1 1Nephrology, St. Luke’s International Hospital, Tokyo, Japan; 2Biostatistics, Kurume Univ Graduate School of Medicine, Fukuoka, Japan.

Background: Administration of intravenous (IV) iodinated contrast medium has been associated with acute kidney injury (AKI), known as contrast induced nephropathy (CIN). Of interest, there are some subjects whose serum creatinine (sCr) is decreased and kidney function seems to be improved after contrast use. We have termend this condition “Acute Creatinine Improvement (ACI)”. The purpose of this study was to clarify the incidence and prognosis of “ACI” as well as CIN in patients undergoing CT with and without IV contrast. Methods: 1833 patients who had had, either enhanced CT (Exposure, n=3671) or unenhanced CT (Comparison, n=3368), at St. Luke’s international hospital in Tokyo between 2003 and 2010. CIN is defined as a 0.5 mg/dL increase in sCr or a 25% or greater decrease in eGFR within 7 days after CT, while “ACI” is defined as a 0.5 mg/dL decrease in sCr or a 25% or greater increase in eGFR as opposed to CIN. The survival rate was compared in “ACI” and Non-“ACI” subjects as well as CIN and Non-CIN subjects using Kaplan-Meier curves. Results: In exposure group, 72% of patients developed CIN and 79% of patients developed “ACI”, while in comparison group, 14% of patients developed “ACI”. The prognosis of patients with CIN was significantly worse than that without CIN (P<0.001 by log-rank). Although the prognosis of patients with “ACI” and Non-“ACI” in exposure group were not significantly different (P=0.32 by log-rank), the prognosis of patients with “ACI” was significantly worse than that without “ACI” in comparison group (P=0.001 by log-rank).

Conclusions: We identified a high incidence of “ACI” in both exposure group and comparison group. Remarkably, development of “ACI” has poor impact on prognosis as CIN does. This suggests that any fluctuation of sCr, either rise or fall, in one week period is related to worse prognosis.

SA-PO007
Hydration prior to CT-Pulmonary Angiography Is Not Required for Prevention of Contrast Induced-Acute Kidney Injury: The Randomized Nefros Trial Judith Kooman,1 Yvo W.J. Sijpkins,2 Marjolijn Van Buren,1 Aart J. Molen, Van der,3 Nicolas Jm Aarts,4 Cornelis J. Van Roorden,3 Suzanne Cannegiezer,1 Hen Putter,1 Ton J. Rabelink,1 Menno V. Huisman.1 1Leiden Univ Medical Center; 2Bromovo Hospital,3 Haga Teaching Hospital,4 Medical Center Haaglanden.

Background: Hydration to prevent contrast induced-acute kidney injury (CI-AKI) results in a diagnostic delay when performing CT-pulmonary angiography (CTPA) in patients presenting with clinically suspected acute pulmonary embolism (PE). The aim of our study was to analyze whether withholding hydration is non-inferior to one hour 250ml 1.4% sodium bicarbonate (Na-bic) hydration prior to intravenous contrast administration for CTPA in patients with a GFR<60 mln/min.

Methods: Primary outcome of this randomized trial was the increase in serum creatinine 48-96 hours post CT. Secondary outcomes were the incidence of CI-AKI (increase in serum creatinine ≥25% or 0.5mg/dl), recovery of renal function, and the need for dialysis. Withholding hydration was considered non-inferior if the mean relative serum creatinine increase was at most 15% higher compared with Na-bic.

Results: From 2009-2013, 135 patients with clinically suspected PE undergoing CTPA were included in the bioimpedance-based protocol and 20 patients in standard protocol for hydration. For a comparable age, sCr and GFR at baseline, incidence of AKI was significantly lower in bioimpedance-based than in standard protocol (14% vs 40%, respectively; P=0.04). In multivariate analysis adjusted for age, the bioimpedance-based protocol (OR 0.17 if performed; 95%CI 0.03-0.99; P<0.05) and high baseline GFR (OR 0.92 for 1 mL/min/1.73 mL increase; 95%CI 0.87-0.98; P=0.005) reduced the risk of CI-AKI.

Conclusions: The bioimpedance-based control of hydration is useful to reduce CI-AKI incidence in patients undergoing abdominal or thoracic computer tomography.

SA-PO008
Evaluation of the Risk Factors for Contrast Induced Nephropathy in Hypertensive Patients with Normal Renal Function Osman Z. Sahin,1 Fatih Sumner,2 Mehmet Bostan,3 Teslime Ayza,4 Yavuz Uguurlu.1 1Nephrology, Recep Tayyip Erdogan Univ Faculty of Medicine, Rize, Turkey; 2Internal Medicine, Recep Tayyip Erdogan Univ Faculty of Medicine, Rize, Turkey; 3Cardiology, Recep Tayyip Erdogan Univ Faculty of Medicine, Rize, Turkey.

Background: Coronary angiography which requires intravascular administration of iodinated contrast media (CM) is a leading cause of contrast induced nephropathy (CIN). The aim of this study was to assess the risk factors on the development of CIN in hypertensive patients who have normal renal function undergoing coronary angiography.

Methods: This retrospective study included all consecutive patients who underwent elective coronary angiography at our center between September 2011 and May 2012. Coronary angiography was performed 254 hypertensive patients. Before the procedure, IV saline infusion and N-acetylcysteine were given to all the patients. ACEi or ARB was discontinued 2 days before the procedure. CIN was defined as >0.5 mg/dL increase or >25% rise in serum creatinine (SCr) concentration within 48 hours of contrast exposure compared to baseline.

Results: The study population consisted of 254 patients, aged 19-84 years (mean: 57.67 ± 9.7) and 57% of them were male. 29.1% of the patients had type 2 diabetes. CIN occurred in 7% of the patients. Clinical data of the patients are presented in table 1.

Conclusions: Hyperuricemia can be a predictor of contrast induced nephropathy in hypertensive patients with normal renal function.

SA-PO009
Sodium Bicarbonate, N-Acetylcysteine, Both, or Saline Alone for Prevention of Contrast-Induced Nephropathy: A Network Meta-Analysis Seth Wright, Katherine H. Michener, Amy Earley, Ravendhara R. Bannuru, Katrin Uhlig. Tufts Medical Center, Boston, MA.

Background: Trials have shown inconsistent results on whether contrast-induced nephropathy (CIN) can be prevented by giving IV sodium bicarbonate (Bic) instead of IV saline or by adding oral N-acetylcysteine (NAC) to IV saline. Furthermore, it is uncertain which intervention is superior or whether they should be combined.

Methods: We conducted a systematic review in MEDLINE and the Cochrane Central Register of Controlled Trials (1995-4/2013) of trials using these interventions and reporting outcomes of CIN (based on creatinine rise ≥25% or 0.5 mg/dL) or dialysis for a network meta-analysis. Analysis was by a Bayesian random effects multiple treatment comparison model with non-informative priors, using Markov Chain Monte Carlo implement through OpenBUGS software.

Results: 38 studies (n=6466) provided data on CIN. Mean patient age ranged from 59-78 years. Most patients had CKD stage 3 (range 1-4) and received intra-arterial contrast (predominantly for coronary angiography). The Figure shows the odds ratios for CIN for the different comparisons by network meta-analysis. There was consistency between direct and indirect effect estimates. For the dialysis outcome, odds ratios showed the same order but with wide, non-statistically significant credibility intervals due to fewer events and comparisons (12 studies, 2587 patients).
Cisplatin to maintain their volume status. The mean age was 45.7 years and 65% were females. The most common diagnosis for prescribing Ketorolac was Osteoarthrosis. The conventional prescribed dose was 30 mg IV every 6 hours. AKI developed in 6.4% of patients. In patients with AKI, 68% were 65 years or older, 68% had hypertension, 41% were diabetic, 40% were concomitantly receiving insulin for an ACE-i or an ARB and 40% were also being given diuretics. The mean pre dose creatinine was 1.09 mg/dl and mean post dose creatinine was 1.72 mg/dl. During the time of AKI, 72% still received Ketorolac.

Conclusions: AKI occurs more commonly than previously anticipated in Ketorolac treated patients even at average doses. Hypertension and diabetics are the two most common comorbidities in patients who developed AKI. Those who are older than 65 years old may be at higher risk. Concomitant use of drugs that affect renal function, such as ACE-i, ARBs and diuretics, may also increase the risk of AKI. Ketorolac prescribing in the acute care hospital should consider individual comorbidities, and use of other drugs that can increase AKI risk. Awareness of current renal function through diligent review of daily labs may help prevent administration of Ketorolac in those with already impaired renal function.

SA-P0012
Creatine Production Is Reduced in Acute Kidney Injury Patients with Sepsis Rolando Clauere-Del Granado1, Josse Bouchard2, Glenn M. Chertow3, Jonathan Himmelfarb4, T. Alp Ikizler5, Ravindra L. Mehta6,7, School of Medicine, IBISSMED, Universidad Mayor de San Simon, Bolivia; 8Univ of Montreal, Canada; 9Stanford School of Medicine; 10Kidney Research Institute, Univ of Washington; 11Vanderbilt Univ Medical Center; 12Univ of California San Diego.

Background: Diagnosis and staging of acute kidney injury (AKI) uses the serum creatinine concentration (sCr). In a previous animal model of AKI, Doi et al. have shown that sepsis dramatically decreases the kidney clearance of creatinine. This decreased clearance would limit early detection of AKI. We evaluated the effect of sepsis on sCr, creatinine production (Pc'), and creatinine degradation (Dc') in patients with AKI. We hypothesized that sepsis will reduce creatinine production and sCr.

Methods: We analyzed data from 234 critically ill non-diayosed patients with AKI from five centers included in the PICARD study. Creatinine production was calculated using Cockcroft-Gault formula and using the Morán et al. formula (Kidney Int 1985, 27:928-937), which adjusts sCr for fluid balance. Creatinine degradation was computed using the Mitch et al. equation (Clin Sci 58:327-335, 1980) and adjusted for fluid balance.

Results: Of the 234 patients, 139 were septic (59%). Non-adjusted and adjusted sCr levels were lower in patients with sepsis (non-adjusted sCr median 2.0 mg/dl IQR [1.5 – 2.8] vs. 2.5 mg/dl IQR [1.8 – 3.5] and adjusted sCr 2.0 mg/dl IQR [1.4 – 2.7] vs 2.4 mg/dl IQR [1.8 – 3.6]; p < 0.001). Pc' was significantly lower in septic than in non-septic (1,211 mg/day IQR [934 – 1,472] vs. 1,278 mg/day IQR [1,017 – 1,538] mg/day; p < 0.001); and after adjusting Pc' for fluid balance (1,092 mg/day IQR [828 – 1,295] vs. 1,124 mg/day IQR [892 – 1,344]; p < 0.001). Dc' was also significantly lower in septic than in non-septic patients.

Conclusions: Sepsis reduces creatinine production and reduces serum creatinine in critically ill patients with AKI thereby blunting the expected increases of serum creatinine. These observations could confound the early diagnosis of AKI. Sepsis also affects creatinine degradation.

Funding: NIDDK Support

SA-P0013
Remote Ischaemic Preconditioning Does Not Prevent Kidney Injury after Cardiac Surgery in Patients with Chronic Kidney Disease Sean Gallagher1, Dan A. Jones1, Steven Michael Harwood2, Rakesh Uppal2, Magdi Yaqoob2, 1Cardiology, Barts Health NHS Trust, London, United Kingdom; 2Nephrology, Barts Health NHS Trust, London, United Kingdom; 3William Harvey Research Institute, Queen Mary Univ, London, United Kingdom.

Background: Perioperative complications of cardiac surgery including myocardial infarction and acute kidney injury (AKI) are associated with substantial morbidity and mortality. We assessed the impact of remote ischaemic preconditioning (RIPC) upon these complications in patients with chronic kidney disease (CKD).

Methods: 86 patients with CKD (defined as eGFR <60 ml/min) undergoing coronary surgery were randomized 1:1 to standard care with (n=43) or without (n=43) RIPC. RIPC consisted of three 5-minutes cycles of forearm ischaemia and reperfusion. Primary end point was development of AKI defined as a 0.3 mg/dL increase in serum creatinine within 48 hours of surgery. Secondary end points included a comparison of biomarkers of renal injury (serum cystatin C (CyC), serum and urinary neutrophil gelatinase associated lipocalin (NGAL)) and a comparison of myocardial enzyme release (defined by 72 hour troponin T area under the curve (72 hrs AUC TnT)).

Results: Clinical and operative characteristics were similar between RIPC and control groups. 27.9% (24/86) of the study cohort developed AKI following surgery. The incidence of AKI in the two groups was RIPC 27.9% (12/33) vs. control 27.9% (12/33); p=1.0. There was no difference in biomarkers of renal injury or myocardial enzyme release between the groups following surgery.

Conclusions: RIPC using forearm ischaemia confers no meaningful additional renal or myocardial protection in patients with CKD undergoing cardiac surgery.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
SA-PO014

Effect of Hospital Volume on Acute Kidney Injury in Percutaneous Nephrolithotomy Admissions

Ankit Sarkharia,1 Manoj Monga,2 Juan C. Calle,1
1Nephrology, Cleveland Clinic, Cleveland, OH; 2Urolgy, Cleveland Clinic, Cleveland, OH.

Background: Acute Kidney Injury (AKI) is an important cause of morbidity and mortality in hospitalized patients. In general, procedural volume has been shown to be associated with worse outcomes. However, not much is known about AKI in hospitalized patients treated in the setting of percutaneous nephrolithotomy (PCNL). We, therefore, designed this study to look at the frequency and effect of hospital volume on AKI in hospitalized patients undergoing PCNL.

Methods: We designed a retrospective cohort study using Nationwide Inpatient Sample database which is the largest all-payer inpatient care database in US and contains a 20% stratified sample of US community hospitals. Patients aged ≥18 years undergoing PCNL in year 2010 were identified using ICD-9-CM codes. AKI was identified using ICD-9-CM codes 584.X. End Stage Renal Disease Patients were excluded. Chi square test was used to compare categorical variables. Hospital procedure volume for the year studied was generated and divided into low volume (<50), medium volume (50-100), high volume (>100) hospitals.

A multivariable logistic regression was used to assess the effect of hospital volume on AKI.

Results: Of estimated 46,899 (95% CI: 42,710-51,088) PCNL admissions in the year 2010, 34.1% (6,101) had AKI. Patients with AKI tended to be more older males, African Americans and on Medicare. They also more often had chronic kidney disease (CKD), Urinary Tract Infection (UTI) and hydronephrosis with UTI. Patients with AKI also seemed to be admitted more often to lower volume hospitals (57.0% vs 66.3% of those with no AKI; p<0.001). On multivariable regression, in comparison to low volume hospitals, admission to high volume hospitals was associated with decreased odds of AKI (OR 0.59; 95% CI 0.42-0.80).

Conclusions: AKI seems to occur over a third of hospitalized patients undergoing PCNL. Hospital volume of PCNL is an predictor of AKI with a protective effect of high volume hospitals.

SA-PO015

The Economic Impact of Acute Kidney Injury in England

Marion Kerr,1 Michael Bedford,2 Beverley Matthews,3 Donal O’Donoghue,4 Insight Health Economics; 1East Kent Hospitals Univ NHS Foundation Trust; 2NHS Kidney Care; 3Salford Royal NHS Foundation Trust.

Background: Acute kidney injury (AKI) is one of the most serious and common complications affecting hospital inpatients. We estimate the prevalence of AKI in hospital inpatients in England, and the impact on mortality, length of stay and National Health Service (NHS) costs.

Methods: National data (Hospital Episode Statistics, HES) were examined to identify all recorded cases of AKI among adult inpatients in English hospitals in 2010-11. The findings were compared with data from East Kent Hospitals, where AKI was identified from laboratory records and classified using AKIN criteria, with the lowest serum creatinine recorded in the 12 months before admission used to estimate baseline. Multivariable regressions were used to estimate the impact of AKI on mortality and length of hospital stay. Unit costs were derived from national tariffs and NHS Reference Costs.

Results: AKI was recorded in 2.4% of hospital admissions in HES, and in 13.22% of admissions at East Kent (laboratory-identified and age- and gender-adjusted to match the HES population). The odds ratio for in-hospital mortality associated with AKI was 10.52 (95% confidence interval 9.93-11.16) in HES data and 5.58 (4.42-5.4) in East Kent data. AKI duration was associated with a length of stay 2.92 (2.59-2.62) times as high as that for admissions without AKI in HES data and 1.96 (1.68-2.13) times as high in East Kent data. The annual cost of AKI-related care recorded in HES is estimated at £337 million. Based on the higher prevalence estimated from East Kent data, the annual cost of AKI-related care is estimated at £492 million, 5% of inpatient spending in England.

Conclusions: AKI prevalence in inpatients may be considerably higher than previously thought, and up to four fifths of cases may not be captured in routine hospital data. AKI is associated with large numbers of in-hospital deaths and with high NHS costs. Comparison of HES and East Kent data suggests that most of the cases recorded in HES may be relatively severe AKI (AKIN 2-3). These estimates do not include AKI in the non-hospitalised population.

SA-PO016

Minocycline to Prevent Kidney Injury After Cardiac Surgery: A Randomized Double-Blinded Placebo-Controlled Pilot Study

Ladan Golestaneh,1 Ziyad AI-Aly,1 Michael I. Rauchman,2 Kevin J. Martin,3 Allison N. Friedman,4 Pierre C. Dugher,1 Tarek M. El-Achkar,1 Montefiore Medical Center, Bronx, NY; 2St. Louis VA Medical Center, St. Louis, MO; 3St. Louis Univ; 4Indiana Univ, Indianapolis, IN.

Background: Acute Kidney Injury (AKI) after cardiac bypass surgery (CABG) is a grave complication associated with significant morbidity and mortality. Minocycline therapy attenuates kidney injury in animal models of AKI but effects in humans are unclear.

Methods: Study Design: Randomized, double-blinded, placebo-controlled, multi-center study.

Setting & Participants: We screened high risk patients who were scheduled to undergo CABG in 2 medical centers between Jan 2008 and June 2011. 40 patients were randomized and 19 patients in each group completed the study. Intervention: Minocycline prophylaxis given twice daily, at least for four doses prior to CABG to prevent AKI.

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

Underline represents presenting author/disclosure.

Outcome: Primary outcome defined as AKI (0.3 mg/dl increase in Creatinine (Cr)) within 5 days after surgery. Measurement: Daily serum Cr for 5 days, various hemodynamic measures and length of stay (LOS).

Results: The two groups had similar baseline and intra-operative characteristics. The primary outcome occurred in 52.6% of patients in the minocycline group compared to 36.8% of patients in the placebo group (p=0.51). Peak Cr was 1.6±0.7 vs. 1.5±0.7mg/dl (p=0.45) in minocycline and placebo groups, respectively. Death within 30 days occurred in 10.5% in the minocycline and placebo groups, respectively (p=0.48). There were no differences in post-operative LOS, and cardiovascular events between the two groups, though there was a trend towards lower diastolic pulmonary artery pressure (16.8±4.7vs. 20.7±6.6 mmHg) and central venous pressure (11.8±4.3 vs. 14.6±5.6mmHg(p=0.13) in the minocycline group compared to placebo on the first day after surgery. In univariate analysis, obesity, peripheral vascular disease, duration of surgery and intraoperative hypotension were all significantly associated with developing AKI.

Conclusions: Minocycline may reduce the potential effects of minocycline on pulmonary and cardiac compliance warrant a larger trial.

Funding: Pharmaceutical Company Support - Triax Pharmaceutical, Private Foundation Support

SA-PO017

The Mechanism Underlying Nesiritide’s Renal Protective Effects in Cardiac Surgery

Thomas M. Beaver,1 Jessica A. Cobb,2 Debra Robertson,1 Maria Cecilia Lopez,2 Henry V. Baker,2 Lyle L. Molderau,2 Tomas D. Martin,1 Philip J. Hess,3 A. Ahsan Ejaz,2 1Surgery, Univ of Florida, Gainesville, FL; 2Medicine, Univ of Florida, Gainesville, FL; 3Molecular Genetics & Microbiology, Univ of Florida, Gainesville, FL.

Background: Acute Kidney Injury (AKI) following cardiac surgery continues to be a problem; however, studies have demonstrated natriuretic peptides have renal protective effects. This study examined the protective mechanism of nesiritide, a human recombinant brain natriuretic peptide.

Methods: 29 cardiac surgery patients at risk for AKI were randomized to 48 hrs of nesiritide (0.01 mcg/kg/min) or placebo starting prior to surgery. AKI was based on KDIGO urine output criteria (<0.5ml/kg/hr over 6 hrs) and the biomarkers urineNGAL and urine IL-18. Serum pro-inflammatory cytokines and endothelin-1 were evaluated up to 24 hrs post cardiopulmonary byssus (CPB). In addition, microarrays of RNA from circulating neutrophils were examined. Statistical analyses were done with Mann-Whitney U and Fisher’s exact tests.

Results: There was a trend towards decreased AKI based on urine output (57% of nesiritide group had AKI vs. 80% of placebo) and urineNGAL and IL-18 levels. Proteomic analysis found nesiritide had a mild anti-inflammatory effect (IL-6 and IL-10 levels decreased in the first hr after CPB). There was also a trend of lower endothelin-1 levels. Comparison of microarray expression patterns in patients with AKI vs. no AKI showed no significant difference. Table1: (1) denotes time post CPB in hrs. Values expressed as mean±SEM; NGAL in ng/ml; all others in pg/mL.

Conclusions: AKI patients showed trends towards less AKI by biomarkers and greater urine output. A short-term anti-inflammatory effect and a trend of lower endothelin levels may explain nesiritide’s renal protective effect.

Funding: Government Support - Non-U.S.

SA-PO018

Clinical Acquired Resistance to Cisplatin-Induced Acute Kidney Injury in Cancer Patients

Naoko Tsuji,1 Hideo Yasuda,1 Takayuki Tsuji,1 Naro Ohashi,1 Akiko Kato,1 Yoshitake Fujigaki,1 1st Dept of Medicine, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan; 2Dept of Medicine, Teikyo Univ, Tokyo, Japan.

Background: Animals that are recovering from cisplatin-induced acute kidney injury (AKI) are known to be resistant to kidney injury by repeated administration of cisplatin. This phenomenon, which is so-called acquired resistance, has not been reported in a clinical setting. We pick up cancer patients who had cisplatin-induced AKI and investigated subsequent chemotherapy and kidney injury.

Methods: 54 cancer patients to which cisplatin were given in otorhinolaryngology/head and neck surgery and gastroenterology units of Hamamatsu University School Hospital from January 2007 to December 2011 were consecutively enrolled. We retrospectively investigated their clinical background and outcome. AKI was diagnosed by the criteria of Kidney Diseases: Improving Global Outcomes.

Results: 26 of 54 patients developed AKI after administration of cisplatin. Among 26 patients affected by cisplatin-induced AKI, cisplatin was administrated to 13 patients repeatedly in the following cycles. In the following cycles, only 3 patients (23.1%) developed AKI and but 10 patients (76.9%) did not. In 10 patients who did not repeat AKI in following cisplatin administrations, blood pressure, dosage of cisplatin, baseline serum creatinine, urine specific gravity, hydration volume, use of diuretics and blockades of renin-angiotensin systems, and other nephrotoxic agents such as non-steroidal anti-inflammatory drugs were not significantly different between the chemotherapeutic cycles with AKI and subsequent cycles without AKI. This suggested the first increases in serum creatinine were
SA-P0019

High Performance Information Search Filters for Acute Kidney Injury Content in PubMed, Ovid Medline, and Embase

Background: We frequently fail to identify relevant articles when we search the large bibliographic databases PubMed, Ovid Medline or Embase. We used computer automation to create information search filters to better identify articles relevant to acute kidney injury in these databases. We first manually reviewed a sample of 22,992 full text articles and used reference criteria to determine if each article contained acute kidney injury content or not. In the development phase (two thirds of the sample) we developed and tested the performance of over 1.6 million unique filters. Filters with high sensitivity and high specificity for the identification of acute kidney injury articles were then retested in the validation phase (remaining third of the sample).

Methods: We used computer automation to create information search filters to better identify articles relevant to acute kidney injury in these databases. We first manually reviewed a sample of 22,992 full text articles and used reference criteria to determine if each article contained acute kidney injury content or not. In the development phase (two thirds of the sample) we developed and tested the performance of over 1.6 million unique filters. Filters with high sensitivity and high specificity for the identification of acute kidney injury articles were then retested in the validation phase (remaining third of the sample).

Results: We succeeded in developing and validating high-performance acute kidney injury search filters for each bibliographic database with sensitivities and specificities in excess of 90%. Filters optimized for sensitivity reached at least 97.2% sensitivity and filters optimized for specificity reached at least 99.4% specificity. The filters were complex, for example one PubMed filter included over 140 terms used in combination, including ‘acute kidney injury’, ‘tubular necrosis’, ‘azotemia’, and ‘ischemic injury’. In proof of concept searches physicians found more articles relevant to topics in acute kidney injury with the use of the filters.

Conclusions: These high performance information filters are now available online and can be used to better identify acute kidney injury content in large bibliographic databases.

SA-P0020

Sepsis Six Bundle of Care May Reduce the Incidence of Severe Acute Kidney Injury in Hospital

Background: Systemic sepsis is estimated to be a contributory cause in 47% of episodes of in-hospital acute kidney injury (AKI). There is limited evidence for interventions to reduce the incidence of sepsis-associated AKI. The Sepsis Six bundle uses fixed physiological cutoffs (triggers) on the bedside observation chart to identify patients at risk of severe sepsis. The bundle specifies six mandatory interventions (oxygen, fluid balance chart, arterial blood gas, intravenous fluid, blood vessels, antibiotics) to be performed within one hour of trigger. We investigated whether compliance with this bundle of care was associated with improved acute renal outcome.

Methods: We collected data on 415 consecutive patients who triggered for Sepsis Six shortly after introduction of the bundle to the Royal Free Hospital in London. We compared baseline with peak creatinine up to 10 days post-trigger to classify renal outcome. We compared baseline with peak creatinine up to 10 days post-trigger to classify renal outcome. We constructed for outcomes.

Results: We calculated relative risk ratio (RRR) for developing each stage of AKI (versus no AKI) with all six interventions completed and corrected for the presence of hypertension when triggering: AKI 1 RRR=0.9 (95% CI 0.5-1.7, p=0.73); AKI 2 RRR=1.5 (95% CI 0.8-3.1, p=0.24); AKI 3 RRR=0.3 (95% CI 0.1-0.6, p<0.01).

Conclusions: Sepsis Six triggers (simple bedside observations) identified a cohort with a high incidence of AKI (32%). Full compliance with the Sepsis Six bundle was associated with a 70% reduction in the risk of developing AKI 3, compared with incomplete compliance. A non-significant rise in the incidence of AKI 2 suggests potentially severe renal injury may have been converted to moderate injury by good compliance with the bundle. These data support the hypothesis that a simple, protocol-based intervention, performed early in the course of sepsis, could protect against severe AKI.
SA-PO23

Diverse Hemostasis Results in Cancer Patients with Acute Kidney Injury (AKI) Evaluated by Standard Coagulation Methods or Thromboelastography

James Hun,1 Tania Rubia Flores Rocha,2 Elbio Antonio D’amicco,1 Luis Yu,1 ICESP, Universidad de Sao Paolo, 2Universidade de Sao Paolo.

Background: Routine tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT) are frequently ordered to assess clotting function but they might be inadequate. Thus, we compared the results of conventional tests with thromboelastography (TEG), which assesses clot formation in whole blood, including plasma and cellular components, in cancer patients with AKI.

Methods: We prospectively analysed patients admitted to the ICU of a Cancer University Hospital with sepsis. Renal dysfunction was classified according to the AKIN criteria. Besides standard coagulation tests (PT, aPTT and TT), TEG was used to evaluate the entire process of hemostasis.

Results: We included 103 patients: mean age 61±15y, 57% male, 85% solid tumors, 15% hematological tumors, 67% on vasopressors, 68% developed AKI (AKIN 1 - 19 patients, AKIN 2 - 20 patients, AKIN 3 - 31 patients).

Methods:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AKIN 1</th>
<th>AKIN 2</th>
<th>AKIN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT (sec)</td>
<td>1.12</td>
<td>1.28</td>
<td>1.41</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>8.5</td>
<td>8.5</td>
<td>8.5</td>
</tr>
<tr>
<td>TT (sec)</td>
<td>24.6</td>
<td>24.6</td>
<td>24.6</td>
</tr>
</tbody>
</table>

Conclusions: Severe AKI caused impaired coagulation in cancer patients as evaluated by standard assays of hemostasis, suggesting a bleeding risk in this situation. In contrast, a normal result was shown in the same cancer patients using TEG. Thus, diverse hemostasis status was demonstrated in AKI cancer patients that may lead to distinct diagnostic and therapeutic maneuvers.

Funding: Government Support - Non-U.S.

SA-PO024

Acute Kidney Injury (AKI) Is Associated with Bronchopulmonary Dysplasia (BPD) in Very Low Birth Weight (VLBW) Infants


Pediatrics, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Lung dysfunction has been linked with AKI in animal models and is thought to contribute to poor outcomes in critically ill children and adults with lung injury. Chronic lung injury is very common in neonates; yet the association between AKI and lung outcomes has not been explored.

Objective: To evaluate association between AKI and BPD in VLBW infants.

Methods: Between February 2012 to February 2013, 91 VLBW Infants (birth weight <=1200 gm. or gestational age <31 weeks) had serum creatinine (SCr) values prospectively collected according to the AKIN criteria. AKI was defined as SCr ≥ 1.5 mg/dl or ≥ 150-200% from lowest previous value. AKI stages were defined according to SCr values: stage 1, 1.5-1.9 mg/dl; stage 2, 2.0-2.9 mg/dl; stage 3, ≥ 3.0 mg/dl. The following parameters were analyzed: plasma and cellular components, in cancer patients with AKI.

Conclusions: Acute kidney injury with this study con

SA-PO26

Effects of Schizolobium Parahyba Extract on Experimental Bothrops Venom-Induced Acute Kidney Injury

Monique Silva Martinez, Miriam Mendes, Maria H.M. Shimizu, Veridiana Avilla, Iue De Castro, Sebastian R. Ferreira-Filho, Denise M.A.C. Malheiro, Luis Yu, Emanuel A. Burdmann.

Univ of Sao Paulo Medical School; 1Uberlândia Federal Univ:

Background: Venom-induced acute kidney injury (AKI) is a frequent complication of Bothrops snakebite, carrying relevant morbidity and mortality. The aim of this study was to assess the effects of Schizolobium parahyba (SP) extract, a natural medicine with confirmed anti-phospholipase A2 effects in an experimental model of Bothrops jararaca venom (BV)-induced AKI.

Methods: Groups of 8-10 rats were assessed 20 min after injection of saline (VH), SP 2 mg/kg, BV 0.25 mg/kg and BV plus SP. The following parameters were analyzed: glomerular filtration rate (GFR, ml/min/100g,ulin clearance), renal blood flow (RBV, ml/min, Doppler), blood pressure (BP, mmHg, intra-arterial transducer), renal vascular resistance (RVR, mmHg/ml/min, formula), urinary osmolality (UO, mOsm/kg,freezing point), urinary NGAL (NGAL, μg, ELISA), lactic dehydrogenase (LDH, IU/L, kinetic method), fibrinogen (F, mg/dl, Klauss modified) and blinded renal histology. Results (mean±SE) are shown below (*p<0.05 vs. control).

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VH</th>
<th>SP</th>
<th>BV</th>
<th>BV+SP</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min/100g)</td>
<td>0.87±0.04</td>
<td>0.88±0.04*</td>
<td>0.63±0.04*</td>
<td>0.52±0.07*</td>
</tr>
<tr>
<td>RBV (ml/min)</td>
<td>8.6±2.7</td>
<td>7.2±1.8</td>
<td>6.7±1.8</td>
<td>6.7±1.8</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>152±4</td>
<td>152±4</td>
<td>152±4</td>
<td>152±4</td>
</tr>
<tr>
<td>UO (mOsm/kg)</td>
<td>1305±113</td>
<td>1279±111*</td>
<td>569±48*</td>
<td>669±54*</td>
</tr>
<tr>
<td>NGAL (μg)</td>
<td>11.8±2.3</td>
<td>11.3±2.5</td>
<td>8.6±4.5</td>
<td>8.5±4.2</td>
</tr>
</tbody>
</table>

Conclusions: BV caused acute tubular necrosis, which was not prevented by SP.

Methods: SP administered simultaneously with BV, in an approximate 10:1 concentration, was not able to prevent BV-induced AKI, hemolysis and fibrinogen consumption. SP alone caused GFR decrease.

SA-PO027

IgA Nephropathy with ANCA Seropositivity: A Case Series

Angela K. Muriithi,1 Lynn D. Cornell,2 Fernando C. Fernanova,3 Mary E. Fisher,2 Sanjeev Sethi,2 Samih H. Nasr.2

1Dys of Nephrology, Mayo Clinic; 2Anatomic Pathology, Mayo Clinic, Rochester, MN.

Background: Anti-neutrophil cytoplasmic antibodies (ANCA) are typically associated with pauci-immune necrotizing and crescentic glomerulonephritis (GN). There have been rare reports and small case series of ANCA positivity in patients with crescentic IgA nephropathy (IgAN). It is unclear if ANCA positivity in IgAN correlates with prognosis or type of crescents.

Methods: We report the clinical and pathologic findings of 18 patients with IgAN and concomitant ANCA positivity.

Results: We identified 13 men and 5 women from 1993 to 2012 among 425 patients with known IgAN who had ANCA positivity by ELISA (4%), of whom 58% had a mean age of 50 years. 15 had myeloperoxidase (MPO), 1 proteinase-3 (PR3) and 2 both.

8 patients (47%) presented with proteinuria/microhematuria, 4 (24%) with rapidly progressive GN (RPGN), 4 (24%) with chronic kidney disease and 1 patient with acute kidney injury. 18 had proteinuria (mean 3.4 ± 0.24), and 15/17 (88%) microhematuria. 2/17 (12%) had pulmonary involvement and 5/17 (29%) skin lesions. Mean serum creatinine was 2.5 mg/dl.

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

SA-PO025

Lysozyme-Induced Acute Tubular Injury: An Under-Recognized Cause of Acute Renal Failure

Larry N. Cossey, Christopher Patrick Larsen.

Nephropath, Little Rock, AR.

Background: Increased serum lysozyme has been reported in association with many conditions, however only rare case reports have shown lysozyme-induced tubular injury leading to acute renal failure. This report attempts to more fully describe the clinical and laboratory findings associated with this disease.
Histologically, 6 (35.3%) had crescents involving a mean of 35% glomeruli (range 10-59). 4 (24%) had glomerular necrosis; none had arteritis. All patients had IgA dominant monoclonal or polyclonal staining on immunofluorescence. Mesangial deposits were seen in all 15 cases studied ultrastructurally. Follow-up was available for 15 patients; 2 received ACE inhibition and/or fish oil only and 11 immunosuppressive therapy: cyclophosphamide/stereoids then mycophenolate/ azathioprine (n=6), mycophenolate/stereoids (n=3), steroids only (n=2). Of the 6 with crescentic IgAN, 3 had RPGN and 4 received cyclophosphamide-based therapy. At a mean follow-up of 46 months, 2 died of unrelated causes, 4 progressed to ESRD (all had RPGN, 3 with crescentic IgAN), and 9 had stabilized or improved their kidney function. Conclusions: ANCA positivity is rare in patients with IgAN. Contrary to previous reports, we found that ANCA was associated with RPGN in only a quarter of IgAN patients and with crescentic disease in only a third. The outcome in crescentic IgAN patients with ANCA appears to reflect that of crescentic IgAN who present with RPGN.

SA-PO028

The Incidence, Etiology, and Outcome of Acute Kidney Injury in Patients with Liver Abscess Seong Eun Yun, Dong Jun Park, Se-Ho Chang, Hyun Seop Cho, Yeojin Kang, Eunjin Bae. Div of Nephrology, Dept of Internal Medicine, Gyeongsang National Univ Hospital, JinJu, Republic of Korea.

Background: Acute kidney injury (AKI) can occur in various infectious conditions. Liver abscess is relatively rare disease leading to severe complications. Study about AKI in patients with liver abscess is rare.

Methods: We retrospectively reviewed the medical records of 404 patients who were diagnosed as liver abscess from January, 2000 to March, 2013.

Results: Male to female ratio was 61:39 and the mean age was 62.9 ± 13.1 years old. AKI occurred in 137 patients (34%). As per RIFLE classification, renal injury was in risk (35.8%), injury (47.4%), and failure (16.5%). One hundred fourteen patients (83.2%) initially had AKI on admission whereas others progressed to AKI during hospitalization. Fifty six (41%) patients had pre-renal azotemia whereas 19 patients (14%) were compatible with sepsis. Histologically, 6 (35.3%) had crescents involving a mean of 35% glomeruli (range 10-59). Immunosuppressive treatment after antibiotics such as sh oil was used in 32 patients. Twenty patients (50%) had chronic kidney disease (CKD). AKI is significantly more frequent in patients with CKD (P=0.04). Mortality had no difference between AKI and non-AKI. One hundred fourteen patients (83.2%) had AKI during hospitalization. AKI occurred frequently in men and patients with liver cirrhosis (P=0.001 and P=0.005). Lower serum albumin and highest ALT level were in patients with AKI, compared to patients with non-AKI. Isolation of organisms from blood culture and liver abscess aspirates were more frequent in AKI patients (P=0.001 and P=0.007). Hospitalization period was also longer in AKI patients (mean 76 years) who were newly co-prescribed clarithromycin (n=96,226) or azithromycin (mean 76 years) who were newly co-prescribed clarithromycin (n=96,226) or azithromycin was also associated with hospitalization with acute kidney injury and two secondary outcomes were assessed within 30 days of a hospitalization with AKI: Clinical - III

Conclusions: We developed a powerful and accurate risk model based on eight simple preoperative variables. This model was greatly improved by the addition of EO level as marker of kidney and vascular subclinical damage. Both these models are straightforward, useful and readily applicable at the bedside.

SA-PO029

Clinical Characteristics of Acute Kidney Injury in Patients with Scrub Typhus – RIFLE Criteria Validation In-O Sun, Kwang Young Lee, Delta Medical Centre, Jeonju, Korea.

Methods: From 2010 to 2012, 238 patients were diagnosed as scrub typhus. Of these, we included 223 patients who were followed up until renal recovery or for at least 3 months, and evaluated the incidence, clinical characteristics and severity of AKI based on RIFLE classification.

Results: Of 223 patients, 47 (21%) had scrub typhus-associated AKI. The incidence of AKI was 21.1%; of which, 10.7%, 9.4% and 1% were the Risk, Injury and Failure classes, respectively. In comparison with patients in non-AKI group, the patients in AKI group were older (70 ± 9 vs 61 ± 14 year, P<0.01) and had more comorbidities such as hypertension, diabetes and chronic kidney disease (77% vs 22%, P=0.01). The patients in AKI group had worse renal function than that of Non-AKI group at admission (37 ± 15 vs 82 ± 19ml/min/1.73m², P<0.01). Forty-five had AKI prior to admission, whereas 3 patients experienced AKI during their hospitalization. By multivariative logistic regression analysis, age and comorbidty were significant predictors of AKI. All patients recovered baseline renal function without renal replacement therapy following antibiotics such as doxycycline and supportive care.

Conclusions: The incidence of AKI in patient with scrub typhus is 21%. Age and co-morbidity are significant predictors of AKI in scrub typhus. In case of scrub typhus-induced AKI, physician should make an effort to prevent, detect, and manage AKI early in patients with liver abscess.

SA-PO030

A New Clinical Model for Postoperative AKI: Role of Endogenous Ouabain Marco Simonini,1 Nunzia Casamasimina,1 Chiara Lanzani,1 Elena Bignami,1 Elena Frati,1 Roberta Meroni,1 Elisabetta Messaggio,1 John Hamlyn,2 Paolo Manunta,1 1San Raffaele Scientific Institute, Milan, Italy; 2Univ of Maryland, Baltimore.

Background: AKI is a frequent complication of cardiosurgery. A lot of models predicting AKI have been proposed, but only few focused on milder AKI not requiring dialysis (AKI-ND), which is very common and contributes to several in-hospital outcomes. Endogenous Ouabain (EO) is an adrenal stress hormone with hemodynamic and renal effects. Recently it has been reported that higher pre-operative EO levels are associated with a worse renal outcome after surgery. Our aim is to develop a new risk model of AKI-ND using clinical aspects and EO as biomarker.

Methods: AKI according to AKIN was studied. We built predictive risk model (CLIN-AKI) considering clinical variables (see figure 1 for details). A further risk score (CLIN-EO-AKI) was developed adding preoperative EO values to the CLIN-AKI score. NNECDSG model, the only predictive model for AKI-ND reviewed, was used for comparison.

Results: All models were tested on 802 patients admitted for elective cardiac surgery. 79 patients developed AKI (9.9%). NNECDSG model was confirmed as a good predictor of AKI (AUC 0.73, value comparable to the reference population). CLIN-AKI model has a better predicting power for AKI per se (AUC 0.79). Adding the preoperative EO level to the clinical model AUC increased to 0.83 (CI 0.79-0.87). Inclusion of EO improved the risk prediction over the clinical models alone (AUAAC respectively +0.06, P<0.03 and +0.1, P<0.01).

Conclusions: We developed a powerful and accurate risk model based on eight simple preoperative variables. This model was greatly improved by the addition of EO level as marker of kidney and vascular subclinical damage. Both these models are straightforward, useful and readily applicable at the bedside.

SA-PO031

Acute Kidney Injury from Calcium Channel Blocker-Clarithromycin Drug Interactions Amit X. Garg,1,2,3 Sonja Gandhi,1,2 Jamie L. Fleet,2 David G. Bailey,1 Eric McArthur,1 Ron Wald,1 Faisal Rehman,1 1Western Univ; 2London Health Sciences Centre; 3Institute for Clinical Evaluative Sciences; 1London Health Sciences Centre; 2Institute for Clinical Evaluative Sciences; 3Institute for Clinical Evaluative Sciences; 1London Health Sciences Centre; 2Institute for Clinical Evaluative Sciences; 3Institute for Clinical Evaluative Sciences

Background: AKI is a frequent complication of cardiosurgery. A lot of models predicting AKI have been proposed, but only few focused on milder AKI not requiring dialysis (AKI-ND), which is very common and contributes to several in-hospital outcomes. Endogenous Ouabain (EO) is an adrenal stress hormone with hemodynamic and renal effects. Recently it has been reported that higher pre-operative EO levels are associated with a worse renal outcome after surgery. Our aim is to develop a new risk model of AKI-ND using clinical aspects and EO as biomarker.

Methods: We developed a powerful and accurate risk model based on eight simple preoperative variables. This model was greatly improved by the addition of EO level as marker of kidney and vascular subclinical damage. Both these models are straightforward, useful and readily applicable at the bedside.
SA-PO032

Bioelectrical Impedance as Prognostic Predictor in Acute Kidney Injury. Importance of Na/K Ratio, Total Water Corporeal Volume and Its Distribution. Risk Stratification


Background: Evaluate prognostic implication of bioimpedance (BIA) in acute kidney injury (AKI). Importance of bioelectrical parameters, total body water and its distribution.

Methods: In 133 patients (64 years, EE: 1.57; 76 males) with AKI and bioimpedance analysis. We evaluated bioelectrical (phase angle -PA- and Na/K exchange ratio -Na/K-) and volumetric (liters -L-) (total body water -TBW-, extracellular water -ECW-, intracellular water -ICW- and ECW/ICW ratio), and relationship with prognostic index (Positive Variable Index -PVI-), C reactive protein (CRP), prealbumin (PRA) and natriuretic (BNP). Statistical analysis with SPSS 15.0.

Results: The PA, Na/K and ECW/ICW were associated with prognostic index, chronic health status, inflammatory status and protein metabolism.

The Na/K was independently associated with death risk (p = 0.02 OR 5.95; 95% CI: 1.251-23.7), area under the curve of 0.714 p = 0.036 and cutoff of 1.1, sensitivity (0.889) and specificity (0.759). Mortality analysis showed differences in ECW/ICW, with greater values in deceased patients (1.5 EE EE 0.07 vs 1.97 0.20, p = 0.027).

Conclusions: The biological evaluation can anticipate the Na/K exchange ratio with the risk of death, mainly with values greater than 1.1. The volume distribution is mostly related with prognosis, especially with extracellular-intracellular shift.

SA-PO033

Acute Kidney Injury in Pediatric Patients after Cardiac Surgery: Risk Factors and Prognosis

Maria Goretti M.G. Penido,1 Nilzete Liberato Bresolin,2 Andresa Elisa Baldissera,3 Almeia Patricia Alves Pereira Bianchini.4 1Pediatric Nephrology Unit, Federal Univ of Minas Gerais, Belo Horizonte, MG, Brazil; 2Joana de Gusmão Infant Hospital, Federal Univ of Santa Catarina, Florianopolis, SC, Brazil; 3Dr J Amarante Faria Infant Hospital, Florianopolis, SC, Brazil; 4Syrian Lebanese Social Responsibility Institute, Sao Paulo, SP, Brazil.

Background: Studies on acute kidney injury (AKI) after cardiac surgery in children using the pediatric pRIFLE criteria are rare. The aims of this study were to analyze the relationship between AKI and volemic parameters (liters -L-) (total body water -TBW-, extracellular water -ECW-, intracellular water -ICW- and ECW/ICW ratio), and relationship with prognostic index (Individual Severity Index -ISI- and Multi-Organ Failure Index -MOFI -), C reactive protein (CRP), prealbumin (PRA) and natriuretic (BNP). Statistical analysis with SPSS 15.0.

Results: The relationship between cholesterol levels and CI-AKI.

Conclusions: Low HDL cholesterol level is associated with an increased risk of CI-AKI in non-diabetic MI patients. More intensive strategies should be implemented for preventing CI-AKI in patients with low HDL cholesterol levels, and HDL cholesterol can be a new target in CI-AKI prevention.

SA-PO034

Association between Low High-Density Lipoprotein Cholesterol Level and Increased Risk of Contrast Nephropathy in Non-Diabetic Patients with Myocardial Infarction

Hyung Wook Kim, Hoon Suk Park, Kyungyoon Chang. Internal Medicine, St. Vincent’s Hospital, The Catholic Univ of Korea, Siwon, Gyeonggi-do, Korea.

Background: Hypercholesterolemia is a well-known risk factor for cardiovascular disease (CVD), and HDL cholesterol is a protective effect against CVD. However, whether hypercholesterolemia or hyperlipidemia is a risk factor for contrast induced acute kidney injury (CI-AKI) is not established. We performed this study to find the relationship between cholesterol levels and CI-AKI.

Methods: This study included 289 non-diabetic patients with myocardial infarction (MI) undergoing percutaneous coronary intervention. Demographic data and clinical findings were compared between patients with and without CI-AKI. Logistic regression analysis was performed to identify independent risk factors. We also compared clinical courses between the 2 groups.

Results: HDL cholesterol level (odds ratio [OR] 0.82, 95% confidence interval [CI]: 0.72-0.94; p = 0.003) was an independent risk factor for CI-AKI in multivariable logistic regression analysis, besides MDRD eGFR (OR 0.86, 95% CI: 0.79-0.95; p = 0.002) and troponin T level (OR 1.50, 95% CI: 1.13-1.99; p = 0.005). The group with CI-AKI had a longer hospital stay (10.2 ± 6.5 days vs. 6.6 ± 4.6 days, p = 0.047), increased in-hospital death (50% vs. 29%, p < 0.001), and poorer patient survival (p < 0.001) than the group without CI-AKI.

Conclusions: Low HDL cholesterol level is associated with an increased risk of CI-AKI in non-diabetic MI patients. More intensive strategies should be implemented for preventing CI-AKI in patients with low HDL cholesterol levels, and HDL cholesterol can be a new target in CI-AKI prevention.

SA-PO035

Residual Blood Flow Characterization in Critically Ill Patients with and without Acute Kidney Injury

Huy Hvty, Manish Kaushik, Han Khim Tan. Renal Medicine, Singapore General Hospital, Singapore.

Background: Although the clinical manifestations of acute kidney injury (AKI) are well-known, much less is known about the changes in renal perfusion in this setting. The study focused on critically ill patients with severe AKI.

Methods: This was an observational cohort study of 16 critically ill patients from medical intensive care unit: 10 patients with AKI requiring renal replacement therapy (CRRT) (AKI group) and 6 patients with normal renal function (non-AKI group). Bedside trans-abdominal Doppler ultrasound interrogation of the renal arterial and aortic circulation was performed by cardiovascular technicians upon successful informed consent taking. The indices measured were abdominal aortic blood flow, renal arterial blood flow and resistive indices (RI).

Conclusions: The machine algorithm converted blood flow velocities into blood flow rates (ml/min).

Results: The median age in years of patients in AKI and non-AKI group were 57 (interquartile range 49-74) and 72 (49-75), p=0.36, respectively. The male to female ratio was 8.2 in AKI group and 5:1 for non-AKI group. The median hospital admission creatinine (umo/L) was 236 (102-391) for the AKI group and for the non-AKI group, 69 (54-81); p=0.02. Comparing AKI versus non-AKI groups respectively, the median abdominal aorta flows (ml/min) were: 3117 (Interquartile range 2743-3506) versus 3119 (2348-5440, p=0.875), the median renal arterial blood flows (ml/min) 440 (307-570) versus 735 (529-940), p=0.02; and, the median resistivity indices 0.83 (0.78-0.86) versus 0.75 (0.72-0.8), p=0.02. 3Div of Pediatric Cardiology, Levine Children’s Hospital, Charlotte, NC; 4Div of Pediatric Cardiology, Univ of Arizona, Tucson, AZ; 5Dept of Pediatrics, Univ of Virginia, Charlottesville, VA.
Conclusions: We report the first renal biopsy case series of thrombotic microangiopathy associated with the intravenous abuse of reformulated Opana ER. All of the cases were young adults presenting with hemolytic anemia and acute renal failure. Treatment involved hemodialysis as well as therapeutic plasma exchange. Early follow-up suggests renal outcome is poor. The specific component or components of reformulated Opana ER responsible for endothelial injury remains to be elucidated.

SA-PO039
Eculizimab Therapy for Gemicitabine Induced Hemolytic Uremic Syndrome
Ashok K. Ananthasayanam,1 Pradeep Arora,1 Rajiv Ranjan,2 James W. Lohr,2
1Medscape, SUNY at Buffalo, Buffalo, NY; 2Medical, VAMC, Buffalo, NY.

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare but serious complication associated with gemicitabine therapy. We identified 4 cases of gemicitabine-induced aHUS over a 2 month period in patients being treated for lung cancer and biliary cancer.

Results: Three patients had kidney biopsies due to the atypical presentation of HUS (no schistocytes), confirming the diagnosis of aHUS. After stopping gemicitabine, all patients were initially or subsequently treated with eculizumab, a recombinant humanized monoclonal antibody that binds to terminal complement C5 protein. Treatment with eculizumab resulted in stopping hemolysis and improvement in renal function in all 4 patients. Details are shown in the table.

Conclusions: Gemicitabine induced aHUS is a rare but serious entity that has significant morbidity and mortality that requires early recognition and intervention. In view of the fact that we identified 4 cases over a 2 month period, we would recommend that patients being treated with gemicitabine be monitored for the development of HUS by serum haptoglobin levels on a regular basis. Eculizumab appears to be a well-tolerated, safe and effective treatment for gemicitabine-induced HUS.

SA-PO040
Women Are Prone to Develop a More Severe Course of Shiga Mediated HUS
Levya Ramazan,1 Jan Beneke,1 Jan T. Kielstein,1 Ulrich Kunzendorf,2 Hermann G. Haller,1 Rolf A. Stahl,1 Jan Menne,1 1Medical School Hannover, Germany; 2Uni Medical Center Hamburg-Eppendorf, Germany; 3Uni Hospital Schleswig-Holstein, Kiel, Germany; 4Klinikum Region Hannover, Germany.

Background: In the 2011 German EHEC O104:H4 outbreak a high number of EHEC-HUS patients (68%) were women even so they represented only 58% of all EHEC cases. We analyzed in this study if gender did influence the clinical course of the disease.

Methods: 612 adult EHEC-HUS patients treated during German 2011 outbreak in 45 hospitals are included. Patients suffering from EHEC-associated enterocolitis without HUS were excluded. We prospectively and retrospectively collected demographic, clinical, and laboratory data on a standardized case-history form.

Results: 443 (72.4%) of patients were female and 169 (27.6%) male. The median age was comparable (45 vs. 43; n.s.). 50% of patients were admitted until day 3 of diarrhea. On admission the baseline laboratory values (LDH and platelets) were not different between m and f. Hemoglobin (Hb) was slightly lower and the eGFR was 51.2 vs. 68.5 mL/min. More women (62.5% versus 47.9%; p<0.001) required dialysis and time on dialysis was longer (median 10 vs. 8 days; n.s.). Furthermore, >100 days after the start of the disease 17.8% vs. 10.4% had still an eGFR <60 ml/min. Additionally, more women required intensive care treatment (60.3% vs. 45%, p<0.001). The ventilation rate was higher (25.3% vs. 17.8%, p=0.054) and the mortality was increased (3.6% vs. 0.6%; p=0.04). More women than men required intestinal surgery (2.9% vs. 1.2%, n.s.). The frequency of blood transfusions was higher in women (70.4% vs. 53.3%; p<0.001) and the median blood units given were 4 vs. 2 (p=0.002). Hospitalization was also longer in women compared to men (median 22 vs. 18 days, p=0.007). Surprisingly neurological symptoms (55.5% vs. 52.7%) and seizures (17.2% vs. 22.5%) were not significantly different. In both groups 85% of patients were treated with plasma exchange.

Conclusions: Women are more susceptible to develop severe clinical symptoms of HUS. The causes of these findings are unclear. Further investigations are required.

Funding: Clinical Revenue Support

Poster/Saturday

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

634A
SA-PO041

E. coli O104:H4 Induced HUS-Outbreak in Germany 2011: Symptoms and Clinical Course
Jan Menne,1 Jan Beneke,1 Leyla Ramazan,1 Ulrich Kunzendorf,2 Jan T. Kielstein,1 Hermann G. Haller,1 RolF A. Stahl.1
Medical School Hannover;2Univ Eppendorf Hamburg;1University Schleswig-Holstein Kiel.

Background: Consumption of sprouts contaminated with the Shiga-toxin 2 producing E.coli (STE) O104:H4 resulted in the largest reported outbreak ofhemolytic-uremic syndrome (HUS).

Methods: For the present analysis, we collected demographic, clinical, and complete laboratory data of 658 EHEC-HUS patients (80% of total affected patients).

Results: The disease consists of four phases. The incubation phase from sprout consumption to the start of diarrhea lasted 7.4±3.3 days. The gastrointestinal (GI) phase started with the onset of GI symptoms (day 0 of the disease). Diarrhea was documented in 97.3%. During the early phase of the disease nausea and vomiting was common. 2.3% of the patients required intestinal surgery.

During the HUS phase between day 5-15, 50-60% of patients developed peripheral edema, dyspnea, and more than 50% also pleural effusion and/or ascites. During this phase of the disease 362 patients (55%) were treated on intensive care units and 22.6% of the patients required ventilation. Importantly, most patients (53.5%) developed neurological symptoms usually between day 10 and 14. 18.4% of patients had seizures and some patients had convulsions.

The recovery phase was characterized by fatigue and weakness which started after day 5 and persisted in most patients for several months. Additionally some patients had symptoms comparable to a post-traumatic stress syndrome with night mares and anxiety for months. Neurological symptoms disappeared; however, some mild residual symptoms were present. 6 (0.9%) remained permanently on dialysis (younger than 30 years) and in 15% an eGFR <60 ml/min persisted. 18 (2.7%) of the patients died due to the following three main causes: 1. infection, 2. patient’s refusal of advanced live support, or 3. interventional complications.

Conclusions: Shiga-toxin HUS is a severe and life-threatening disease. A high percentage of patients need dialysis and ventilation. Most patients were severely affected and require a long rehabilitation and eventually life long follow up.

Funding: Clinical Revenue Support

SA-PO042

Scleroderma Renal Crisis versus Atypical Hemolytic Uremic Syndrome
Ganev, A. Ahsan Eja.2 Nephrology, Baypines VA Medical Center; 1Nephrology, Univ of Florida.

Background: We report a case of successful treatment of aHUS associated with scleroderma with the novel terminal complement inhibitor humanzied monoclonal antibody eciluzumab.

Methods: 62 year old WM with tSCl-70/AC/sclerosis presented with recent onset nausea, abd pain, SOB, weakness, uncontrolled BP (150-170mmHg) for the previous 2 months. PMH was significant for COPD, esophageal strictures, gastric antral vascular ectasia, Raynauds with digital ulcers and sclerodactyly, CV A with residual aphasia and edema (often marked) and >50% also pleural effusion and/or ascites. During this phase the disease 362 patients (55%) were treated on intensive care units and 22.6% of the patients required ventilation. Importantly, most patients (53.5%) developed neurological symptoms usually between day 10 and 14. 18.4% of patients had seizures and some patients had convulsions.

The recovery phase was characterized by fatigue and weakness which started after day 5 and persisted in most patients for several months. Additionally some patients had symptoms comparable to a post-traumatic stress syndrome with night mares and anxiety for months. Neurological symptoms disappeared; however, some mild residual symptoms were present. 6 (0.9%) remained permanently on dialysis (younger than 30 years) and in 15% an eGFR <60 ml/min persisted. 18 (2.7%) of the patients died due to the following three main causes: 1. infection, 2. patient’s refusal of advanced live support, or 3. interventional complications.

Conclusions: Shiga-toxin HUS is a severe and life-threatening disease. A high percentage of patients need dialysis and ventilation. Most patients were severely affected and require a long rehabilitation and eventually life long follow up.

Funding: Clinical Revenue Support

SA-PO043

Thrombotic Microangiopathy Associated with Hemolytic Uremic Syndrome: A Single Center 10 Year Experience
Prebhash Bairacharya,1 Rossana Baracoo,2 Amrish Jain,2 Tek J. Mattoo,1 Gaurav Kapur.1
1Pediatric Nephrology and Hypertension, Children’s Hospital of Michigan, Detroit, MI; 2Pediatric Nephrology and Hypertension, Children’s Hospital of Michigan, Detroit, MI.

Methods: A retrospective chart review (2003-2012) of patients aged 1 to 18yrs admitted with a diagnosis of HUS. Patients with no history of bloody diarrhea & absence of infection with Shigella, and E coli O157:H7 were grouped as aHUS.

Results: In aHUS group; 1 patient had C3 mutation & 1 had negative evaluation for known genetic mutations. In others (n=9) genetic evaluation was not done based on normal C3 & resolution of renal failure & hematological abnormalities. Clinical profile of patients with aHUS was similar to typical HUS group.

Funding: None

SA-PO044

Complement Activation and Plasmatic Membrane Attack Complex in Acute Kidney Injury of Different Etologies
Eva Rodriguez, Marta Riera, Judit Rigol, Clara Barrios, Maria Jose Soler, Carlos Enrique Arias, Julio Pascual.
Nephrology, Parc de Salut Mar-IMIM, Barcelona, Spain.

Background: Final component of complement pathway, membrane attack complex (MAC), has been demonstrated to be involved in models of ischemia-reperfusion. After injury, complement pathway is activated leading to the production of MAC and proinflammatory cytokines. The aim of this study is to establish if complement pathway is activated in different patterns of Acute Kidney Injury (AKI).

Methods: Prospective cohort study 135 patients with different conditions known to be at high risk of AKI. Overall, 53% had AKI and 47% normal kidney function. Plasma-EDTA sample was collected, four groups were classified according to the main risk factor for developing AKI: 1) septic model, patients admitted in intensive care unit with the diagnosis of sepsis (n=26, 50% AKI), 2) ischemia-reperfusion model, kidney transplant patients (n=46, 54% AKI), 3) nephrotic model, patients under colistin treatment (n=37, 48% AKI) and 4) multifactsorial AKI (n=24, 62% AKI). Samples were tested for IL-6 and MAC using ELISA kit.

Results: AKI patients were classified according ADQI as Risk (n=14, 19.7%), Injury (n=12, 16.9%), Failure (n=25, 35.2%) and Loss (n=20, 28.2%). Among the 71 AKI patients, 23 (32.5%) needed renal replacement therapy. Eleven AKI patients died; 31 survivors recovered full renal function, whereas 29 patients did not recover or recovered partially. Plasmatic MAC level was statistically different in patients with AKI as compared to normal renal function controls, regardless of the etiology of AKI (501±247 vs 388±150 mAU/mL, p=0.015). In AKI-patients, plasmatic MAC levels >460 mAU/mL were related with the probability of not recovering renal function but no reached statistic significance whereas plasmatic MAC levels >460 mAU/mL were related with the need of renal replacement therapy (p=0.03). Plasmatic IL-6 levels were significant higher in a AKI patients compared to normal kidney function (10,47±2.8 vs 7.37±3.0 pg/mL, p=0.02).

Conclusions: Our data show that in AKI, regardless etiology, the complement system is activated, leading to an increase in MAC and pro-inflammatory cytokine stimulation (IL-6). High MAC levels are related to AKI severity.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
SA-PO045
Genetic Polymorphisms of Heme-Oxygenase 1 May Impact on Acute Kidney Injury, Bronchopulmonary Dysplasia and Mortality in Very Low Birth Weight (VLBW) Infants

Background: The enzyme Heme Oxygenase 1 (HO1) catalyzes the rate-limiting step in heme degradation, producing biliverdin, iron and carbon monoxide. These products have anti-inflammatory and anti-oxidant properties which protect against AKI in several animal models. Genetic polymorphisms of HO-1 are associated with poor clinical outcomes in several critically ill cohorts.

Methods: Between Feb 2012 and Feb 2013, 91 VLBW Infants (birth weight ≤1200 gm. or gestational age ≤31 weeks) were prospectively followed. Serum creatinine (Scr) values on first two weeks of life were used to determine AKI status according to KDIGO, whereby AKI was defined if Scr ≥ 0.3 mg/dl or ≥ 150-200% from lowest previous value. Bronchopulmonary dysplasia (BPD) was defined if an infant was receiving oxygen at 28 days of life. DNA was collected (Genotek OraGene) isolated (Quiagen Gentra Puregene) and the promoter region of HO-1 was sequenced (Quiagen Type-It Mutation Detect PCR Kit). The number of GT(n) repeats were counted for each infants’ alleles and classified as short (≤ 27) or long (> 27). The –413 snp allele (A vs T) was documented for each allele.

Results: AKI occurred in 27/87 (31%); mortality occurred in 9/87 (10.3%) and 36/78 (46.1%) survivors had BPD. The average number of GT repeats were not different by AKI or BPD category but those who died tended to have higher average GT repeats (27.7 +/- 1.12 vs. 25.7 +/- 0.4; p < 0.09). Categories of allele length (SS vs. SL vs. LL) did not differ by survival, AKI or BPD. A vs. T at –413 tended towards differences for AKI (p < 0.09), BPD (p < 0.08) and survival (p = 0.2), and was significant for the composite of BPD, AKI or mortality.

Conclusions: In this small pilot study of VLBW infants, the number of tandem GT(n) repeats did not appear to predict AKI, BPD or mortality. However, a single polymorphism at position –413 before the HO-1 promoter may predict clinical outcomes.

SA-PO046
Levamisole-Associated Glomerulonephritis in a Habitual Cocaine User
Jonathan Scott Kurche,1 Julie M. Simpson,1 Shalini Tayal,1,2 Jie Tang.1,2
1Univ of Colorado Denver, Aurora, CO; 2Denver Health Medical Center, Denver.

Background: Use of levamisole as a cutting agent for cocaine has resulted in increasing incidence of cutaneous vasculitis and agranulocytosis among abusers. Transient autoantibodies, including perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are often present, and could lead to renal pathology. Levamisole has only been loosely associated with glomerular disease and the renal implications of levamisole-associated vasculitis are unknown.

Methods: We describe a 49-year-old female habitual cocaine user with a history of cocaine-associated cutaneous vasculitis characterized by a high p-ANCA titer, who developed acute renal failure with new nephrotic-range proteinuria. Urine sediment demonstrated dysmorphic erythrocytes, consistent with rapidly-progressing glomerulonephritis (RPGN) in the setting of recent cocaine use and laboratory-demonstrated levamisole exposure. Renal biopsy demonstrated crescentic glomerulonephritis (GN) involving more than 50% of glomeruli, as well as membranous nephropathy (MN) with immune complex deposition in the mesangium and subepithelium (figure). She developed granulocytopenia and signs of cutaneous vasculitis (figure). She was treated with IV steroids and cyclophosphamide and had significant improvement in her creatinine clearance and resolution of her skin rash.

Conclusions: We believe this to be the first description of biopsy-proven RPGN in the setting of levamisole exposure. This case demonstrates progression of disease in a patient with previously diagnosed cocaine-associated vasculitis, the presence of both GN and MN on biopsy, and the potential link of levamisole to MN. Levamisole is chemically similar to a class of characterized Toll-like receptor (TLR) agonists; we hypothesize that the variable presentation of this disease may be related to pleiotropic effects of TLR agonists on the immune system.

Funding: NIDDK Support

SA-PO047
Synthetic Cannabinoids Triggered Thrombotic Microangiopathy Leading to Acute Kidney Injury
Jagadish B. Khanagavi,1 Savneek S. Chugh,2 Prajikta M. Phatak,1 Randy A. Goldberg,1 Praveen N. Chander.3 1Internal Medicine, New York Medical College(NYMC), Valhalla, NY; 2Internal Medicine, Div of Nephrology, NYMC, Valhalla, NY; 3Pathology, NYMC, Valhalla, NY.

Background: Synthetic cannabinoids (SCs) like SPICE are psychoactive compounds marketed as bath salts, incense products and smoked as drugs of abuse. A few cases of acute kidney injury (AKI) attributed to it have been reported but the underlying pathophysiology is unknown. We report the first biopsy proven case of SCs-induced thrombotic microangiopathy (TMA) leading to AKI.

Methods: A 20-year-old man with no prior medical history presented with seizures, nausea, vomiting but no diarrhea. Blood Pressure was 178/88 mmHg and heart rate 104/minute. Physical exam was otherwise unremarkable. Lab data showed anemia, thrombocytopenia, elevated serum creatinine (SCr) (3.6 mg/dl) and LDH levels, low haptoglobin and schistocytes confirming thrombotic microangiopathic hemolytic. ADAMTS13 and Complement levels were normal. Urinalysis showed 1.018, 3+ protein, 5-10 WBCs and 5-10 RBCs per high-power field and occasional muddy brown and RBC casts. Urine toxicology revealed tetrahydrocannabinol. ANA, ANCA, anti-GBM antibodies, hepatitis screens, and HIV antibody screen were negative. Renal ultrasound was unremarkable. A diagnosis of atypical hemolytic uremic syndrome was made and plasmapheresis initiated. Patient showed clinical improvement but SCr remained elevated necessitating hemodialysis (HD). Patient later admitted to daily use of marijuana and SPICE over few months. Serum toxicology showed two SCs: SPICE (CP 47,497) and 1-THC. Renal biopsy showed thrombotic vasculopathic lesions affecting glomeruli as well as acute tubular necrosis possibly due to vasculopathy. Three months later he remains on HD but is now non-oliguric.

Conclusions: We believe AKI associated with SCs in some cases is secondary to TMA possibly due to drug induced endothelial damage. Strong clinical suspicion and systematic analysis for such agents is required to promptly diagnose cases of unexplained AKI with TMA in young and otherwise healthy patients.
SA-PO048
Carbonyl Stress Induced Protein Modification – A New Link in Pathogenesis of Malarial Acute Kidney Injury Pinaki Mukhopadhyay, Debarati Mukherjee, Raghwendra Mishra, Monoj Kar, Piyali Banerjee, Gautam Mukherjee. 1Nephrology, NRS Medical College, Kolkata, India; 2Biochemistry, NRS Medical College, Kolkata, India; 3Medicine, Bagnan Rural Hospital, Howrah, India; 4Gyna & Obstetrics, North Bengal Medical College, Siliguri, India.

Background: 1.To find out the incidence and degree of parasitism of falciparum malarial induced acute kidney injury (FMAKI) and the outcome.
2. To measure the carbonyl and oxidative stress of FMAKI patients and correlation with outcome.

Methods: In all P.F malaria cases AKI was diagnosed by RIFLE criteria. Demographical, clinical and biochemical parameter were analyzed and they are followed from hospitalization to discharge/death. Oxidative and carbonyl stress markers [Advanced oxidation protein product (AOPP), Advanced Glycation End product (AGE), Pentosidine, Dityrosine, Thiobarbituric acid reactive substance (TBARS) and Methyl glyoxal (MG)] were measured consecutively in 15 patient according to standard protocol. All data were analysed in appropriate statistical tool.

Results: Among 174 pts 50 (28.7%) had AKI (FMAKI): M:F was 2:1. About 45 had very low GFR (10.65 ±3.07ml/min). Among 50 cases of FMAKI 42% had paradoxic density <5%, 26% had 5-10% and 32% had >10%. Out of 29 cases of severe AKI 9 patients had paradoxic density <5% and 20 had >5%. Dialysis was required in 62%. Total 13 patients died of them majority belong oliguric severe AKI. There is positive correlation between paradoxic density, renal failure and surrogate outcome. The Oxidative stress indexes (OSI) of FMAKI patients were 1.89 times higher than normal control. The TBARS, MG level were 6.49 and 5.56 times higher indicating a significant carbonyl stress in these patients. AOPP level the marker of protein modification was also 2.33 times higher than normal control indicating that proteins are highly insulted in FMAKI. Areas under the curves for AOPP and MG were (0.735, ±0.001)(0.691, p<0.005) respectively. Mortality and need for dialysis was high in these patients.

Conclusions: 1. Parasitic index is independent surroguet predictor of FMAKI.
2. The carbonyl stress marker(MG) along with oxidative stress(AOPP) are significantly raised and possibly linked to the final kidney injury.

SA-PO049
ANCA-Associated Pauci-Immune Glomerulonephritis Presenting as Cryptogenic Organizing Pneumonia Manish K. Sahai, Tarek Hamieh, Vishal Sagat, Medicine, Regions Hospital, St. Paul, MN; 2Nephrology, Regions Hospital, St. Paul, MN.

Background: Cryptogenic organizing pneumonia (COP), formerly bronchiolitis obliterans-interstitial pneumonia is usually idiopathic but has been associated with connective tissue disorders, infections and drug toxicity. Association of ANCA-related renal vasculitis with COP is rare.

Methods: A 68 year old male with history of type 2 diabetes mellitus presented with six weeks of fever, profuse night sweats and a nonproductive cough. His vital signs were normal. Physical exam revealed basilar crackles at bases. White blood cell count of 11.5k/ul, hemoglobin 6.8 g/dl, creatinine 1.53 mg/dl with cGFR 55.7 ml/min/1.73m². His baseline creatinine was 1.15mg/dl. Urinalysis showed 8 rbc/hpf with 30 mg/dl proteinuria. His white cell count was 11.5k/ul, hemoglobin 6.8 g/dl, hematocrit 20.7%, WBC 11.5 k/cu mm with 73% segmented neutrophils. Total protein creatinine ratio was 0.5. CRP was 26.1 mg/dl. CT chest showed patchy infiltrate in left upper lobe and prominent bilateral interstitial infiltrate. Bronchoalveolar lavage was non-diagnostic. Cultures were negative. He underwent left lung biopsy which was suggestive of organizing pneumonia .There were no granulomas, or evidence of vasculitis. MPO ANCA (myeloperoxidase-antineutrophil cytoplasmic antibodies) >100 with normal proteinase-3. Viral hepatitis serology was negative. With active urine sediment and worsening renal function, kidney biopsy was performed. Pathology revealed pauci-immune type of focal segmental crescentic glomerulonephritis with no immuneactivity and electron microscopy was normal. With the diagnosis of organizing pneumonia and ANCA-positive pauci-immune glomerulonephritis, he was given a pulse dose methylprednisolone and started on Rituximab for four weeks. After completion of Rituximab and Prednisone taper, his creatinine was 1.26 mg/dl and ANCA was 0.6. Urinalysis was bland. A repeat CT chest suggested improvement in patchy interstitial infiltrate.

Conclusions: In the appropriate clinical setting, even with minimal active sediment and mild renal insufficiency, the association of ANCA-related renal vasculitis and organizing pneumonia should be considered for timely evaluation and treatment to prevent progression of acute kidney injury.

SA-PO050
Midkine–A Novel and Early Biomarker of CI-AKI in Patients Undergoing Percutaneous Coronary Interventions-PCI Jolanta Malyszko,1 Jacek S. Pcher,2 Dariusz Katagiri,1 Yoshifumi Hamasaki,1 Kent Doi,1,2 Koji Okamoto,1 Kousuke Negishi,1 Masaomi Nakagawa,1 Eiset Noiri,1,2 1Nephrology, NRS Medical College, Kolkata, India; 2Biochemistry, NRS Medical College, Kolkata, India.

Methods: Midkine, serum and urinary NGAL, cystatin C were evaluated before, and after 2, 4, 8, 24 and 48 hours after PCI using commercially available kits. Serum creatinine was assessed before, 24 and 48 hours after PCI.

Results: We found a significant rise in serum midkine as early as after 2 hours (p<0.001) when compared to the baseline values. It was also significantly higher 4 and 8 hours after PCI, than returned to the baseline values after 24 hours and started to decrease after 48 hours. Serum NGAL increased after 4, 2, and 8 hours, and in urinary NGAL after 4, 8, and 24 hours after PCI. We found a significant rise in serum NGAL after 2, 4, and 8 hours, and in urinary NGAL after 4, 8, &24 after PCI. Serum cystatin C increased significantly 8 hours, reaching peak 24 hours after PCI and then decreased after 48 hours. When contrast nephropathy was defined as an increase in serum creatinine by ≥25% of the baseline level 8 hours after PCI, the prevalence of CI was 10%; Patients with CI received significantly more contrast agent (p=0.01), but duration of PCI was similar.

Midkine were significantly higher 2, 4, 8 hours after PCI in patients with CI, while urinary NGAL levels were significantly higher in patients with CIN starting 2 hours after PCI (serum NGAL) or 4 hours (urinary NGAL). Cystatin C were higher only 8&24 hours after PCI in patients with CI.

Conclusions: Since the “window of opportunity” is narrow in CI-AKI and time is limited to introduce proper treatment after initiating insult, particularly when patients are discharged within 24 hours after the procedure, midkine needs to be investigated as a potential early marker for renal ischemia and/or nephrotoxicity. Inhibition of midkine can prevent the migration of inflammatory cells to the injured epithelial layer, reducing the severity of renal damage.
anti-apoptotic in the AG-treated mice were significantly lower than those of the untreated mice. Blood GLP-1 showed significantly higher in the AG-treated mice, whereas other DPP-4 substrates (SDF-1, NPY) increased with the decline of renal function in the untreated mice and decreased according to AG treatment. Ex-4 also attenuated CP-AKI. Suppressing GLP-1R expression in the kidney by using siRNA injection reversed the protection of AG against CP-AKI.

Conclusions: These data suggest that a gut-released hormone GLP-1 would ameliorate CP-AKI via anti-apoptotic effects and this gut-kidney axis could be anticipated as a new drug target in AKI.

Acute Kidney Injury in Mice Induces Specific Changes in Gut Microbiota

Daniel A. Peterson,1 Yu Chen,2,3 Sanjeev Noel,3 Samatha Bandapalle,3 Maria Noel Martina Lingua,1 James Robert White,4 Abdel Hamad,1 Hamid Rabb,2

1Dept of Pathology, Johns Hopkins Univ, Baltimore, MD; 2Dept of Medicine, Johns Hopkins Univ, Baltimore, MD; 3Dept of Medicine, Nanjing Medical Univ, Nanjing, Jiangsu, China; 4Independent.

Background: Acute kidney injury (AKI) leads to distant organ effects. Crosstalk between organs may worsen or attenuate AKI. Prior work in germ-free mice demonstrated a direct effect of intestinal microbiota on experimental AKI (Jang & Rabb, Am J Physiol 2009). Thus current study examines how AKI modulates the bacterial composition of the gut microbiota by pyrosequencing. To identify changes specific to AKI we employed two different models of AKI, ischemia reperfusion injury (IRI) and nephrotoxic (cisplatin-CNP), and two different strains of mice. IRI was induced by bilateral clamping of the renal pedicles in C57Bl/6 mice for 30 minutes, or chemical AKI induced by CPN injection. Sham operated groups were also studied. To assess the microbiota, DNA was extracted from the fecal pellets (n=4-5 per group), before and day 3 intervention, and subjected to DNA extraction and PCR amplification of the 16S rDNA V3-V5 gene region using the 357F/806R primer set, amplicons were sequenced in multiplex using the Roche/454 platform. The sequences were clustered into 95% operational taxonomic units (OTUs) and taxonomic analysis performed by RDP classifier (rdp.cme.msu.edu).

Results: We observed a dramatic change in the gut microbiota that appears specific to AKI. There were key differences between IRI vs CPN-induced AKI effect on gut. The relative abundance of the taxonomic class Erysipelotrichi, was expanded in AKI mice, IRI (21.3%) vs. CPN (2.6%, p < 0.02) and in the CPN (3.5%, semi-1.2%, p < 0.01). The level in the Sham group (0.4%) was similar to the average of the pretreated mice, (0.35%). This dramatic expansion (~11-65 folds) was compensated by a decrease in primarily the class Bacilli, but also other taxonomic classes.

Conclusions: The impact of both ischemic and nephrotoxic AKI on gut microbiota is profound, with key similarities and differences between IRI and CPN. Future studies are warranted to examine the microbiota as a target to improve our understanding and outcomes during AKI.

Funding: Other NIH Support - R01DK08445, R21AI097419, RO1GM099525

SA-PO084

C5AR Deficiency and C5AR Blockade Protect Mice from Acute Pyelonephritis

Ke Li,1,2 Naheed Chowdary,1,2 Steven H. Sacks,1,2 Wuding Zhou.1,2

1Core Research Laboratory, The Second Afﬁliated Hospital of Nanjing Medical University; 2MRC Centre for Transplantation, King’s College London.

Background: UTIs are mainly caused by uropathogenic E. coli (UPEC), and infections can progress from the bladder to the kidneys. Recent studies have suggested that complement (C5aR) axis is involved in UTIs by activating immune cells. However, the detailed mechanism is not fully elucidated. Our previous study showed that C5aR is a major mediator in UTIs via positive regulation in infected sites.

Methods: We employed a well-established mouse model of ascending UTI leading to kidney infection and used C5AR-/- mice or C5aR antagonist to assess whether the severity of pyelonephritis is dependent on C5aR signaling. Using bone marrow chimeras between wild type (WT) and C5AR-/- mice, we evaluated the relative contribution of C5aR signaling on bacterial burden, kidney damage and the infiltrating cells.

Results: We found that deficiency of C5AR or blocking C5AR significantly protected mice from kidney infection at 72h after bladder inoculation of E. coli. Compared with wild type (WT) mice, C5AR-/- mice exhibited a lower rate of kidney infection (31% vs 79%) and reduced bacterial load in the kidney and tissue damage, however, leukocyte accumulation was similar in both groups. C5AR antagonist treated mice also protected from the kidney infection with a similar protection level as that observed in C5AR-/- mice. Chimeric studies showed that the absence of C5AR on renal or circulating cells attenuated kidney infection, suggesting that C5AR on both renal and circulating cells contribute to the infection. In vitro, C5a stimulation significantly increased TNF-a, IL-6 and KC production by macrophages and REC, while impaired neutrophil functions (bacteria uptake, reactive oxygen species activity), in the presence of LPS or uropathogenic E. coli.

Conclusions: Our results demonstrate a pathogenic role for C5AR in pyelonephritis, implicating therapeutic potential of blocking C5AR in human UTI. It also suggest a mechanism by which activation of C5AR cross-talk with TLR4 exaggerates local inflammation, but impairs neutrophil bactericidal function, thus promoting kidney infection.

Kidneys Recovering from Ischemia/Reperfusion Injury Modulate Specific Cytokine Responses to Subsequent Polymicrobial Sepsis in Mice

Takayuki Tsuji,1 Ana C. Souza,2 Xuexun Hu,2 Peter S.T. Yuen,2 Robert A. Star,2

11st Dept of Medicine, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan; 2NIDDK, Bethesda, MD.

Background: Sepsis frequently develops post-AKI and portends a poor prognosis. We previously showed that sepsis, induced 48 hr after partial recovery from AKI, had worse renal function and survival vs sepsis alone, despite less liver, muscle, spleen damage, and systemic cytokine response (HMGB1, IL-6, IL-10). Thus, partial recovery from AKI unexpectedly dissociated renal and systemic effects of sepsis. To test how recovering kidneys might affect cytokines, we measured the kidneys 0 hr post CLP (48hrs post-IR), then measured serum cytokines.

Methods: We performed sham I/R surgery or 40% bilateral ischemia/reperfusion (IR) in male C57BL/6 mice. 48 hr later we induced polymicrobial sepsis by cecal ligation and puncture (CLP), then bilateral nephrectomy (Nx) or sham Nx. We measured outcomes pre-CLP (48 hr post-IR) or 24 hr post-CLP.

Results: Bilateral nephrectomy at the time of CLP did not alter HMGB1 response after sham-IR→CLP or IR→CLP. However, IL-10 was significantly increased after Nx vs sham Nx) after both sham-IR→CLP and IR→CLP. Strikingly, Nx increased IL-6 levels (vs sham Nx) in IR→CLP but not sham IR→CLP.

Conclusion: After partial recovery from AKI, HMGB1, IL-6, and IL-10 had diminished responses to sepsis. Kidney removal did not affect the reduction of HMGB1, reversed the reduction in IL-6, and derepressed IL-10. Thus, the post-AKI kidneys selectively after circulating cytokines, suggesting a complex interplay between systemic responses to infection and kidneys.

Funding: Government Support - Non-U.S.

SA-PO085

The o-Interleukin 15 Cross-Talk With CCR5 and Defends the Urinary Tract Against Bacterial Infections

Tadashi Yoshida, Maho Yamashita, Matsuhiko Kishimoto,3 Toshihiro Hara,3 Naoko Hirose,3 Yuta Kato,3 Takeshi Iwamoto,3 Noejiro Tanaka,3 Yuki Sakaue,3 Masaaki Matsumoto,3 Kojiro Okajima,3 Takahiro Ueda,3 Takeshi Fujii,3 Masahide Koyama,1,2,3

1Department of Immunology, 2Department of Veterinary Medicine, University of Tokyo, Tokyo, Japan; 3Department of Veterinary Medicine, Tokyo Women’s Medical University, Tokyo, Japan.

Background: The cytokine IL-15 is produced by immune cells and by the kidney. Although IL-15 is a growth factor, it is primarily involved in antiviral, anti-tumor and anti-bacterial responses. IL-15 administration provides protection against several bacterial infections. The mechanism through which IL-15 prevents infection remains poorly understood. The CCR5 receptor is involved in lymphocyte trafficking to the gut and possibly the kidney. We investigated the role of CCR5 in the protective anti-bacterial effect of IL-15.

Methods: C57BL/6 mice were subcutaneously injected with recombinant IL-15 (2 mg/kg) daily for 3 days and then challenged with E. coli (105 CFU i.v.) or with two different strains of Enterococcus faecalis (E. faecalis) (5×107 CFU i.v. per mouse) in the absence or presence of anti-CCR5 antibody (200 µg) given 2 hours before infection. Organ bacterial counts were determined on day 1 and 3 post-infection.

Results: IL-15 protects the bladder and kidneys against E. coli, but not against E. faecalis. IL-15 protects the bladder and kidneys against E. coli, but not against E. faecalis. IL-15 protects the bladder and kidneys against E. coli, but not against E. faecalis. IL-15 protects the bladder and kidneys against E. coli, but not against E. faecalis.

Conclusion: IL-15 protects the bladder and kidneys against E. coli infection via a CCR5-dependent mechanism. These results suggest that IL-15 provides protection against E. coli by recruiting immune cells to the urinary tract, which effectively limit bacterial growth and prevent infection.

Funding: Grant-in-Aid for Scientific Research (C) (JP16K09189)
where it plays anti-inflammatory and anti-thrombotic roles. However, the role of Klf4 in the kidney remains unknown. The aims of the present studies were to determine the expression of Klf4 in the kidney, and examine if Klf4 plays a role in renal ischemia-reperfusion injury.

Methods: Klf4 expression in the kidney was determined by immunohistochemistry. Role of Klf4 in renal ischemia-reperfusion injury was investigated in EC-specific Klf4 knockout mice, which were generated by breeding Tie2-Cre transgenic mice and Klf4 floxed mice.

Results: Results showed that Klf4 was expressed in ECs in the kidney of control mice. but not of EC-specific Klf4 knockout mice. Following renal ischemia-reperfusion injury, EC-specific Klf4 knockout mice exhibited significantly enhanced acute tubular necrosis, enhanced expression of pro-inflammatory molecules such as Vcam-1, and highly elevated serum levels of urea nitrogen, as compared to control mice. Results in human umbilical vein endothelial cells showed that Klf4 inhibited cytokine-induced expression of Vcam-1 by binding to p65, an active component of NF-κB.

Conclusions: Results suggest that Klf4 in ECs plays a protective role in renal ischemia-reperfusion injury.

Funding: Government Support - Non-U.S.

SA-PO058
Low Energy Extracorporeal Shock Wave (SW) Ameliorates Renal Tubular Injury in a Rodent Acute Kidney Injury (AKI) Model: Mai Yoshida,1 Takashi Nakamichi,1 Takefumi Mori,1 Kenta Ito,2 Hiroaki Shimokawa,2 Sadayoshi Ito.1

1Div of Nephrology, Endocrinology, and Vascular Medicine, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan; 2Dept of Cardiovascular Medicine, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan.

Background: SW therapy recovers ventricular function in ischemic cardiomyopathy, which is associated with upregulation of angiogenic factors such as vascular endothelial growth factor (VEGF) and nitric oxide (NO) expression. Recent SW is available to patients with angina pectoris. VEGF and NO are known to play important roles in AKI. The aim of our study is to investigate whether SW ameliorates AKI in a rodent model.

Methods: Renal ischemia reperfusion (I/R) surgery was performed for left kidney in male Sprague-Dawley rats. The operated rats were divided into the following 2 groups: SW-treated group (SW, n=11) and no SW-treated control group (CON, n=11). Both kidneys of only SW group were treated with SW (200 shocks/day for each kidney, 0.09 mJ/mm2) for 24 hours after I/R operation, day 1 and day 2. The rats of both groups were sacrificed immediately after the last SW treatment. Then, plasma, urine, and both kidneys were collected to determine plasma creatinine concentration, urinary NO, renal VEGF mRNA expression, and histological changes of the kidneys.

Results: On day 2, the left kidney weight was decreased in SW (0.45±0.02 vs. CON 0.52±0.02 g/100 g body weight, P<0.05) and plasma creatinine of SW was significantly lower than CON (0.3±0.03 vs. CON 0.4±0.03 mg/dl, P<0.05). A light microscopy revealed that tubular injury scores in the outer medulla of SW were significantly lower than CON (0.3±0.02 vs. 0.43±0.03 mg/dl, P<0.05). The rats of both groups were sacrificed immediately after the last SW treatment. Then, plasma, urine, and both kidneys were collected to determine plasma creatinine concentration, urinary NO, renal VEGF mRNA expression, and histological changes of the kidneys.

Conclusions: SW improved renal tubular injury and its function, in which angiogenic factors might play roles. SW may be an effective and non-invasive treatment for ischemic AKI.

Funding: NIDDK Support

SA-PO061
Induction of Hypoxia-Inducible Factor Up-Regulates microRNA-miR-21 in Renal Ischemia/Reperfusion: Xilian Xu,1 Xiaoyao Jiao,1 Yi Fang,1 Mingyu Liang,2 Xiaoqiang Ding.1

1Nephrology, Fudan Univ Zhongshan Hospital, Shanghai, China; 2Physiology, Medical College of Wisconsin, Milwaukee, WI.

Background: Hypoxia-inducible factor (HIF) is an important transcriptional regulator in cellular response to hypoxia. We have found that microRNA-miR-21 protects mice kidney ischemia/reperfusion injury. This study investigated the role of HIF in the regulation of miR-21 in renal human epithelial cells. In present study, we examined the role of HIF induction in the regulation of miR-21 expression in C57BL/6N mice.

Methods: Mice received intraperitoneal injection of saline or cobalt chloride (CoCl2), a class I/II inducer of HIF activation. Mice were killed by bilateral renal ischemia and 24h reperfusion was induced in mice after two injections. Renal injury and miR-21 abundance were analyzed.

Results: Compared with the sham group, elevation of Scr (2.49±0.88 vs 0.53±0.05 mg/dl, P<0.01, n=6/group) and morphological injury were induced in the I/R group. Pretreatment with CoCl2 afforded striking functional improvement (Scr 0.71±0.11 vs 2.49±0.88 mg/dl, P<0.01, n=6/group) associated with amelioration of tubulointerstitial damage. In the kidneys of mice treated with CoCl2, protein levels of HIF-1α were upregulated significantly. Ischemia/reperfusion induced up-regulation of miR-21 expression in the kidney. Renal abundance of miR-21 was increased in the CoCl2 + I/R group by 236% ± 54% compared to the saline + I/R group (P<0.05, n=6/group).

Conclusions: These data, together with our previous findings, suggest HIF activation might mediate up-regulation of miR-21 in the kidney. miR-21 may be involved in the mechanism of HIF-conferred renal protection against ischemic injury.

Funding: Government Support - Non-U.S.

SA-PO062
Induction of Mir-489 during Renal Ischemia-Reperfusion Protects against Acute Kidney Injury: Jingjing Wei,1 Yong Liu,2 Pengyuan Liu,2 Mingyu Liang,2 Zheng Dong.1,2

1Dept of Cellular Biology and Anatomy, Georgia Regents Univ; 2Dept of Physiology, Medical College of Georgia, Augusta, GA; 3Dept of Pathology, Medical College of Wisconsin, Milwaukee, WI; 4Charle Norwood VA Medical Center, Augusta, GA.

Background: MicroRNAs have been implicated in acute kidney injury (AKI). While some microRNAs contribute to cell injury/death and tissue damage in AKI, others may protect kidney cells and tissues. By microarray analysis, we profiled microRNA expression during renal ischemia-reperfusion in mice and identified over a dozen of microRNAs showing significant changes. Among them, mir-489 was significantly induced both in vivo and in ischemically injured kidney tissue and in vitro in hypoxia-treated renal proximal tubular cells (RPTCs).

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

639A
Methods: Mir-489 induction during hypoxia was attenuated in HIF-1a knockout cells, indicating that the induction is HIF-1 dependent. Consistently, proximal tubule-specific HIF-1a knockdown mouse mice showed lower mir-489 induction during renal ischemia-reperfusion than wild type. Functionally, transfection of anti-mir-489 in RPTCs increased apoptosis following ATP-depletion, suggesting a protective role of mir-489. Deep sequencing (RNA-Seq) was further conducted to identify the target genes of mir-489.

Results: Ago2-2-bound RNAs in the presence or absence of mir-489 were immunoprecipitated, sequenced and compared. The analysis identified several classes of mir-489 targets, including the genes involved in cell stress response, wound-healing, cell communication, and cell differentiation.

Conclusions: Together, the results suggest that mir-489 is induced during renal ischemia-reperfusion to target some of the key pathways to protect kidney cells and tissues from AKI.

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

SA-PO065

Isomorph-Specific Increases in Histone Deacetylase (HDAC) Activity Contribute to the Progression of Renal Fibrosis

Scott R. Manson, Paul F. Austin.
Dept of Surgery, Washington Univ, Saint Louis, MO.

Background: Histone deacetylases (HDACs) are among the most widely expressed and important regulators of gene transcription. While the 10 HDAC isoforms function by similar biochemical mechanisms, they elicit disparate biological responses dependent upon their target genes. In this study, we examine the role of individual HDAC isoforms during the progression of renal injury along with their potential therapeutic importance.

Methods: Renal injury was modeled in mice by acute ischemia-reperfusion (IR) and chronic unilateral ureteral obstruction (UUO). The effects of HDAC inhibition were determined by treatment with the broad spectrum inhibitor Trichostatin A (TSA) and the isoform-specific inhibitors MS-275 (HDAC1-3), MC1568 (HDAC4, 5, 7, 9), CAY10603 (HDAC6, 10), PC134051 (HDAC8).

Results: Each of the 10 HDAC isoforms demonstrates cell type-specific localization in the normal kidney. UUO leads to a 52.0% increase in total HDAC activity along with a 4.0-fold decrease in histone H3 acetylation. This coincides with a decrease in the expression of Class IIA HDAC proteins (HDAC4, 5, 7, 9), including an 11.3-fold increase in HDAC7 and a 6.7-fold increase in HDAC9 that localizes primarily to the proximal tubular epithelium. Additionally, inflicting pro-fibrotic pericytes exhibit high levels of HDAC8 expression. Broad spectrum inhibition of HDAC activity with TSA results in a 31.1% decrease in renal fibrosis and a 43.4% decrease in the loss of renal architecture following UUO. While treatment with each of the isoform-specific HDAC inhibitors resulted in varying levels of renal protection, these compounds appeared to function by different mechanisms. [All results p < 0.05]

Conclusions: Increased HDAC activity contributes to the progression of renal fibrosis following both acute and chronic renal injury. This is primarily the result of an upregulation in the expression of Class IIA HDAC proteins. While broad-spectrum HDAC inhibition had significant renal protective effects, isoform-specific HDAC inhibition may provide a means of targeting specific cell populations and pathologic mechanisms during the progression of renal injury.

Funding: NIDDK Support, Private Foundation Support

SA-PO066

Vitamin D Deficiency-Inuced Inhibition of p21 Upregulation in Ischemic Acute Kidney Injury: Negative Effects

Ana C. de Braganca, Rildo A. Volpini, Janaina Garcia Goncalves, Daniele Canale, Maria H.M. Shimizu, Rosa M.A. Moyaes, Antonio C. Seguro, Lucia Andrade.
Nephrology, Univ of Sao Paulo, Brazil.

Background: Vitamin D deficiency (VDD) is a major predictor of mortality in critically ill patients. Coordinated cell cycle inhibition via increased expression of the cyclin-dependent kinase inhibitor p21 is necessary for optimum recovery from ischemia/reperfusion-induced acute kidney injury (IR-AKI). Because p21, a genomic target of 25-hydroxyvitamin D [25(OH)D], acts via vitamin D receptors (VDR), VDD-induced inhibition of p21 upregulation could aggravate IR-AKI.

Methods: Mice were fed 25(OH)D-depleted or normal diets for 30 days. We studied four groups: control (C), VDD, IR (both renal arteries clamped for 45 min on day 28) and VDD+IR. At 48 h after IR, we measuredulin clearance (Cin); serum 25(OH)D, acts via vitamin D receptors (VDR), VDD-induced inhibition of p21 upregulation could aggravate IR-AKI.

Results: Mice fed were fed 25(OH)D-depleted or normal diets for 28. We studied four groups: control (C), VDD, IR (both renal arteries clamped for 45 min on day 28) and VDD+IR. At 48 h after IR, we measuredulin clearance (Cin); serum 25(OH)D, acts via vitamin D receptors (VDR), VDD-induced inhibition of p21 upregulation could aggravate IR-AKI.

Results: Mice were fed 25(OH)D-depleted or normal diets for 28. We studied four groups: control (C), VDD, IR (both renal arteries clamped for 45 min on day 28) and VDD+IR. At 48 h after IR, we measuredulin clearance (Cin); serum 25(OH)D, acts via vitamin D receptors (VDR), VDD-induced inhibition of p21 upregulation could aggravate IR-AKI.

Conclusions: Mice were fed 25(OH)D-depleted or normal diets for 28. We studied four groups: control (C), VDD, IR (both renal arteries clamped for 45 min on day 28) and VDD+IR. At 48 h after IR, we measuredulin clearance (Cin); serum 25(OH)D, acts via vitamin D receptors (VDR), VDD-induced inhibition of p21 upregulation could aggravate IR-AKI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
PK1) were treated with 200 μM NIC for 24 hours after which cell injury was induced by 400 μM H₂O₂. Extent of phosphorylation (U0126), duration of activation (via EGF or constitutive activation of MEK1 in vitro) or subcellular localization of activated ERK (cytoplasmic or nuclear constitutively active ERKs) was manipulated. Activation of the HO-1 promoter and the antioxidant response element (ARE) was determined in reporter luciferase assays. Results: Ch-NIC attenuated ERK-AKI-mediated induction of HO-1 while increased phosphorylation, duration of phosphorylation and nuclear localization of the phosphorylated ERK (pERK) in the kidney. In vitro, H₂O₂-mediated activation of the HO-1 promoter was dependent on pERK-mediated activation of the ARE. Ch-NIC mitigated this induction of the HO-1 promoter through pERK-dependent attenuation of the ARE. Transient activation (by EGF) of phosphorylated ERK construct and prolonged HO-1 dependent activation of the ARE while sustained activation (by constitutive MEK) or nuclear overexpression of an activated ERK construct mitigated it. Conclusions: The activated ERK elicits opposing effects in induction of the HO-1 promoter; undifferentiated stress ERK activation is transient and cytoplasmic that induces the ARE. In contrast, upon exposure to Ch-NIC the activated ERK is sustained and nuclear, which mitigates oxidative stress-dependent induction of the ARE. These results may offer therapeutic means to ameliorate adverse effects of Ch-NIC.

Funding: NIDDK Support

SA-PO068

The Role of Nicotinic Acetylcholine Receptor in Adverse Effects of Chronic Nicotine Exposure on Renal Acute Ischemic Injury

Istvan Arany, Dustin Reed, Robert Kampen, Luis A. Juncos. Univ of Mississippi Medical Center.

Background: Earlier we reported that chronic nicotine (Ch-Nic) exposure exacerbates acute renal ischemic injury (IR-AKI). Nicotine, a major component of cigarette smoke, is an agonist of the α7-nicotinic acetylcholine receptor (α7nAChR) and is a modulator of the renin angiotensin system. Earlier we reported that chronic nicotine (Ch-Nic) exposure exacerbates acute renal ischemic injury (IR-AKI). Nicotine, a major component of cigarette smoke, is an agonist of the α7-nicotinic acetylcholine receptor (α7nAChR). While acute activation of the α7nAChR is connected to anti-inflammatory signaling, its desensitization via Ch-Nic may activate signaling pathways that support inflammation and injury. In this work we tested the hypothesis that Ch-NIC exerts its adverse effects on IR-AKI through α7nAChR.

Methods: IR-AKI was established in wild type or α7nAChR knockout mice that were subjected or not to chronic NIC. 24 hours post-reperfusion, oxidative stress, renal dysfunction, injury and markers of survival/death signaling and inflammation were determined. In vitro, renal proximal tubule cells (LLC-PK1) were treated with 200 μM NIC for 24 hours followed by treatment with 400 μM H₂O₂. α7nAChR was inhibited by the antagonist α-bungarotoxin (α-BTX); ROS production, mitochondrial depolarization, cell injury as well as activation of the MCP-1 gene were determined.

Results: NIC-mediated renal dysfunction and cell injury, injurious glucocorticoid translocation and inflammation (MCP-1) and oxidative stress (MDA and nitrotyrosine expression) was attenuated in α7nAChR-k.o. mice compared to their wild type counterparts. In vivo, α-BTX attenuated NIC/H₂O₂-mediated production of ROS, mitochondrial depolarization and injury as well as activation of the MCP-1 promoter.

Conclusions: Our results suggest that the α7nAChR plays a pivotal role in transducing injury signals in the presence of Ch-Nic. Thus, manipulation of the receptor activity may offer therapeutic means to ameliorate adverse effects of chronic NIC/smoking.

Funding: NIDDK Support

SA-PO069

High-Mobility Group Protein B-1—Toll-Like Receptor 4 Pathway in Acute Lung Injury Induced by Bilateral Nephrectomy

Kent Dori,1 Tomoko Ishizu,2 Yoshiyuki Harnasaki,2 Tetsushi Yamashita,2 Masaomi Nangaku,2 Naoki Yahagi,2 Eisie Noiri,3 Istvan Arany, Dustin Reed, Robert Kampen, Luis A. Juncos. Univ of Mississippi Medical Center.

Background: Acute lung injury (ALI) and acute kidney injury (AKI) are severe complications in critically ill patients. These two organ dysfunctions synergistically increase mortality in intensive care units. Organ cross-talk between the kidney and the lung has been suggested recently as amplifying each organ injury. This study was conducted to identify a possible mechanism of AKI-induced ALI using a mouse bilateral nephrectomy (BNx) model.

Methods: Bilateral nephrectomy was conducted with TLR4-mutant C3H/HeJ and their TLR4 wild-type control strain C3H/HeN mice. Neutrophil infiltration, neutrophil elastase (NE) activity and cytokine expression (IL-6, KC, TNF-α) in the lung were examined. Plasma HMGB1 concentration was measured by ELISA. Anti-HMGB1 neutralizing antibody treatment and spleenocyte transfer from C3H/HeN to C3H/HeJ mice were conducted to demonstrate the contribution of HMGB1—TLR4 pathway to lung injury.

Results: TLR4-mutant C3H/HeJ mice were resistant to lung injury including neutrophil infiltration and increased NE activity caused by BNx. Injection of spleenocytes isolated from C3H/HeN to C3H/HeJ mice reversed the suppression of NE activity in C3H/HeJ mice. Blood concentrations of HMGB1 in C3H/HeJ and C3H/HeN mice were increased significantly by BNx. Blockade of HMGB1 by neutralizing antibody reduced lung injury not in TLR4-mutant C3H/HeJ but in TLR4 wild-type C3H/HeN mice.

Conclusions: Our results suggest that enhanced HMGB1—TLR4 pathway contributes to lung injury induced by BNx. Targeting the HMGB1—TLR4 pathway will enable development of a new therapeutic strategy to improve the outcome of severely ill patients with ALI and AKI.

Funding: Government Support - Non-U.S.

SA-PO070

BMP and NF-κB Signaling Interaction in Acute Kidney Injury

Emilia Vigo,1 Lajos Marko,2 Giulieta Roei,3 Dominik Muller,2 Ruth Schmidt-Ullrich,1 Kai M. Schmidt-Ott.3 Max Delbrueck Center for Molecular Medicine, Berlin, Germany; 2Experimental and Clinical Research Center, Charité - Universitätsmedizin, Berlin, Germany; 3Dept of Nephrology, Charité - Universitätsmedizin, Berlin, Germany.

Background: Renal ischemia-reperfusion injury (IRI) is a major cause of AKI. Both bone morphogenic protein (BMP) and nuclear factor-kB (NF-κB) signaling have been implicated in the pathogenesis of AKI. However, the precise timing of their activity and interconnection remain unknown. We hypothesized that BMP and NF-κB signaling interact to modulate the pathogenesis of AKI.

Methods: We induced IRI by clamping the renal pedicle for 25 minutes in NF-κB specific reporter (x-luc) mice and Emx1-Cre;IκBΔNtransgenic (Emx1-ΔN) mice, in which NF-κB activity is specifically suppressed in renal tubules. We analyzed serum creatinine, renal neutrophil gelatinase-associated lipocalin (NGAL) mRNA expression, and histological damage scores. BMP signaling activation was detected by pSmad1/5/8 immunostaining.

Results: x-luc mice displayed a gradual increase of NF-κB activity with a significant peak after 3 days following IRI, whereas tubular canonical BMP signaling was downregulated immediately as verified by pSmad1/5/8 staining. To address the specific function of NF-κB in tubular cells, we generated the Emx1-ΔN mice. The mRNA expression of the NF-κB target genes IkBa, IL6, ICAM1 and VCAM1 was up-regulated in control, but not in Emx1-ΔN ischemic kidneys. 24 hours after IRI, Emx1-ΔN mice displayed reduced tubular injury, serum creatinine and NGAL expression compared to control littermates. Additionally, extracellular matrix expansion, inflammatory cell infiltration and CTGF expression were strongly reduced in the postischemic Emx1-ΔN mice compared to littermate controls. Conversely, tubular pSmad1/5/8 was increased in postischemic Emx1-ΔN kidneys suggesting that NF-κB signaling suppresses the intrinsically tubular BMP activity.

Conclusions: These data provide initial evidence of a cross-talk between NF-κB and canonical BMP signaling in the postischemic kidney. Importantly, NF-κB-mediated repression of BMP signaling may participate in the maladaptive aggravation of tubular injury and perturbed regeneration following renal ischemia.

SA-PO071

The Effects of Aging on the Development of Renal Ischemia-Reperfusion Injury

Eun Hee Koh, Hye Ryoun Jung, Jang Eun Lee, Dae Joong Kim, Yoon-Goo Kim, Ha Young Oh, Wooseong Huh. Dept of Medicine, Div of Nephrology, Samsung Medical Center, Seoul, Korea.

Background: Ischemia-reperfusion injury (IRI) is the leading cause of ischemic acute kidney injury in both native and transplanted kidneys. IRI is known to increase acute rejection and have deleterious effect on long term outcome of allografts. Previous studies have reported that the elderly are more prone to ischemic acute kidney injury. In this study, we investigated how aging affects the development of renal IRI.

Methods: Both renal pedicles were clamped for 25 minutes on 9-week (9W, n=15), 6-month (6M, n=15), and 12-month-old (12M, n=11) male C57BL/6 mice. Renal function changes were evaluated with serum creatinine and cystatin C for 48 hours. Tubular injury, infiltration of CD45 positive leukocytes, and cytokine expression on post-ischemic kidneys were analyzed.
Results: There was no difference in serum creatinine among groups, although serum cystatin C level was higher in 12M mice compared with 9W mice. Both 6M and 12M mice showed higher proportion of damaged tubules in the cortex than AKI, but medullary tubular damage was comparable. There was no difference in the infiltration of leukocytes into the post-ischemic kidney. Interleukin (IL)-6 expression was higher in 6M and 12M mice than 9W mice. The expression of interferon-γ was comparable. Both IL-4 and IL-10 were comparable among groups on baseline and day 2 after IRI. Vascular endothelial growth factor (VEGF) was lower in 6M and 12M mice at baseline. VEGF significantly decreased in all groups after IRI, but was much lower in 6M and 12M mice compared with 9W mice on day 2 following IRI.

Conclusions: Older mice showed more severe cortical tubular injury compared to young mice. Pronounced increase of IL-6 and decrease of VEGF on the post-ischemic mice. A pronounced increase of IL-6 and a decrease of VEGF on the post-ischemic kidneys in older mice seem to be the cause. However, pathologic changes did not correlate with age or changes in renal function.

SA-PO072

In Vivo Hydrogen Sulfide Measurements during Renal Ischemia Reperfusion

Bernardo Lopez, Cayetano Perez, Moises Hernandez, Francisco J. Fenoy, Miguel G. Salom, Francisca Rodriguez. Physiology, School of Medicine at Universidad de Murcia, Campus de Espinardo, Murcia, Spain.

Background: Hydrogen sulfide (H2S) has recently been classified as a member of the gasotransmitter family. The enzymes involved in its production are mainly cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) that generate H2S from L-Cysteine (L-Cys). Recent studies highlight H2S protective effects on renal ischemia-reperfusion injury (IRI), a major cause of acute renal failure and renal transplant dysfunction. The aim of this study was to determine the real-time cortical levels of the gaseous signaling molecule H2S during renal IRI.

Methods: Anesthetized SD rats were subjected to 45/60 min of warm ischemia/reperfusion during intraureal infusion of saline (IRI, n=8), 80 μmol/Kg/min NaHS (IRI+HS, n=6), 80 μmol/Kg/min L-Cys (IRI+L-Cys, n=4) or 2 μmol/Kg/min propargylglycine (PGP, a CSE inhibitor) (IRI+PGP, n=5). Cortical H2S concentration was measured electrochemically; renal blood flow (RBF), and glomerular filtration rate (GFR) were also assessed. In other rats set, GFR was measured 24 h after ischemia in nonischemic, and in ischemic rats kidneys i.v. given (in mg/Kg) either saline (IRI+H2O, n=6), 1 NaHS (IRI+HS, n=10), 5 L-Cys (IRI+L-Cys, n=8), or 40 PGP+3 AOA/AA (IRI+Inh, n=5).

Results: Renal ischemia increased cortical H2S levels, which dropped to preischemic values on reperfusion. Ischemic H2S increase was significantly blunted in the IRI+Inh rats group. H2S level was 1.8±0.5 μmol/l/min in nonischemic kidneys, 24 h after ischemia, GFR decreased in ischemic kidneys of IRI+HS, IRI+L-Cys, and IRI+Inh (153.2±67.1) rats. The GFR fall was significantly blunted in the IRI+L-Cys rats pre-treated with NaHS (579.8±131.1) or L-Cys (698.2±15.3) (p<0.001). Cortical H2S concentration was measured electrochemically; renal blood flow (RBF), and glomerular filtration rate (GFR) were also assessed. In other rats set, GFR was measured 24 h after ischemia in nonischemic, and in ischemic rats kidneys i.v. given (in mg/Kg) either saline (IRI+H2O, n=6), 1 NaHS (IRI+HS, n=10), 5 L-Cys (IRI+L-Cys, n=8), or 40 PGP+3 AOA/AA (IRI+Inh, n=5).

Conclusions: Renal ischemia produces a rise in endogenous renal cortical H2S levels, but only a pretreatment with an exogenous H2S source seems to contribute to the significant amelioration of the renal failure observed 24 h after reperfusion.

Funding: Government Support - Non-U.S.

SA-PO073

Urinary Excretion of Nidogen-1 by Meprin A during Acute Kidney Injury

Christian Herzog,1 Randy S. Haun,2,3 Our P. Kaushal.1 1Medicine, UAMS, Little Rock, AR; 2Pharmaceutical Sciences, UAMS, Little Rock, AR; 3CAVHS, Medical School Hannover, Hannover, Germany; 4Silence Therapeutics AG, Berlin, Germany.

Background: Nidogen-1 (NDOG-1) is a molecule H2S during a renal IRI.

Methods: At 1 h and 4 h, while it was dramatically increased to 260% at 8 h and remained elevated (150% of baseline level) after 16 and 24 h.

Conclusions: Upon oxidative stress, DJ-1 has been shown to undergo irreversible oxidative modification, leading to its inactivation and rapid degradation. Collectively, the transient decrease and reversal of DJ-1 protein level in combination of upregulation of DJ-1 mRNA abundance suggest that DJ-1 is highly regulated at both protein and mRNA levels during renal IRI; 2) DJ-1 causes oxidative modification and degradation of DJ-1 protein which is restored by the feedback upregulation of DJ-1 mRNA synthesis; 3) DJ-1 may serve as a potential drug target in the prevention/treatment of AKI.

Funding: NIDDK Support

SA-PO076

Sildenafil (SIL) Protects against Acute Kidney Injury (AKI)-Induced Cardiac Dysfunction via Direct Effects on Myocardial Cells

Alessia G. Diaz,1 Darnamori Rodriguez,1 Istvan Aszodi,2 Rodrigo Maranon,4 Kiran B. Chandrashekar,1 Ruisheng Liu,4 Luis A. Juncos.1 1Medicine-Nephrology, Univ of Miss Med Center; 2Biochemistry, Univ of Miss Med Center; 3Pediatrics, Univ of Miss Med Center; 4Physiology, Univ of Miss Med Center.

Background: AKI causes cardiac dysfunction. We reported that SIL protects against AKI and its associated cardiac inflammation. However, we did not discern if this beneficial cardiac effect was due to the less severe AKI or its direct cytoprotective effect (via heme

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

462A

AKI: Signals, Mechanisms, and Effects Poster/Saturday
Oxygenase-1; HO-1) in myocardial tissue. Therefore, we tested if Silden fina not only augments AKI-induced cardiac HO-1 (despite the less severe renal injury) in vivo, but also whether this augmentation was due to a direct effect on myocardial cells in vitro.

**Methods:** *In Vitro Studies:* SD rats treated with vehicle or Sil were subjected to 40 mins of bilateral renal ischemia-reperfusion (IR). Blood and tissue were collected at 72 h. In Vitro Studies: H9c2 cells (embryo cardiomyoblasts) treated with vehicle or Silden fina (10 μM) were exposed for 24 h to 24 h to rat serum collected 48 h post either 40 min of IR-AKI or a sham surgery.

**Results:**

<table>
<thead>
<tr>
<th>In vivo</th>
<th>BUN mg/dl</th>
<th>Erine NAU G/l</th>
<th>IFP μg/g</th>
<th>Proteinuria mmol/24h</th>
<th>HO-1 μg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>1.2</td>
<td>166</td>
<td>0.25</td>
<td>0.01</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>TRIS</td>
<td>1.5</td>
<td>200</td>
<td>0.28</td>
<td>0.01</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>TR-AKI</td>
<td>3.5</td>
<td>150</td>
<td>0.30</td>
<td>0.01</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>TR-AKI-Sil</td>
<td>1.5</td>
<td>200</td>
<td>0.28</td>
<td>0.01</td>
<td>0.10 ± 0.01</td>
</tr>
</tbody>
</table>

**Conclusions:** Sil directly enhances UR-increases in HO-1 in myocardial cells, and blunts IR-AKI-induced cardiac inflammation and apoptosis, suggesting that Sil-induced HO-1 has a protective role to its protective effect during AKI.

**Funding:** Other NIH Support - NIH DK073401.

**SA-PO077**

Common Genetic Variation and Risk for Acute Kidney Injury in Trauma-Related Critical Illness - Paramita Mukherjee, Grant O'Keefe, Amber Burt, Jonathan Himmelfarb, Mark M. Wurfel. Kidney Research Institute, Univ of Washington, Seattle, WA.

**Background:** Acute kidney injury (AKI) is seen in 5-20% of critically ill patients. Better molecular and genetic markers are needed to assess individual risk for AKI. Our objective was to identify common genetic variants in the form of single nucleotide polymorphisms (SNPs) that influence susceptibility to AKI after major trauma by using a genome-wide association study (GWAS).

**Methods:** We used the Illumina Human610 Quad Beadchip to genotype 975 subjects from a cohort of Caucasian patients (age > 18) enrolled from the trauma ICU at Harbormview Medical Center between 2003-2005 and followed for development of AKI. AKI was defined using a modified Acute Kidney Injury Network (AKIN) based on difference between the highest and lowest creatinine during the first 4 days of ICU admission and were coded as a 3-level ordinal outcome variable: stages 0, 1, and 2 combined.

**Results:** The 975 subjects genotyped had a mean age of 45 years, were 74.2% male, and included 7% with chronic kidney disease. Injury was quite severe for most subjects as evidenced by a mean trauma related injury severity score (TRISS) of 33.7. Stage 1 and combined stage 2+3 AKI occurred in 52.8% and 5.9% of subjects respectively and was not correlated with the TRISS. Although, no associations achieved genome-wide significance, the top two SNP identified were in CACNA2D4 encoding a voltage-gated calcium channel and ATP2C2 encoding a secretory Ca2+ ATPase responsible for calcium uptake with p=2.1 x 10-6 and p=2.8 x10-5 respectively. We also identified 50 SNPs with p<1x10-4 that fell within genes related to polycystic kidney disease, cell cycle and T cell regulation.

**Conclusion:** Finally, these associations need to be validated in independent AKI cohorts.

**Funding:** Other NIH Support - T32 training grant # T32DK007467-29; 5U01DK084012-03

**SA-PO080**

NRF2 Activators as Potential Modulators of Injury in Human Kidney Cells - Melanie S. Joy, Amanda Attilano, Xia Wen, Lauren Aleksunes.1, 2Dept of Integrated Biology, UC Davis; 3Dept of Internal Medicine, UCI Health, Irvine, CA.

**Background:** NRF2 is a transcriptional factor that mediates cellular protection against oxidative stress. NRF2 activation can protect against renal injury and increase expression of prototypical target genes. NRF2 activators such as sulforaphane and oleanolic acid (OA) have been shown to inhibit oxidative stress-mediated inflammation responses. This study evaluated the effects of OA on NRF2 activation and expression of its target genes in human renal cells.

**Methods:** Human renal proximal tubule epithelial cells (RPTECs) and HEK293 cell lines were exposed to OA with and without N-acetylcysteine. Apoptosis was con

**Results:** OA showed cell toxicity in dose- and time-dependent patterns in the RPTECs and HEK293.

**Conclusions:** Treatment of RPTECs with OA with exposure to clinically-relevant OA concentrations enhances human renal cell viability and increases expression of detoxifying genes (NQO1 and GCLC) and NRF2 itself.NRF2 activators are potentially novel treatments to mitigate drug-induced kidney injury.

**Funding:** NIDDK Support
SA-P0081

Renalase Protects against Ischemic and Toxic Acute Kidney Injury via a Receptor-Mediated Mechanism Independently of Cathecolamines Metabolism

Gary V. Desi,1 Ling Wang,1,3 Heino Velazquez,2 John J. Chang,1 Ahrom Ham,3 H. Thomas Lee,2 Robert L. Saffristein,1 Tale, VACHS; Columbia School Med; 2Renji Hosp.

Background: Acute kidney injury (AKI) is an important clinical syndrome predominantly caused by ischemic and toxic renal insults, for which effective therapies are currently unavailable. Renalase, a secreted flavoprotein, oxidizes cathecolamines, and certain general polymorphisms are associated with essential hypertension, stroke, and diabetes. Gene deletion aggravates acute ischemic kidney (AKI) and cardiac injury. Recombinant renalase prevents ischemic injury in wild type mice. Although renalase’s crystal structure has been solved, its mechanism of action remains uncertain.

Methods: The effect of renalase and renalase peptides in cell models of cisplatin and hydrogen peroxide toxicity, and in vivo models of cisplatin and ischemic acute kidney injury were determined. Cell signaling pathways were examined by western blot. Renalase peptides were chosen by examining renalase’s crystal structure and by testing the effect of peptide antibodies on renalase function.

Results: Renalase increased the survival of human proximal tubular (HK-2) cells exposed to cisplatin or hydrogen peroxide. We identified a 20 amino acid renalase peptide (RP-220) conserved in all known isoforms, and with no detectable oxidase activity, that was as effective as renalase at protecting HK-2 cells against toxic injury, and wild type mice against ischemic AKI. RP-220 and recombinant renalase rapidly activated AKT, ERK, and p38, and down-regulated. Inhibition of ERK and AKT activation abrogated RP-220’s protective effect against ischemic AKI.

Conclusions: These data indicate that renalase protects against ischemic AKI independently of its enzymatic properties, and interacts with a yet to be identified receptor to activate intracellular signaling in a manner that promotes cell survival. Renalase and related peptides show potential as therapeutic agents for the prevention and treatment of AKI. We predict that the eventual identification of the renalase receptor will catalyze the development of additional novel therapeutic agents.

Funding: NIDDK Support, Veterans Affairs Support

SA-P0082

Paricalcitol Attenuates Renal Ischemia-Reperfusion Injury via Prostaglandin E2 Receptor EP4

Hyeyeon Seok Hwang,1 Cheol Whee Park,2 Yoon-Kyung Chang,1 Chuol Woo Yang,2 Suk young Kim,1 Sangju Lee.1

Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea, Daejeon, Republic of Korea; 2Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: Paricalcitol has protective effects in several kidney injury models but the mechanism by which this occurs remains unclear. We investigated whether paricalcitol regulates the prostaglandin E2 (PGE2) receptor EP4, and whether paricalcitol prevents renal ischemia-reperfusion injury (IRI) through the EP4 in models.

Methods: Human proximal tubular cell line (HK-2) was exposed to lipopolysaccharide (LPS) and ischemia by mineral oil monolayer. Male C57BL/6 mice were subjected to 23 min of bilateral kidney ischemia and 24 h reperfusion. The effects paricalcitol pretreatment with AH-23848 (EP4 antagonist) was investigated in both in vitro and in vivo models.

Results: Paricalcitol pretreatment significantly increased the cyclooxygenase (COX)-2 expression, PGE2 production and EP4 expression in HK-2 cells. Paricalcitol increased the viability of HK-2 cell exposed to ischemia or LPS. The cotreatment of AH-23848 with paricalcitol offset these protective effects of paricalcitol. LPS-induced p65 NF-κB phosphorylation was abolished in paricalcitol-treated HK-2 cells, and AH-23848 (EP4 antagonist) was investigated in both in vitro and in vivo models.

Conclusions: In conclusion, our study demonstrated that paricalcitol attenuates prostaglandin E2 receptor and cell death and inflammatory infiltration after renal IRI through the PGE2 receptor EP4.

SA-P0083

Vitamin D Deficiency Is a Risk Factor for Iodinated and Gadolinium Contrast Media Nephrotoxicity

Wevertton M. Luchi, Maria H.M. Shimizu, Danielane Canale, Pedro H.F. Gois, Antonio C. Seguro. Nephrology, Univ of Sao Paulo - School of Medicine, Brazil.

Background: Vitamin D deficiency (VDD) is widespread in general population. Iodinated (IC) and Gadolinium (Gd) contrasts may decrease renal function in high risk patients. The aim of this study was to evaluate the effect of VDD on IC and Gd nephrotoxicity.

Methods: We did a cross-sectional study. Male Wistar rats fed a standard diet (control (C)) or iodinated (IC) or gadolinium (Gd) contrast medium were subjected to renal injury or sham operation. At 24 h post-CLP, we evaluated mean arterial pressure (MAP), baroreflex efficiency (VDD) and inflammation and oxidative stress. Klotho (Kl) has been shown to protect against renal ischemia-reperfusion injury and to be an antioxidant. We used a cecal ligation and puncture (CLP) model to determine the protective effects of Klotho in kidney injury.

Results: In 2 additional groups (n=5) on VDD for 60 days, a greater fall of GFR occurred: VD 24 h ± SEM: IC = 0.48 ± 0.04; VD+IR = 0.46 ± 0.04.

Conclusions: Our findings suggest that VDD is a risk factor for contrast nephropathy by oxidative stress and endothelial dysfunction.

SA-P0084

Critical Role of Vitamin D Receptor Downregulation on Triggering the Inflammatory Process and Subsequent Fibrosis Formation in Vitamin D-Depleted Rats Submitted to Renal Ischamia/Reperfusion

Janaina Garcia Goncalves, Ana C. de Braganca, Daniele Canale, Maria H.M. Shimizu, Antonio C. Seguro, Lucia Andrade, Rosa M.A. Moyes, Rildo A. Volpini. Nephrology, Faculty of Medicine - Univ of Sao Paulo, Sao Paulo, Brazil.

Background: Renal diseases are generally followed by Vitamin D deficiency (VDD) which increases with the progression of CKD. Studies suggest that Vitamin D Receptor (VDR) could be a potential mechanism connecting inflammation and fibrosis development. We investigated the VDR expression and its relationship with TGF-β, macrophages infiltration and fibronectin/collagen expression in VDD rats submitted to renal ischemia/reperfusion (IR).

Methods: For 90 male, Wistar rats, were fed a standard diet (control (C)) and IC contrast medium. We divided them into 6 groups, of 10 each, according to the treatment schedule. We used a cecal ligation and puncture (CLP) model to determine the protective effects of Klotho in kidney injury.

Results: In 2 additional groups (n=5) on VDD for 60 days, a greater fall of GFR occurred: VD 100gBW) BP(mmHg) RVR(mmHg/mL) TBARS(nmol/24h) AII(%) eNOS(%)

Conclusions: Taken together, these data indicate that VDD combined with VDR downregulation may contribute to progressive chronic kidney disease.

Funding: Government Support - Non-U.S.

SA-P0085

Klotho Deficiency Aggravates Sepsis-Related Multiple Organ Dysfunction

Leticia Jorge,1 Fernanda O. Coelho,1 Tatiana R. Sanches,1 Maria Irigoyen,1 Maria H.M. Shimizu,1 Antonio C. Seguro,3 Niels O.S. Camara,2 Makoto Kurok,2 Lucia Andrade.1

1Univ of Sao Paulo, Brazil; 2UT Southwestern Medical Center at Dallas.

Background: Sepsis-induced organ failure is characterized by a massive inflammatory response and oxidative stress. Klotho (Klotho) has been shown to protect against renal ischemia-reperfusion injury and to be an antioxidant. We used a cecal ligation and puncture (CLP) model to analyze the role of Klotho in sepsis-related organ dysfunction.

Methods: 8-12 week old mice KI- and KI- mice (n=32) underwent CLP or sham operation. At 24 h post-CLP, we evaluated mean arterial pressure (MAP), baroreflex sensitivity, serum biochemistry, oxidative stress, and cytokines, as well as immunoblotting for Klotho in kidney tissue. We also evaluated 14-day survival.

Inulin clearance (GFR), blood pressure (BP), renal vascular resistance (RVR) were measured 48 h after contrast infusion. Renal tissue was immunoblotted for angiotensin II (AngII) and endothelial nitric oxide synthase (eNOS). Data are mean±SEM.

Results: Serum 25(OH)D(ng/mL) was 15.4±1.0 in Sham and 4.1±0.8 in VDD normal in IC and Gd. VDD increased BP, RVR, TBARS, Ali and eNOS. VDD+IC and VDD+Gd showed higher TBARS and Ali and reduced eNOS, decreasing GFR.

In 2 additional groups (n=5) on VDD for 60 days, a greater fall of GFR occurred: VD 24 h± SEM: IC = 0.48±0.04; VD+IR = 0.46±0.04.

Conclusions: Taken together, these data indicate that VDD combined with VDR downregulation may contribute to progressive chronic kidney disease.

Funding: Government Support - Non-U.S.
Results: Data are mean±SEM.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham K1</th>
<th>CLP K1</th>
<th>Sham +/−</th>
<th>CLP+/−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>77±14 a,b</td>
<td>57±4 c</td>
<td>39±8</td>
<td>40±8</td>
</tr>
<tr>
<td>Lactate (mg/dl)</td>
<td>60±23 a,b</td>
<td>31±12 c</td>
<td>19±12</td>
<td>20±15</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>77±14 a,b</td>
<td>57±4 c</td>
<td>39±8</td>
<td>40±8</td>
</tr>
<tr>
<td>Blood Glucose (μmol/ml)</td>
<td>1.34±0.1 a,b</td>
<td>1.72±0.3</td>
<td>2.4±0.3</td>
<td>1.9±0.6</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>92±39 a</td>
<td>39±12</td>
<td>40±19</td>
<td>37±11</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td>2495±2411 a,b</td>
<td>170±276 c</td>
<td>2.5±4</td>
<td>1.4±2.6</td>
</tr>
<tr>
<td>TNFα (pg/ml)</td>
<td>83±13.5 a,b</td>
<td>11.4±8.4 c</td>
<td>3.6±1.8</td>
<td>3±0.5</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>114±28 b</td>
<td>111±27</td>
<td>141±10</td>
<td>135±18</td>
</tr>
<tr>
<td>GSH (μmol/ml)</td>
<td>56±15</td>
<td>67±16</td>
<td>78±14</td>
<td>73±12</td>
</tr>
</tbody>
</table>

Conclusions: Renal Angpt-2 expression by tubular epithelial cells is upregulated after IRI. Its role in kidney recovery after injury merits further study.

Funding: Government Support - Non-U.S.

SA-PO086

Increased Expression of Angiopoietin-2 in Renal Tubular Epithelial Cells after Ischemia-Reperfusion Acute Kidney Injury

Chun-Fu Lai, Shuei-Jun Lin, Wen-Chih Chiang. Dept of Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Angiopoietin-2 (Angpt-2) has been identified as a regulator of vascular homeostasis, as well as a link between angiogenesis and inflammation. Clinical studies observed that circulating Angt-2 levels were elevated in patients experiencing acute kidney injury (AKI). The present study aimed to examine the expression of Angpt-2 in the kidney after ischemic injury.

Methods: Using mouse unilateral ischemia-reperfusion injury (IRI) and contralateral nephrectomy model, we analyzed gene and protein expression of Angpt-2. In addition, we used proximal tubular epithelial (NRK-52E) cells to investigate Angpt-2 expression under hypoxia.

Results: In response to the IRI, Angt-2 transcripts, measured by Q-PCR, increased in the kidneys significantly since day 5 after surgery and remained high thereafter. Western blot of kidney lysates showed that the expression levels of Angt-2 protein were enhanced at day 5 and 7, and then decreased toward baseline at day 14. [Fig. A] Immunofluorescence staining indicated that Angt-2 was expressed mainly in injured and non-injured proximal tubular epithelial cells after IRI. [Fig. B] This was further supported by in vitro experiments showing that low-oxygen condition (under 1% O2) stimulated Angt-2 expression in cultured NRK-52E cells.

Conclusions: Renal Angpt-2 expression by tubular epithelial cells is upregulated after IRI. Its role in kidney recovery after injury merits further study.

Funding: Government Support - Non-U.S.

SA-PO087

Mechanism of Protection by Renalase against Cisplatin-Mediated Cytotoxicity

Gary V. Desir,1 Ling Wang,2 Heino Velazquez,3 Robert L. Safirstein,1 Yale Univ School Med, VA/CHS; 2Renji Hospital, Shanghai.

Background: Acute kidney injury (AKI) is an important clinical syndrome most commonly caused by ischemic and toxic renal insults. Renalase is a secretory protein that oxidizes catecholamines, and protects against toxic and ischemic injury by its interaction with an as yet unidentified receptor leading to activation of intracellular signaling in a manner that promotes cell survival. A twenty amino acid renalase peptide (RP-220), which is conserved in all known isoforms but is devoid of any detectable oxidase activity with an as yet unidentified receptor leading to activation of intracellular signaling in a manner that promotes cell survival. A twenty amino acid renalase peptide (RP-220), which is conserved in all known isoforms but is devoid of any detectable oxidase activity.

Methods: To examine the mechanism of protection against cisplatin cytotoxicity, the effects of renalase peptide RP-220 on HK-2 cells exposed to cisplatin were determined.

Results: RP-220 increased the survival of cisplatin treated HK-2 cells by 45% at 24 hrs (n=4, p<0.002). It rapidly increased the phosphorylation of AKT, p38 mitogen activated protein kinase (p38) and ERK. Chemical inhibition was used to determine the critical mediator of RP-220’s protective effect. In control studies in the absence of cisplatin and RP-220, ERK and p38 inhibition had no effect on HK-2 cell survival rates, while AKT decreased cell survival by 37% (n=4, p<0.001). In the presence of cisplatin alone, inhibition of ERK and p38, were protective and increased cell survival by 38 and 35% respectively (n=4, p<0.01), while that of AKT was not. With the addition of cisplatin and RP-220, ERK inhibition was still protective, but p38 inhibition completed abrogated RP-220’s protective effect.

Conclusions: These data indicate that p38 activation is the critical mediator of RP-220’s protective action against cisplatin cytotoxicity, and suggest that renalase and related peptides show potential as therapeutic agents for the prevention and treatment of AKI.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO088

Post-Conditioning the Kidney – A Cautionary Tale...

Kieran McCafferty, Conor J. Byrne, Magdi Yaqoob. Dept of Translational Medicine, William Harvey Research Institute, Queen Mary Univ London, London, United Kingdom.

Background: We have previously shown (Byrne/McCafferty, Circulation, 2012) that ischemic preconditioning (iPOST) is a potent cytoprotective strategy in the uremic heart. Others have shown that iPOST can confer cytoprotection in other organs including the kidney. Because iPOST can be applied at the point of reperfusion, it has led to increasing interest in the field of transplantation to reduce reperfusion injury and improve graft function. However, iPOST may be detrimental if the index injury is low, or may be ineffective at reducing reperfusion injury if the injury too great.

The role of the duration of ischemia on the effectiveness of iPOST in the setting of renal IRI is currently unclear.

Methods: 56 Male Wistar rats underwent a unilateral nephrectomy with contralateral renal ischemia (for 0, 25, 30 or 45 minutes) followed by either an iPOST procedure (5x106 sec ischemia/reperfusion) or a sham procedure. All animals were left to recover for 48h at which point they were sacrificed and assessed for renal injury.

Results:

See figure 1: Using a 2-way ANOVA there was a highly significant association between the duration of ischemia and the serum creatinine concentration (p<0.0001), however surprisingly, at all time points studied the addition of iPOST did not alter serum creatinine concentrations (p=0.63). In addition, other markers of renal injury showed similar trends, with a longer ischemic phase leading to higher urea, phosphate and potassium concentrations and oliguria, with no impact seen with iPOST.

Conclusions: Reassuringly iPOST does not appear to be deleterious even at low levels of injury. However in contrast to other studies, our experiments do not confirm cytoprotection over a spectrum of renal injury with iPOST. Further work is required before translational studies of iPOST in the context of renal transplantation are performed.

SA-PO089

Increased Transforming Growth Factor-β (TGFβ) Receptor Type 2 (TGFBR2) Expression in Regenerating Proximal Tubule (PT) Cells Occurs by Phosphatidylinositol 3-Kinase (PI3K) Activity Mediated Transcription and Decreased Protein Degradation

Hoi Geng,1 Rongpei Lan,2 Pragjali Karati Surya,1 Pothana S. Saikumar,1 Joel M. Weinberg,3 Manjeri A. Venkatchalam,1 U Texas; 2U. Michigan.

Background: TGFβ signaling increases after renal ischemia reperfusion injury (IRI), accompanied by enhanced expression of TGFβ and its receptors in regenerating PT. Failure of TGFβ signaling to regress during recovery induces tubule atrophy and fibrosis. PT regeneration in a tissue culture model is accompanied by increased TGFβ signaling and TGFBR2 expression, and to a lesser extent, of TGFBR1.

Methods: We studied TGFBR2 regulation in confluent differentiated PT cell cultures induced to regenerate by wounding or subconfluent passage, and localized signaling molecules related to TGFβ after IRI of rat kidneys.

Results: Wounding to remove ~90% cell mass or subconfluent passage of confluent PT cells cultured induced to regenerate by wounding or subconfluent passage, and localized signaling molecules related to TGFβ after IRI of rat kidneys.

Conclusions: TGFβ signaling does not appear to be deleterious even at low levels of injury. However in contrast to other studies, our experiments do not confirm cytoprotection over a spectrum of renal injury with iPOST. Further work is required before translational studies of iPOST in the context of renal transplantation are performed.

SA-PO090

Underline represents presenting author/disclosure.
Conclusions: The data suggest that TGFß2 becomes increased in regenerating PT due to enhanced PI3K activity dependent transcription as well as diminished protein degradation.

SA-PO090

A Model of Townes-Brocks Syndrome Is Protected from Acute Renal Ischemia Reperfusion Injury
Sara Hirochi,1 Tarek M. El-Ashkar,2 Michael I. Rauchman,1,3,4 
1Biochemistry, Saint Louis Univ, St. Louis, MO; 2Medicine, Indiana Univ, Indianapolis, IN; 3Internal Medicine, Saint Louis Univ, St. Louis, MO; 4Medicine, Saint Louis Veterans Affairs Medical Center, St. Louis, MO.

Background: Acute kidney injury (AKI) affects 2-10% of hospital patients. Ischemia reperfusion injury (IRI) often contributes to the development of AKI. The cellular and molecular processes that govern injury and recovery from renal IRI are not well understood. Genes that are required for kidney development are upregulated following IRI, but their function in IRI is unknown. Sall1 is a transcription factor required for kidney development. Truncating mutations of Sall1 cause Townes-Brock Syndrome (TBS). Renal manifestations of TBS include congenital hypoplasia and renal insufficiency.

Methods: We bred genotypes of Sall1 mice to the nuclear and functional differences that could predispose to AKI. CLIC4 KO mice were found to redistribute to the nucleus and potentiate TGFß signalling. We investigated whether absence of CLIC4 alters the course of AKI.

Results: Absence of CLIC4 increased susceptibility to acute kidney injury (median day 2 BUN 65 and 143 for WT and KO respectively, p<0.02), but did not alter functional recovery from AKI. There was no significant difference in day 21 BUN between WT and KO. Sall1 was indirectly affected by day 21 kidney weight. There was no difference in the relationship between severity of initial injury and final kidney size between the WT and KO mice. Phosphorylation of Smads 2/3 increased following injury and there was no difference in Sall1 expression in kidney cells following injury suggesting that Sall1 is not a critical non-redundant regulator in the relationship between severity of initial injury and recovery from AKI.

Conclusions: Sall1+/− mice are protected from renal injury within 24 hours of IRI. Normal tubular epithelial cell proliferation (Sall1+/−) nor conditional knockout of Sall1 replicate the protection observed in Sall1+/+ mice, indicating that Sall1 loss-of-function is not protective. Sall1−/− mice are also susceptible to IRI, suggesting that the protection observed in Sall1+/− mice is not due to mutation Sall1 protein interacting with WT Sall1-4 or NRd function. We propose that Sall1−/− mice are protected from renal IRI through a novel, gain-of-function mechanism.

Funding: Veterans Affairs Support

SA-PO093

Early Intervention Prevents Sepsis-Induced Tubule-Interstitial Fibrosis, Endothelial Dysfunction and Tubular Apoptosis: Role of Coupled Plasma Filtration Adsorption
Andre Castellano,1 Alessandra Stasi,1 Anna Maria Di Palma,1 Margherita Gigante,1 Angelica Itrini,1 C. Divella,1 Giuseppe Stefano Nuzzo,1 Gaia Curi,1 Enrico Fiaccadori,2 G. Grandaliano,2 G. Pertosa,1 Loreto Gesualdo1,2 DETO, Univ Bari, Italy; 3Med and Surg Sciences Dept, Univ Foggia, Italy; 4Consorzio Carso, Univ Bari, Italy; 5Clin and Exp Med Dept, Univ Parma, Italy.

Background: Sepsis-induced acute kidney injury (AKI) is characterized by tubulopathy and fibrosis. Early intervention in sepsis is useful, but the best moment to start therapy is not evident. Our aim was to investigate the effects of an early treatment by Coupled Plasma Filtration Adsorption(CPFA) in a swine model of sepsis-induced AKI.

Methods: After LPS infusion, 8 pigs developed AKI and underwent to renal biopsies at different time points. In the treatment group, 8 animals received CPFA for 6 h, after 3 h from LPS infusion. Endothelial cells (ECs) were cultured in presence of different swine sera for 12h and were analyzed by FACS.

Results: We found an acute reduction of tubule-interstitial fibrosis in Sepsis-induced AKI, as indicated by extensive collagen deposition (Masson Trichrome staining); in addition, tubular apoptosis was an early event as indicated by intense caspase-3 staining. Finally, tubular damage was associated with dysfunction of ECs that expressed myofibroblast marker (α-SMA). Early treatment by CPFA was able to reduce collagen deposits (25.29 ± 8.9 vs. septic 51.54±8.28 p=0.04), tubular apoptosis (Caspase-3: 20.96 ± 2.68% vs. septic 40.44±3.96 p=0.004 and α-SMA ECDs (CD31/α-SMA) 4.05±2.19% vs. septic 16.53±5.33% fold change, p=0.04). In vitro, EC cultured with septic sera showed reduced expression of specific EC markers (CD31 49.9±0.5 MFI and VE-cadherin (11.12±3 MFI), with increased expression of markers of EC dysfunction such as N-cadherin and Vimentin. Surprisingly, sera of treated pigs preserved EC phenotype (CD31: 94.97±3.4 p=0.04; VE-cadherin: 24.07±4.9 p=0.03) with up-regulation of N-cadherin and Vimentin.

Conclusions: Our data indicated that an early treatment by CPFA might be pivotal to counteract the acute effects of LPS on renal tissue, by removing the cytokine responsible for EC dysfunction and tubule-interstitial damage.

SA-PO094

Protection against H2O2-Induced Cell Death by Angelica Sinensis and Astragalus Membranaceus in HK2 Human Kidney Cells
Muhammad Shahzad,1,2 David M. Small,1 Christudas Morais,1 Glenda C. Gobe,1 Centre Kidney Disease Res Sch Medicine, Univ Queensland, Brisbane, Australia; 2Dept Pharmacol, Univ Health Sch, Lahore, Pakistan.

Background: Oxidative stress is an important mechanism for renal epithelial cell destruction in several kidney diseases, including nephritic syndrome. Angelica and Astragalus sinensis have a long history of medicinal use in traditional Chinese medicine, including for treating patients with nephrotic syndrome. The aim was to investigate the protection of Astragalus membranaceus and Angelica sinensis against H2O2-induced cell death in HK2 proximal tubular cells.
Effects of Leucine-Rich Repeat Kinase 2 (LRKK2) Deletion in Normal and Injured Rat Kidneys: Ravindra Boddu,1 Joao Paulo Lima Daheber,2 Kyoko Kojima,3 Lisa M. Curtis,2 Anupam Agarwal,2 Andrew B. West,4 Medicine; Surgery; Veteran's Administration Medical Center, Birmingham, AL; Neurology, UAB, Birmingham, AL.

Background: Leucine-rich repeat kinase 2 (LRKK2) mutations account for 5-6% of familial Parkinson's disease (PD) and 1-3% in sporadic PD. LRRK2 knockout (KO) mice do not develop neuropathological changes in the brain. Previous reports suggest that a loss of LRKK2 causes age-dependent accumulation of α-synuclein (60-fold) and ubiquitinated proteins in the kidney, in which LRKK2 is normally expressed at high levels (~6-fold compared to the brain). The role and biology of LRKK2 in the kidney is not well understood. Aged LRKK2 KO mice (~2 months) display impaired activation of autophagy with increased apoptotic cell death, inflammatory responses and oxidative damage. Objective: To understand the LRKK2 biology in kidney, we sought to characterize a rat model of LRKK2 deletion and evaluate the phenotype after acute kidney injury (AKI).

Methods: We utilized mass spectrometry (MS) and western blot to compare wild-type (WT) and knockout (KO) rat kidneys; and assessed renal function and structure following cisplatin-induced AKI in LRKK2 WT and KO rats. Localization of LRKK2 using immunofluorescence (IF) was also performed.

Results: LRKK2 KO kidneys are dark red in color and significantly heavier than WT kidneys, sinking in 10% sucrose solution. IF studies showed localization of LRKK2 in renal tubules. Protein expression for heme oxygenase-1, H and ferritin and transferrin receptor are significantly decreased in 6 month KO rat kidneys. MS showed increased deposits of hemoglobin and fucosylated glycans (fucopinosan) in 12 month KO kidneys compared to WT kidneys. Following cisplatin-induced AKI, no differences in renal function were noted following cisplatin-induced AKI in LRKK2 WT and KO rats. Localization of LRKK2 using immunofluorescence (IF) was also performed.

Conclusions: The phenotype of the LRKK2 KO animal implicate LRKK2 to have biology significantly different from knockout in the kidney; and further studies to dissect the possible role of LRKK2 in older animals will potentially identify a novel pathway for intervention in kidney injury settings.

Funding: NIDDK Support

SA-PO095

Involvement of Indoxyl Sulfate (IS) in Downregulation of Pulmonary Aquaporin (AQP)-5 in Rats Caused by Bilateral Nephrectomy (BNx)-Induced Acute Kidney Injury (AKI): Masataka Sagata,1 Chiika Saijo,2 Go Yoneeda,1 Yuki Nomura,1 Kazuhiro Nishi,2 Hirofumi Jono,1 Hideyuki Saito.2 Medicine; 1Dept of Clinical and Pharmaceutical Sciences, Kumamoto Univ, Kumamoto, Japan; 2Dept of Pharmacology, Kumamoto Univ Hospital, Kumamoto, Japan; 1Dept of Hemodialysis and Apheresis, Kumamoto Univ Hospital, Kumamoto, Japan.

Background: Despite advances in understanding the pathophysiology, improvements in dialysis and supportive care, the mortality of AKI remains considerably high. The high mortality of AKI is associated with acute lung injury or acute respiratory distress syndrome, which are typical complications of AKI. It is suggested that dysregulation of lung salt and water channels following the AKI plays a pivotal role in ALI, however, the mechanism of dysregulation has not been elucidated. In this study, we examined involvement of a typical oxidative stress-inducing uremic toxin, IS, in dysregulation of pulmonary predominant water channels, AQP-5, in cisplatin-induced AKI model rats.

Methods: AST-120, clinically used oral sphaerical adsorbent, was orally administered to rats (2.5 g/kg) at ~24 -1 h before and 24 h after BNx surgery. Serum was collected at 4 and 48 h following surgery, and IS level was determined by HPLC. AQP-5 protein expression was examined by immunoblot analysis. Results: At 48 h, BNx evoked AKI with the increases in serum creatinine (Scr) (29-fold vs sham-operated rats), BUN (12-fold) and serum IS levels (32-fold) in association with a marked downregulation of pulmonary AQP-5 expression (0.51-fold). Administration of AST-120 resulted in a significant decrease in serum IS level (0.64-fold), which was accompanied with the decreases in IS accumulation in liver and lung. AST-120 treatment had no effects on Scr, BUN and lung Na,K-ATPase expression, whereas the downregulation of AQP-5 was significantly restored (2.2-fold vs BNx rats). At 4 h after BNx surgery, serum interleukin-6 level was not affected by oral AST-120.

Conclusions: These results suggested that BNx-induced AKI causes downregulation and/or dysregulation of pulmonary AQP-5 expression, in which IS could play a toxicopharmacological role as a mediator involved in renopulmonary crosstalk.

Funding: Government Support - Non-U.S.

SA-PO097

Pretreatment with Saline Loading Ameliorates Ischemic Acute Kidney Injury (AKI), and Reduces Intrarenal Upregulation of (Pro)receptor Inhibitor Peptides (PAP) in Rats: Masafumi Ono,1,2 Yukitoshi Sakao,1 Takayuki Tsuji,1 Naro Ohashi,1 Hideo Yasuda,1 Yoshishide Fujigaki,1,2 Akihiko Kato,2 Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan; Blood Purification Unit, Hamamatsu Univ Hospital, Hamamatsu, Shizuoka, Japan; Dept of Internal Medicine, Teikyo Univ School of Medicine, Tokyo, Japan.

Background: (Pro)receptor inhibitor peptides (PAP), a trans-membrane receptor for renin and prorenin, is involved in the local activation of renin-angiotensin system (RAS) in the kidney. PAP also directly stimulates intracellular signaling pathway such as MAPK. However, it remains to be determined whether intrarenal PAP plays a role in the development of AKI.

Methods: Male SD rats were subjected to left renal arterial clamping for 45 min just after right nephrectomy. We assessed the renal expression of PRR, renin/prorenin, angiotensin II (ang II) receptor type (AT)1 and AT2 receptor, and phospho-ERK1/2 protein by western blot and immunohistochemistry at 6, 24, 48 hr and 7 days after the injury. We measured intrarenal angiotensin II (ANG II) level by RIA. We also examined whether pretreatment with oral loading of saline solution (1.0% NaCl) for 48 hr before just before AKI induction modifies intrarenal RAS components and MAPK system in the ischemic kidney.

Results: Serum creatinine (Scr) increased maximally at 48 hr after the reperfusion. Pretreatment with saline loading significantly decreased the peak of Scr (5.3±0.2 vs 3.38±1.74 mg/dL, P<0.05). Renal ischemia increased the abundance of PRR protein at 48 hr, and gradually decreased at day 7. PRR staining was mainly increased in the distal and cortical collecting ducts. There was a significant increase in renal AGT at 24 hr, while renal renin/prorenin remained at same levels. Phospho-ERK1/2 was upregulated at 6-24 hr after ischemia. Prior saline drinking suppressed the increase of PRR, AGT and phospho-ERK1/2 protein.

Conclusions: Renal ischemia increased the abundance of PRR concomitantly with AGT and phospho-ERK1/2. Saline loading mitigated ischemic injury, and prevented the increase of renal PRR abundance. These findings suggest that saline loading ameliorated ischemic AKI, mediating possibly through the suppression of RAS and MAPK systems via PRR downregulation.

SA-PO098

A Mouse Model of Type 1 Hepatorenal Syndrome (HRS): Daniel E. Carl,1 Siddhartha S. Ghosh,1 Todd W. Gehl,1 Internal Medicine/Nephrology, Virginia Commonwealth Univ, Richmond, VA; Internal Medicine, Hepatology, Virginia Commonwealth Univ, Richmond, VA.

Background: Type 1 HRS is a life threatening complication of cirrhosis with limited therapeutic options. The lack of a mouse model of HRS is a major gap in the field as it hinders molecular analysis of HRS and identification of therapeutic targets. The aim of this study was to develop a mouse model of type 1 HRS.

Methods: C57Bl1 mice were administered CCl4 (1 m/l/Kg) for 6-12 weeks to produce cirrhosis. Varying doses of lipopolysaccharide (LPS) were then administered intraperitoneal to identify a sublethal dose of LPS to induce AKI and a dose to cause mortality rate of 12 week CCl4-treated mice; with no fatalities in controls+6mg/Kg LPS.

Results: Mice developed bridging fibrosis with cirrhotic nodule formation after 6 weeks of CCl4. Hyperdynamic circulatory dysfunction (statistically significant increase in cardiac output and drop in systemic venous resistance) developed after 12 weeks of CCl4. Within 16 hours of a sublethal dose of LPS (2mg/Kg), 12 week CCl4-treated mice experienced a certain urine-volume and rise in creatinine. The urine Na decreased and there were no casts or proteinuria. Control mice treated with 2 mg/Kg LPS did not experience AKI.

Conclusions: We describe a viable mouse model of type 1 HRS. Mice treated with 12 weeks of CCl4 develop histology and hemodynamics consistent with cirrhosis. Furthermore, cirrhotic mice develop AKI following LPS consistent with HRS.
Osmotic Nephrosis and Contrast-Induced Acute Kidney Injury Are Prevented by the RIPK1-Inhibitor Necrostatin-1 in Mice

Methods: CASP-8 and caspase-3 proteins were measured in tubular cells by immunostaining in renal cortex. NOS activity was determined in perfused rat kidneys by fluorescence

Results: After 24 hours, 70% of mice went into renal failure and plasma creatinine rose from 0.09±0.02 to 0.95±0.22 mg/dl (p<0.001). The injury pattern at 24 hours was mainly located in the inner stripe of the outer medulla and consisted of capillary congestion, erythrocye extravasation and necrosis, all of which correlated with the degree of renal failure (Figs. 1, 2). There were no signs of cell death in the inter-bundle zone. With progressive degrees of damage, there was increasing loss of endothelial immunohistochemical markers (MECA-32, CD34). Apoptosis of endothelial and tubular epithelial cells could be demonstrated using TUNEL stainings, and apoptotic changes were seen in the vasa recta. 14 days after the acute event, 25% of surviving mice still had renal failure. The injury in the inner stripe of the outer medulla now was chronic and the cortex then showed extensive chronic changes as well, reflecting injury of medullary thick ascending limbs with the loss of their associated convoluted tubules.

Conclusions: This novel mouse model underscores a role for medullary endothelial cell injury in the pathogenesis of CIN and shows that the long-term consequences of acute medullary injury are reflected by chronic changes in both the cortex and medulla.

Funding: Government Support - Non-U.S.

SA-PO102

Iodinated Contrast Media Induce Tubular Necrosis and Dysfunction in Isolated Thick Ascending Limb of Rat

Methods: Iodixanol (n=8) caused significant reduction in vascular conductance and mean arterial pressure (1.7±0.2% vs. 1.7±0.3%, p<0.05). A dose of iodixanol (8 mg/kg) increased creatinine levels significantly in the medium- and high-dose groups (12±6% vs. 22±14%, p<0.05). The injection of iodixanol (8 mg/kg) also caused a significant reduction in glomerular filtration rate (23±5% vs. 32±5%, p<0.05) and a significant increase in tubular epithelial cell apoptosis (13±2% vs. 36±1%, p<0.05). The injection of iodixanol (8 mg/kg) also caused a significant increase in tubular epithelial cell necrosis (24±1% vs. 45±2%, p<0.05).

Conclusions: Iodixanol (8 mg/kg) caused significant reduction in vascular conductance and mean arterial pressure, a significant increase in creatinine levels, a significant reduction in glomerular filtration rate, and a significant increase in tubular epithelial cell apoptosis and necrosis.

Funding: None.

SA-PO103

Angiotensin III/Angiotensin Type 2 Receptor Axis Inhibits Hyperglycemia-Induced Fibronectin Synthesis through Inhibition of NADPH Oxidase Nox4 in the Kidney

Methods: Ang II increased fibronectin expression in MCs and inhibition of AMPK prevented the inhibitory effect of Ang III on Nox4 expression and matrix expansion (including

Conclusions: Ang II increased fibronectin expression in MCs and inhibition of AMPK prevented the inhibitory effect of Ang III on Nox4 expression and matrix expansion. This novel mechanism of Ang II may explain the development of fibrosis in the kidney in response to hyperglycemia.
Conclusions: Ang II activates AT2R to limit fibrotenin accumulation in response to HG via AMPK-dependent inhibition of Nox4 mRNA translation. AT2R activators such as Ang II may become viable therapeutic interventions to complement traditional therapy to treat diabetic nephropathy.

Funding: NIDDK Support, Private Foundation Support

SA-PO104

Angiotensin 1-7 Prevents Systemic Hypertension and Ameliorates Kidney Injury Via Inhibition of Oxidative Stress In Diabetic Akita Mouse Kidneys

Yixuan Shi,1 Chao-Sheng Lo,1 Isabelle Cheniër,1 Janos G. Filep,2 Julie R. Ingelfinger,2 Shao-Ling Zhang,1 John S.D. Chan.1,2 Res. Ct., CHUM-Hôtel Dieu Hosp, Montreal, Canada; 3Res. Ct., Maisonneuve-Rosemont Hosp, Montreal, Canada; 4Pediatr Nephrol Unit, Mass. Gen. Hosp. for Children, Boston, MA.

Background: We investigated whether Ang 1-7 administration could affect systemic hypertension and ameliorate kidney injury via inhibition of oxidative stress in Akita mice with type 1 diabetes.

Methods: Ang 1-7 was administered daily (500 µg/kg body weight (BW)/day, subcutaneously) to male Akita mice starting at 14 weeks of age with or without coadministration of A779 (an antagonist of the Mas receptor) (10 mg/kg BW/day). The animals were euthanized at 18 weeks of age. Wild type (WT) mice of the same age served as controls. Blood glucose (BG), systolic blood pressure (SBP) and albumin/creatinine ratio (ACR) were monitored weekly. Kidneys were processed for histology including dihydroethidium (DHE) staining and immunostaining for HO-1, TGF-β1 (α-smooth muscle actin), α-SMA, WT-1 and Collagen IV. Kidneys were processed for histology including dihydroethidium (DHE) staining and immunostaining for HO-1, TGF-β1 (α-smooth muscle actin), α-SMA, WT-1 and Collagen IV.

Results: The present study aimed to determine the relationship between Ang 1-7 administration, and the effects of Ang 1-7 were reversed by A-779. Finally, Ang 1-7 administration prevented the increased SBP and normalized urinary ACR without affecting BG levels in Akita mice. Akita kidneys exhibited significant increase in DHE staining and immunostaining for HO-1, TGF-β1 and collagen IV, whereas WT-1, nephrin and Ace2 immunostaining were decreased. These changes were normalized with Ang 1-7 administration, and the effects of Ang 1-7 were reversed by A-779. Finally, Ang 1-7 administration decreased glomerular tuft volume and tubular luminal area were assessed morphometrically. Ang 1-7 administration prevented the increased SBP and normalized urinary ACR without affecting BG levels in Akita mice. Akita kidneys exhibited significant increase in DHE staining and immunostaining for HO-1, TGF-β1 and collagen IV, whereas WT-1, nephrin and Ace2 immunostaining were decreased. These changes were normalized with Ang 1-7 administration, and the effects of Ang 1-7 were reversed by A-779. Finally, Ang 1-7 administration decreased glomerular tuft volume and tubular luminal area in Akita mice, and these changes were also reversed by A779.

Conclusions: Our data suggest that intrarenal Ang 1-7 plays a protective role by attenuating SBP and RPTC injury in diabetes, predominantly through decreasing renal oxidative-stress-mediated signaling.

Funding: Government Support - Non-U.S.

SA-PO105

Indoxyl Sulfate Induces Angiotensinogen Expression in Proximal Tubular Cells Through Uptregulation of CREB, NF-κB and NOX4

Toshimitsu Niwa,1 Hidehisa Shimizu,1 Shinnichi Saito,1 Fuyuhiko Nishijima.2 Nagoya Univ Graduate School of Medicine; 1Biomedical Research Laboratories, Kureha Co.

Background: In chronic kidney disease (CKD), indoxyl sulfate, a uremic toxin, accumulates in serum, and the expression of angiotensinogen (AGT) is upregulated in renal proximal tubular cells. The present study aimed to determine the relationship between indoxyl sulfate and the upregulation of AGT expression in proximal tubular cells.

Methods: For in vitro experiment, HK-2 cells derived from human proximal tubular cells were incubated with indoxyl sulfate (250 mM). For in vivo experiment, the rat groups consisted of: (1) Diabetic salt-resistant normotensive rats (DN, n=8), (2) Diabetic salt-resistant normotensive indoxyl sulfate-administered rats (DN+IS, n=8). Indoxyl sulfate (200 mg/kg/day in drinking water) was administered to the rats for 32 weeks.

Results: Indoxyl sulfate induced expression of AGT in rat renal cortex and in cultured human IMR-90 tubular cells (HK-2). In proximal tubular cells, indoxyl sulfate induced phosphorylation of CAMP response element-binding protein (CREB) on Ser-133, and induction of CREB expression in proximal tubular cells.

Conclusions: Indoxyl sulfate induces angiotensinogen expression in proximal tubular cells through upregulation of CREB, NF-κB and NOX4.

SA-PO106

Reactive Oxygen Species Contribute to Angiotensin II Activation of TRPC6 Channels in Rat Primary Podocytes in Isolated Glomeruli

Stuart E. Dryer,1,2 Marc Thomas Anderson.1 1Biology and Biochemistry, Univ of Houston, Houston, TX; 2Nephrology, Baylor College of Medicine, Houston, TX.

Background: Angiotensin II (Ang II) evokes Ca2+ influx into podocytes, but many aspects of its transduction pathway are unknown in this cell type. Some recent analyses have been carried out on immortalized podocyte lines heterologously over-expressing Ang II receptors, which runs the risk of promiscuous activation of non-physiological transduction cascades.

Methods: Whole-cell recordings from primary rat podocytes on the surface of glomeruli isolated by sieving procedure. The podocytes were still attached to the glomerular capillary. Application of Ang II evoked inward currents with current–voltage characteristics of TRPC6. Robust responses were seen at [Ang II] = 1 nM, half-maximal activation occurred at [Ang II] = 10 nM, and responses desensitized rapidly at [Ang II] = 1 μM. Ang II activation of cationic currents was blocked by losartan. Ang II-evoked currents were also inhibited completely by SKF-96365, by 50 μM LA3, and by TRPC6 knockdown with siRNA, suggesting all of the Ang II-modulated cationic currents contain TRPC6 subunits. Responses to Ang II were completely blocked by including GDP-BβS in recording pipette, and by the PLC inhibitor D-609, but not by the PKC inhibitor chelerythrine. Responses to hypoxosmotic stretch persisted under those conditions. Effects of Ang II on TRPC6 were reduced by the NOX2 inhibitors apocynin and diphenylene iodonium and also by the reactive oxygen species (ROS) quencher MtiTBAP.

Conclusions: Ang II acts through G-protein coupled AT1Rs through PLC to activate TRPC6. Generation of ROS through NADPH oxidase NOX2 contributes to TRPC6 activation by Ang II.

Funding: Pharmaceutical Company Support - Pfizer Inc.

SA-PO107

Endogenous NOX2 Interacts with Podocyte TRPC6 Channels and Contributes to Their Activation by Diacylglycerol but Not by Mechanical Stimuli: Essential Role of Podocin in Maintaining the NOX2-TRPC6 Complex

Marc Thomas Anderson,1 Eunyoung Kim.1 1Biology and Biochemistry, Univ of Houston, Houston, TX; 2Nephrology, Baylor College of Medicine, Houston, TX.

Background: The endogenously expressed TRPC6 channels of podocytes become active in response to reactive oxygen species (ROS) generated in several different signal transduction cascades. TRPC6 channels are also expressed normally produced during PLC-dependent cascades, for example in response to angiotensin II.

Methods: Whole-cell recording, immunoprecipitation, flowmetric analysis of ROS generation in immortalized mouse podocytes.

Results: Endogenous TRPC6 channels in mouse podocyte cell lines reciprocally co-immunoprecipitate with the NADPH oxidase NOX2 (gp91phox). However, this interaction is not detected in podocin knockdown cells. In whole-cell recordings, we observed that TRPC6 activation by a DAG analog (OAG, 10 μM) was reduced in podocytes pretreated with the NOX2 inhibitor apocynin, by the pan-NOX2 inhibitor diphenylene iodonium and by the ROS quencher tempol. Tempol had no effect on TRPC6 activation by hypoxosmotic stretch. Application of 10 μM OAG also increased generation of ROS, but not in podocin knockdown cells. OAG also increased surface expression of the NOX2 regulatory subunit p47(phox). Podocin is a cholesterol-binding membrane protein that may function to tether TRPC6 and other slit diaphragm proteins to cholesterol-rich membrane domains. We observed that cholesterol depletion using 10 mM methyl-beta-cyclodextrin reduced but did not eliminate activation of podocyte TRPC6 channels by OAG, and eliminated the NOX2-TRPC6 interaction as assessed by immunoprecipitation.

Conclusions: NOX2 associates with TRPC6 at podocin-organized raft domains, and becomes catalytically active in response to DAG. The localized production of ROS contributes to TRPC6 activation by DAG. Importantly, podocin is required for formation of this signaling complex. 1. Anderson et al. (2013) Am J Physiol-Cell Physiol in press.

Funding: Pharmaceutical Company Support - Pfizer Inc.

SA-PO108

Overexpression of Heterogeneous Nuclear Ribonucleoprotein F Attenuates Systemic Hypertension and Normalizes Angiotensin-Converting Enzyme 2 Expression via Down-Regulation of Transforming Growth Factor-Beta 1/TGF-β Receptor II Signaling in Diabetic Akita Transgenic Mice

Chao-Sheng Lo,1 Shiao-Ying Chang,1 Yixuan Shi,1 Isabelle Chenier,1 Janos G. Filep,2 Julie R. Ingelfinger,2 Shao-Ling Zhang,1 John S.D. Chan.1,2 Res. Ct., CHUM-Hôtel Dieu Hosp, Montreal, Canada; 3Res. Ct., Maisonneuve-Rosemont Hosp., Montreal, Canada; 4Pediatr Nephrol Unit, Mass. Gen. Hosp. for Children, Boston, MA.

Background: We investigated whether heterogeneous nuclear ribonucleoprotein F (hnRNFP) stimulates angiotensin-converting enzyme 2 (Acc2) expression in renal proximal tubular cells (RPTCs) via decreasing transforming growth factor-beta 1/TGF-β2 receptor II (TGF-β1/TGF-β2 RII) signaling in Akita mice.

Methods: Adult (20 weeks of age) male wild type (WT), Akita and Akita hnRNFP-transgenic (Tg) mice were studied. Kidneys were processed for histology, TGF-β1, TGF-β2 RII and Ace2 mRNA and their protein expression in renal proximal tubules (RPTs)
Nuclear Factor Erythroid 2-Related Factor 2 Mediates High Glucose Stimulation of Renal Angiotensinogen Gene Expression and Induction of Hypertension in Diabetic Akita Mice

Shaaban Abdo, Yixuan Shi, Isabelle Chenier, Janos G. Filep, Julie R. Ingelfield, Shao-Ling Zhang, John S.D. Chen, Chet E. Holterman, Jean-Francois Thibodeau, Christopher L. Kennedy, John S.D. Chen, Jean-Francois Thibodeau, Chet E. Holterman, Jean-Francois Thibodeau, Christopher L. Kennedy, John S.D. Chen, Jean-Francois Thibodeau

Background: We investigated whether nuclear factor erythroid 2-related factor 2 (Nrf2) can mediate the effects of high glucose (HG) on stimulation of angiotensinogen (Agt) gene expression in renal proximal tubular cells (RPTCs), and induction of systemic hypertension (sHTN) and renal injury in type 1 diabetic Akita mice.

Methods: Adult male Akita mice specifically overexpressing catalase (Cat) in their RPTCs and Akita mice treated from 12 weeks ± insulin implants for 4 weeks were studied at 16 weeks. Non-Akita mice served as controls. Plasma glucose, systolic blood pressure (SBP) and urinary albumin/creatinine ratio (ACR) were monitored weekly. Kidneys were processed for histology. Renal proximal tubular (RPT) Agt, Nrf2 and Keap1 mRNA and their protein expression were evaluated by real time-qPCR and Western blotting, respectively. Freshly isolated mouse RPTs and rat RPTCs stably transfected with a plasmid, pGL4 containing rat Agt gene promoter ± Nrf2 activator (Oltipraz) or Nrf2 inhibitor (aldehyde trignonelline[C7HN2O2]) were also studied.

Results: Akita mice developed sHTN and exhibited renal hypertrophy. Overexpression of Cat or treatment with insulin normalized sHTN, attenuated renal hypertrophy and decreased urinary ACR in Akita Cat-Tg and Akita mice, respectively. RPT Agt and Nrf2, but not Keap1 expression, were significantly increased; these changes were normalized by Cat overexpression and insulin treatment. Ex vivo, Oltipraz stimulated Nrf2 and Agt expression in mouse RPTs and rat RPTCs and trignonelline abolished its effect. In vitro, HG and Oltipraz stimulated Agt gene promoter activity and its effect was prevented by inhibitors of oxidative stress and trignonelline as well as by transfecting RPTCs with small interfering RNA of Nrf2.

Conclusions: Our data indicate that HG induce RPT injury and sHTN in diabetic mice through, at least in part, Nrf2-mediated stimulation of intrarenal Agt gene expression.

Funding: Government Support - Non-U.S.

SA-PO110

Nox5 Exacerbates Filtration Barrier Damage and Increases Blood Pressure in a Mouse Model of Diabetes

Chet E. Holterman, Jean-Francois Thibodeau, Mark E. Cooper, Rhian Touyz, Chris R. Kennedy, Baker IDI Heart and Diabetes Institute, Melbourne, Australia; Univ of Glasgow, Glasgow, United Kingdom; Kidney Research Centre, Ottawa Hospital Research Institute, Ottawa, Canada.

Background: We have previously demonstrated that Nox5 is upregulated in human diabetic kidney and contributes to ROS-induced podocyte damage and filtration barrier dysfunction. While several studies implicate Noxes 1, 2 and 4 in diabetic nephropathy, nothing is known regarding the role of Nox5. Here we show that podocyte-specific Nox5 expression results in earlier and more severe albuminuria, increased systolic blood pressure, and interstitial fibrosis in streptozotocin (STZ) type 1 diabetes.

Methods: Transgenic mice expressing Nox5 specifically in podocytes (Nox5(S pod+)) were subjected to low dose STZ (50mg/kg) injection daily for five days. Urinary albumin excretion rates from 24 hour urine collections were assessed by ELISA. Systolic blood pressure was measured weekly by tail-cuff plethysmography. Kidney pathology was further assessed by PAS and Masson-Trichrome staining and electron microscopy to determine morphological changes, glomerular sclerosis, and foot process effacement.

Results: Urinary albumin levels in Nox5 pod+ were 6-fold higher and blood pressure was significantly higher 16 weeks post-STZ injection as compared to non-transgenic littermates. Systolic blood pressure was not increased in Nox5 S pod+ mice at 4 weeks post-STZ but showed increases over non-transgenic littermates at 8 and 16 weeks. PAS and Masson-Trichrome staining revealed increased glomerular sclerosis and interstitial fibrosis 16 weeks post-STZ in Nox5 S pod+ animals.

Conclusions: These novel data identify Nox5 as an important NADPH oxidase isoform in the development of diabetic nephropathy. Nox5 may emerge as a novel therapeutic target for reducing the progression of this disease.

Funding: Government Support - Non-U.S.

SA-PO112

TORG2 Signalling Regulates Stress Response and Longevity in C. elegans

Elke Neumann-Haefelin, Vanessa Ruf, Gerd Walz, Universit, Univ Hospital, Freiburg, Germany; Dept of Genetics, Harvard Medical School, Boston.

Background: The evolutionarily conserved target-of-rapamycin (TOR) kinase controls fundamental metabolic processes to support cell and tissue growth. TOR functions within the context of two distinct complexes, TORC1 and TORC2. The TORC2 with its specific component Rictor has been recently implicated in aging and regulation of growth and metabolism.

Methods: We established a C. elegans model system to study functional aspects of TOR signalling in vivo.
SA-PO113
The Regulation of the Nitric Oxide System Can Modulate the Klotho Expression in Kidney via TWIST-2 and E-cadherin
Jae Won Yang, Jae Seok Kim, Minseob Eom, Seung-Ok Choi, Byoung Geun Han.

Methods: The 10th weeks Sprague-Dawley rats (N = 24, 200g male) were divided into four groups. We supplied low salt diet to the control group (N = 6), L-NAME 1 mg/ml in drinking water to the L-NAME group (N=6), and unenflax 5 mg/SQ to the Udenafil group (N=6). The klotho mRNA level in the collection of blood and urine on day 28, both the kidneys were resected surgically.

The serum creatinine, urine nitrate/nitrite, cGMP by ELISA, and tissues were investigated by Immunohistochemical staining, and RT-PCR for klotho, TWIST 1, 2, E-cadherin.

Results: The serum creatinine and urine nitrate/nitrite level did not show the statistical difference between groups. The mRNA level increased 1.90±1.65, 139.27±114.87, 10.33±8.42, 20.19±12.25 (p=0.0163). The E-cadherin mRNA expression showed 0.64±0.32, 1.57±0.97, 1.24±1.27, 13.82±3.04 (p=0.0029). The blocking of NO system decreased the klotho expression via the TWIST-2 increase. The induction of NO system increased the klotho expression via E-cadherin increase.

Conclusions: The regulation of the nitric oxide system can modulate the klotho expression in kidney via TWIST-2 and E-cadherin.

SA-PO114
Semicarbazide-Sensitive Amine Oxidase (SSAO) Inhibitor Inhibits Extracellular Matrix Deposition in Kidney Fibrosis
May Ww Wong, Ye Zhang, Sonia Saad, Carol A. Pollock, Muh Geot Wong.

Methods: A 7 day unilateral ureteric obstruction (UUO) model of acute kidney fibrosis was examined in 6-8 week old male C57BL/6 mice (20-25g, n = 5) as compared to the sham-operated; (i) UUO-control; (ii) UUO-pretreated with losartan (10-5M) 30 minutes before AGEs added, and the changes of angiopoietin-like protein 4 expression and cell lysates were measured by western blot, and cytoskeleton reorganization.

Results: Podocytes were incubated with various concentrations of AGEs (0, 20, 40, 80 µg/ml) for 24 hours, the expression of angiopoietin-like protein 4 was detected by real-time PCR and western blot analysis, the concentration of angiotensin II increased in endothelial permeability [(0.46±0.09) vs. (0.15±0.09) OD, p<0.05]. However, pretreatment with losartan (10-5M) blunted these effects induced by AGEs [(0.19±0.04) vs. (0.13±0.05) OD, p<0.05]. Incubation with AGEs also resulted in a significant increase in endothelial permeability [(0.46±0.09) vs. (0.15±0.09) OD], [0.43(2.82) vs. (7.28±2.64) η2•cm2•P<0.05]. However, pretreatment with angiotensin II receptor blocker losartan (10-5M) blunted these effects induced by AGEs (P<0.05).

Conclusions: AGEs upregulated the expression of angiopoietin-like protein 4 via activation local renin-angiotensin system in endothelial cells, which may be a new mechanism for AGEs increasing endothelial permeability.

Funding: Government Support - Non-U.S.

SA-PO116
Advanced Glycation End Products Upregulated the Expression of Angiopoietin-Like Protein 4 via Activation the Renin-Angiotensin System in Endothelials

Methods: Endothelial cells were incubated with various concentrations of AGEs for 24 hours, the expression of angiopoietin-like protein 4 was detected by real-time PCR and western blot analysis, the concentration of angiotensin II increased in endothelial permeability [(0.46±0.09) vs. (0.15±0.09) OD], [0.43(2.82) vs. (7.28±2.64) η2•cm2•P<0.05]. However, pretreatment with angiotensin II receptor blocker losartan (10-5M) blunted these effects induced by AGEs (P<0.05).

Conclusions: AGEs upregulated the expression of angiopoietin-like protein 4 via activation local renin-angiotensin system in endothelial cells, which may be a new mechanism for AGEs increasing endothelial permeability.

Funding: Government Support - Non-U.S.

SA-PO117
Effects of Advanced Glycation End-Products on Synaptopodin Expression and Cytoskeleton Reorganization in Podocytes

Background: To investigate the effects of advanced glycation end products (AGEs) on the expression of angiotensin-like protein 4 and its mechanisms in endothelial cells.

Methods: Podocytes were incubated with different concentrations of AGEs (0, 20, 40, 80 µg/ml) for 24 hours, the expression of angiopoietin-like protein 4 detected by real-time PCR and western blot analysis, the concentration of angiotensin II increased in endothelial permeability [(0.46±0.09) vs. (0.15±0.09) OD], [0.43(2.82) vs. (7.28±2.64) η2•cm2•P<0.05]. However, pretreatment with angiotensin II receptor blocker losartan (10-5M) blunted these effects induced by AGEs (P<0.05).

Conclusions: AGEs upregulated the expression of angiopoietin-like protein 4 via activation local renin-angiotensin system in endothelial cells, which may be a new mechanism for AGEs increasing endothelial permeability.

Funding: Government Support - Non-U.S.
SA-PO118 

Mpv17 Protects Podocytes against Oxidative Stress and Apoptosis in Experimental Glomerulonephritis 

Gabriella Casalena,1 Stefanie Krick,1 Ilse S. Dach,1 Liping Yu,1 Shaolin Shi,1 Viette D. D’Agati,2 Deltel O. Schondorf,2 Erwin P. Bottiger,2 1Dept of Medicine and The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; 2Dept of Pathology, College of Physicians and Surgeons, Columbia Univ, New York, NY; 3Dept of Medicine, Univ of Miami Miller School of Medicine, Miami, FL; 4Dept of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Mitochondrial dysfunction is increasingly recognized as contributing to several glomerular diseases, including those secondary to mitochondrial DNA (mtDNA) mutations/deletions. Mitochondria maintain cellular redox and energy homeostasis and are a major source of intracellular reactive oxygen species (ROS). ROS accumulation may contribute to mitochondrial dysfunction/mutations and thereby to glomerulosclerosis. In mice, deletion of the Mpv17 gene predisposes to experimental glomerulosclerosis, but the underlying mechanism remains poorly defined.

Methods: Mpv17+/+ and Mpv17−/− C57BL/6J mice were injected with nephrotoxic serum to induce a mild or a severe form of nephritis (NTSN). Mpv17+/+ or Mpv17−/− podocytes were generated by crossing Mpv17+/+ or Mpv17−/− with Immorto® transgenic mice (Charles River, MA).

Results: Mpv17 localizes to mitochondria of podocytes and its expression is reduced in several glomerular injury models and in human glomerular diseases. Using a mild or severe form of NTSN we found that deletion of Mpv17 resulted in increased proteinuria (mild NTSN), and increase in serum creatinine (severe NTSN), and increase in serum creatinine (severe NTSN). Renal defects were associated with mtDNA oxidation and deletion, and loss of protective mitochondrial enzymes (MnSOD, PGC1alpha). In vitro, Mpv17 protects mitochondria and hence podocytes from ROS-mediated damage in the kidney. Another set of rats getting HLP diet were also given Apocynin-supplemented water. Rats were euthanized on day 28 and kidneys were extracted. Microarray analysis was conducted using Illumina bead array reader10. Gene ontology (GO) analysis and the pathway analysis of the genes was done using DAVID (Database for Annotation, Visualization of Integrated Discovery) enrichment analysis tool.

Conclusions: We have already shown that production of reactive oxygen species (ROS) is a crucial factor for renal injury and inflammation following exposure to oxalate (Ox) and calcium oxalate (CaOx) crystals. In this study we looked at the role of ROS in activation of Nucleotide binding oligomerization domain-like receptor family, pyrin domain containing -3 (NLRP3) inflammasome and associated genes involved in inflammation.

Methods: Eight week old male rats (n=6/group) were given hydroxy-l-proline (HLP) to induce hyperoxaluria and CaOx crystal deposition in the kidneys. Another set of rats getting HLP diet were also given Apocynin-supplemented water. Rats were euthanized on day 28 and kidneys were extracted. Microarray analysis was conducted using Illumina bead array reader10. Gene ontology (GO) analysis and the pathway analysis of the genes was done using DAVID (Database for Annotation, Visualization of Integrated Discovery) enrichment analysis tool.

Results: We analyzed a total of 22,226 genes and found that 20 and 24 pathways were highly significant in the cortex and medulla respectively. In the cortex, ECM-receptor interaction, complement and coagulation cascades, focal adhesion and hypertrophic cardiomyopathy were most significant pathways, whereas in medulla, complement and coagulation cascades, ECM-receptor interaction and dilated cardiomyopathy were the major pathways. Genes encoding for PYCARD (ASC: apoptosis–associated speck-like containing a CARD), other isoforms of CARD (Casapse activation and recruitment domains), TXNIP (Trioxiredoxin-interacting protein), caspase-1, IL-1β and IL-18 were significantly upregulated in HLP-fed rats, but the group receiving apocynin had these genes down regulated in the cortex and medulla respectively.

Conclusions: Our results show the role of ROS in the activation of NLRP3 inflammasome via TXNIP leading to a robust inflammatory response in the kidneys of rats with hyperoxaluria and CaOx nephrolithiasis.

Funding: Other NIH Support - Supported by National Institute of Health grant # R01-DK078602 and the University of Florida Center for the Study of Liihaisis

SA-PO119

Oxidative Stress Response and Heme Oxygenase 1 Expression in Human Umbilical Artery Endothelial Cells: Uremic versus Healthy Serum Conditions. Kristien El Daenoen,1 Marc Hoyerlaet,2 Bert Bammens,1 Laboratory of Nephrology, KU Leuven, Belgium; 2Molecular and Vascular Biology, KU Leuven, Belgium.

Background: Heme oxygenase 1 (HO-1), an inducible heme-degrading enzyme, protects against atherosclerosis. Increased oxidative stress (OX) contributes to the accelerated atherosclerosis of CKD. We investigated the effect of oxidative stress on the maintenance of mitochondrial homeostasis and podocyte survival in response to oxidative stress-induced injury.

Methods: HUAECs were conditioned in 30% human serum (pooled from 40 healthy volunteers of both genders) for 72h, followed by exposure to increasing concentrations of ONOO− (0.10-1.00 mM) for 5min or SIN-1 7.5 and 10mM for 8h (resp L.OX and H.OX). Additionally, HUAECs were pre-incubated with 100μM Hemin for 6h. HO-1 expression was evaluated by RT-PCR and western blot. Cell viability 30 minutes ± Hemin pre-incubation (50 μM) was evaluated by western blot for caspase-3 and TUNEL staining by Flow Cytometry.

Results: HO-1 RNA expression and apoptosis: see figure.

Conclusions: Cell viability and apoptosis assays show higher OX-induced vulnerability in US, starting from lower concentrations and to a larger extent as compared to HS. In contrast to previously published animal data on kidney tubular cells, endothelial cell HO-1 inducibility is preserved in US. Whereas mild HO-1 induction is seen in response to oxidative stress, Hemin induces HO-1 significantly stronger. Pretreatment by Hemin reverses apoptosis, suggesting a beneficial role of heme in Uremia.

SA-PO121

Chitosan/siRNA Nanoparticle-Mediated COX-2 Knockdown Regulates Inflammatory and Oxidative Stress Response Induced by Unilateral Ureteral Obstruction in Mice. Line Nilsson,1 Chuanxue Yang,2 Jorgen Frokiaer,1 Jorgen Kjems,2 Rikke Norregaard,1 1Laboratory of Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; 2Dept of Clinical Medicine, Aarhus Univ, Denmark; 3Interdisciplinary Nanoscience Center, Dept of Molecular Biology and Genetics, Aarhus Univ, Denmark.

Background: Cyclooxygenase type 2 (COX-2) is induced in response to unilateral ureteral obstruction (UOO). In this study the role of COX-2 in the progression of inflammation and oxidative stress response in UOO was examined using a chitosan nanoparticle system containing anti-COX-2 siRNA that targets macrophages as a therapeutic strategy.

Methods: Mice were subjected to 3 days UOO and COX-2 knockdown were mediated by intraperitoneal injection of chitosan nanoparticles containing anti-COX-2 siRNA. Sham-operation was performed in parallel. Localization of COX-2 and its expression was determined by in vivo optical imaging for nanoparticle tracking. COX-2 expression was evaluated by QPCR, immunoblot analysis and immunohistochemistry. Inflammation was examined by the expression of tumor necrosis factor-alpha (TNF-α) and interleukin 12 (IL-12). Mice were euthanized 3 days after treatment, and the expression of tumor necrosis factor-alpha (TNF-α) and interleukin 12 (IL-12) was evaluated by QPCR and immunohistochemistry.

Results: COX-2 siRNA attenuated the downregulation of HO1. HE staining showed lesser tubular damage in COX-2 siRNA treated UOO mice. Plasma creatinine and urea were unchanged in COX-2 siRNA treated UOO mice. In contrast to controls, COX-2 siRNA treated UOO mice showed a significant decrease in the expression of tumor necrosis factor-alpha (TNF-α) and interleukin 12 (IL-12) in the kidneys of animals treated with COX-2 siRNA.

Conclusions: Our study demonstrates that nanoparticle-mediated COX-2 knockdown in mice may contribute to attenuate the development of inflammation and oxidative stress in response to 3 days UOO.

SA-PO122

RGD-Peptide Blocks Osteopontin Expression and Oxidative Stress and Prevents Early Diabetic Nephropathy in Type 1 Diabetic Mice. Taehoon Cho, Susanne B. Nicholas.1,2 1Department of Diabetes and Endocrinology, UCLA, Los Angeles, CA; 2Department of Medicine, UCLA, Los Angeles, CA.

Background: Osteopontin (OPN) may have both pro- and anti-inflammatory properties, and may also regulate the cellular response to oxidative stress. We have shown that OPN is highly up-regulated in renal injury and that global deletion of OPN can prevent diabetic nephropathy (DN), but the mechanisms have not been fully explored. OPN contains an
Glucose and 24 hr urinary albumin-to-creatinine ratio (ACR) were measured monthly. At the end of the study, kidney cortex was harvested for protein isolation. Western blots quantified the expression of TGF-β1, OPN, and NADPH oxidase.

Results: Plasma glucose and urine volumes were 3- fold higher in diabetic compared to non-diabetic mice, but there were no differences in blood pressures. Treatment with RGD-peptide significantly attenuated ACR (3-fold, p<0.001) compared to either untreated or RGE-peptide treated mice. Further, RGD treatment significantly down-regulated expression of TGF-β1 (2-fold, p<0.01), OPN (2.3-fold, p<0.01), and NADPH oxidase (p<0.01, p<0.001).

Conclusions: RGD-peptide blockade of αβ-integrin function in type 1 diabetic mice significantly prevented early Type 1 DN possibly via attenuation of OPN and oxidative stress. The results suggest that RGD-peptide may have some therapeutic potential in human diabetes.

Funding: Other NIH Support - U54MD07598, Private Foundation Support

SA-PO123 Lipid Peroxidation in Metabolic Syndrome Affects Podocyte Physiology and Insulin Signaling Kristian Stadler, Christine Howard, Ellen Cleland. Oxidative Stress and Disease, Pennington Biomedical Research Center, Baton Rouge, LA.

Background: Podocytes are essential cells in the structure of the glomerular filtration barrier. Early podocyte loss is characteristic to chronic kidney disease in obesity, metabolic syndrome, and diabetes. The role of redox imbalance has been implicated in chronic kidney diseases but it is not known how metabolic syndrome related accumulation of toxic end products affects podocyte physiology and insulin sensitivity. Lipid radicals are produced in the lipid peroxidation process of end products such as 4 – hydroxynonenal and isoprostanes is well known in human obesity.

Methods: To assess this relationship, we investigated the specific effects of lipid peroxyl radicals on podocyte physiology and function in vitro and in vivo. We used conditionally immortalized podocytes and two animal models of metabolic syndrome and renal impairments, our state of the art immuno-spin trapping approach and specifically lipid radical scavenging.

Results: In vitro, podocytes lipid peroxyl radicals reduced motility of the cells in a dose dependent fashion. Furthermore, these radicals compromised basal Akt phosphorylation affecting insulin sensitivity and cell survival of podocytes. In vivo, uninephrectomized DBA/2J mice on high fat diet and obese SHHF rats showed impaired podocyte expression of fatty acids (FA) overexposure therefore can induce tubular mitochondrial and cellular redox imbalance, ultimately contributing to the activation of redox sensitive apoptotic pathways.

Conclusions: These results suggest that redox imbalance and excess lipid peroxyl radical production, accompanying obesity and metabolic syndrome may affect podocyte physiology and insulin sensitivity and therefore may contribute to the loss of podocytes seen in the early phases of chronic kidney disease.

Funding: NIDDK Support, Private Foundation Support

SA-PO124 Albumin-Bound Fatty Acids Induce a Peroxide Mediated Redox Sensitive Apoptosis of Proximal Tubular Cells – The Role of Peroxisiredoxin 2 Kristian Stadler, Christine Howard, Ellen Cleland. Oxidative Stress and Disease, Pennington Biomedical Research Center, Baton Rouge, LA.

Background: Metabolic syndrome is an independent risk factor for albuminuria and chronic kidney disease (CKD). It is associated with an oversupply of the nutrient pool and the accumulation of related toxic end products from lipid peroxidation and irregular fatty acid metabolism. While podocytes are insulin sensitive, proximal tubular cells are almost completely lacking glycolysis and preferably oxidize fatty acids. We have hypothesized that a fatty acid overexposure therefore can induce tubular mitochondrial and cellular redox imbalance, ultimately contributing to the activation of redox sensitive apoptotic pathways.

Methods: To test this, we have exposed Nkr-52 proximal tubular epithelial cells to pure albumin (BSA), fatty acid contaminated albumin (BSA/FA) and palmitate (Palm) in various doses and time points.

Results: Both BSA/FA and Palm but not BSA compromised mitochondrial viability, potential and decreased basal respiration, ATP turnover and spare respiratory capacity. Apoptosis was evident in cells with longer exposure or higher doses, through the activation of a redox sensitive p53K-caspase-3 pathway. This was associated with a decrease in peroxiredoxin 2 expression and an increase of the overoxidized dimer form Prx-SO3 and catalase. This suggests a peroxide mediated redox sensitive signaling where FA exposure targets peroxiredoxin 2, ultimately leading to the apoptosis of tubular cells. Transfection with Prx2 rescued cells from caspase 3 cleavage and death.

Conclusions: These results suggest that albumin overloaded with fatty acids but not pure albumin itself changes the redox environment in the tubuli, inducing a peroxide mediated redox sensitive tubular cell apoptosis. Thus mitigating FA levels may be an important factor in maintaining redox balance and for the prevention of tubular cell damage in proteinuric diseases.

Funding: NIDDK Support, Private Foundation Support

SA-PO125 Sphingomyelinase Activation Triggers in HIV-Induced Podocyte Injury through Altered Cellular Redox and NFkB Pathways Karmesh R. Ayasolla, Partab Rai, Ashwani Malhotra, Pravin C. Singhal. Medicine, North Shore LIJ Medical School, New York, NY.

Background: Sphingomyelinase- Ceramide (SM-Cer) cascade has been demonstrated to play an important role in several disease processes leading to inflammation, cell death, tissue and organ damage. However, the role of SM-Cer in the development and progression of podocyte injury has not been investigated to date. In the present study, we investigated the effects of HIV-induced SM-Cer activation in altering cellular redox and NFκB pathway in a mouse model of HIVAN (Tg26) as we have in human podocytes.

Results: Renal tissue of Tg26 mice displayed 70-80 percent increases in neutral SMase activity; similar increase in SMase activity was observed in HIV/HIVP. Both Tempol and GW4869 not only inhibited HIV induced podocyte ROS generation but also attenuated podocyte NFκB activation. GW4869 also inhibited HIV-induced MAPK signaling, PKCζ activation, enhanced IkKa, b, p-p65 (Ser311) expressions in HPs. HIV also altered podocyte expression of fibronectin, tenacin, podocin and ZO-1, however, GW4869 and Tempol inhibited these effects of HIV.

Conclusions: HIV-induced sphingomyelinase activity contributes to an altered podocyte phenotype in HIVAN.

Funding: NIDDK Support

SA-PO126 The Uremic Solute Indole-3 Acetic Acid Induces Oxidative Stress via Endothelial Cyclooxygenase-2 Up-Regulation Marion Salles,1, 2 Laetitia Pignier,1, 3 Séverine Gueguen,1, 3 Françoise Dignat-george,1 Bertrand Gondouin,1,2 Noemie Jourde-chiche,1, 2 UMR-S 1076, Aix Marseille Univ, Inserm, Marseille, France; 3Centre de Néphrologie Dialyse Transplantation Rénale, APHM, CHU Conception, Marseille, France.

Background: In chronic kidney disease, uremic solutes induce endothelial dysfunction, inflammation, and oxidative stress, leading to increased cardiovascular risk. Indole-3 acetic acid (IAA) is an indolic uremic solute of tryptophan metabolism. IAA is an agonist of the transcription factor aryl hydrocarbon receptor (AhR). The activation of cyclooxygenase-2 (COX-2) expression by AhR ligands contributes to inflammation and oxidative stress. We therefore hypothesized that IAA participates in inflammation and oxidative stress in chronic kidney disease patients by inducing COX-2 expression via AhR activation.

Methods: In cultured human umbilical vein endothelial cells, we studied the effect of IAA on COX-2 induction and activity and on COX-2-dependent reactive oxygen species (ROS) production. We then analyzed the signaling pathways related to AhR, involved in COX-2 up-regulation. We finally measured IAA, malondialdehyde, and C-reactive protein serum levels in 68 chronic kidney disease patients.

Results: In endothelial cells, IAA increased COX-2 mRNA and protein expression via an AhR-responsive pathway. Further, IAA increased COX-2 activity, reflected by prostaglandin E2 and ROS production. The participation of IAA in oxidative stress and inflammation was corroborated in chronic kidney disease patients by the association between IAA and the markers of oxidative stress and inflammation, respectively malondialdehyde and C-reactive protein.

Conclusions: In conclusion, the uremic solute IAA increases endothelial COX-2 expression via an AhR-mediated pathway, and enhances prostaglandin E2 and ROS production. IAA, via AhR activation and COX-2 up-regulation, could contribute to inflammation and oxidative stress in chronic kidney disease.
absence of cycloheximide, an inhibitor of protein synthesis; 3) C4-H4-P4 incorporation into UCP2, in macrophages treated with STC1 or vehicle; and 4) residual UCP2 C4-H4-P4 in STC1 or vehicle-treated macrophages in the presence of cycloheximide.

**Results:** Induction of UCP2 mRNA by STC1 occurs late (3-fold at 6 h and 4-fold at 24 h). Treatment with actiomycin D abolishes UCP2 mRNA levels within 6 h (3h half-life), and STC1 does not affect UCP2 mRNA stability. STC1 fails to induce UCP2 protein in the absence of cycloheximide, suggesting that UCP2 induction by STC1 is dependent on protein synthesis. Indeed, STC1 induces C4-H4-P4 incorporation into UCP2 10-fold within 3 h; but, does not affect its degradation.

**Conclusions:** Early induction of UCP2 protein by STC1 occurs without significant changes in UCP2 mRNA level, consistent with translational control. STC1 induces UCP2 protein synthesis 10-fold; however, since protein degradation is high, STC1-mediated increase in UCP2 protein abundance is only 2-3-fold. This regulatory scheme allows immediate adjustment of UCP2/ superoxide and the responses of macrophages to antiinflammatory or cytokines.

**Funding:** NIDDK Support

### SA-POI131

**Effect of Statin Treatment on Kidney Function and Metabolic Effects in the AKITA Mouse Model of Prediabetes**

**Background:** Donaghy et al. (2007, PLoS One) reported that rosuvastatin has anti-oxidative effects through increased expression of Nrf2-regulated genes in HUVEC and primary rat podocytes. These effects were characterized by anti-apoptotic and antioxidant effects, including increased expression of HO-1, SOD1, and GST. However, the anti-oxidative effects of rosuvastatin in vivo are not well characterized. We hypothesized that rosuvastatin has anti-oxidative effects in the AKITA mouse model of prediabetes.

**Methods:** AKITA diabetic mice were treated with rosvastatin (P=0.01), and this increase was significantly abrogated in DM rats by BIO treatment (P<0.05). The protein expression of Ucp2 and Gsk-3β was significantly higher in DM glomeruli and HG-stimulated podocytes expressed significantly, indicating that Ucp2 activity was significantly increased in podocytes under diabetic conditions. Western blot analysis revealed that the protein expression of Bax and active fragments of caspase-3 were significantly increased, whereas phospho-Akt, b-catenin, and Bcl-2 protein expression were significantly decreased in DM glomeruli and HG-stimulated podocytes. Apoptosis determined by TUNEL assay and Hoechst 33342 staining were also significantly increased in podocytes under diabetic conditions. The changes in the expression of apoptosis-related molecules and the increase in the number of apoptotic cells in DM glomeruli as well as in HG-stimulated podocytes were significantly ameliorated by BIO.

**Conclusions:** These findings suggest that enhanced Gsk-3β activity within podocytes under diabetic conditions is associated with podocyte loss in diabetic nephropathy.

### SA-POI132

**Beneficial Effects of Insulin in Subtotal Nephrectomy May Involve Atypical AMPK Activation**

**Background:** Chronic kidney disease (CKD) is a progressive disorder impacting kidney function and metabolic efficiency, eventually leading to renal lesions and fibrosis. We have previously shown that 7 AMP-activated protein kinase (AMPK) levels are low stimulated kidney cell ROS generation and DNA damage and compromised DNA repair; however, tempol, losartan (Ang II blocker) and EB1089 provided protection against DNA damage and effects of glucose in vitro studies. HD high down regulated podocyte VDR expression and enhanced renin angiotensin (RAS) activation. Both glucose and HIV

**Funding:** NIDDK Support

### SA-POI133

**Rosuvastatin Activates Transcription Factor Nrf2 through p21**

**Background:** Glycogen synthase kinase-3 (GSK-3) expression is inversely correlated with the pathogenesis of various diseases. In this study, we examined the changes in Gsk-3β activity in podocytes under diabetic conditions and elucidated the functional role of Gsk-3β in podocyte apoptosis, a characteristic finding in diabetic nephropathy.

**Methods:** In vivo, 32 rats were injected with either dinitro (n=16, C), or with streptozotocin intraperitoneally (n=16, DM). Kidney cell ROS generation and oxidative DNA damage by immunolabeling (dihydroethidum and 8-OHdG). In cultured podocytes, ROS generation and DNA damage were increased in DM glomeruli and HG-stimulated podocytes. Apoptosis determined by TUNEL assay and Hoechst 33342 staining were also significantly increased in podocytes under diabetic conditions. The changes in the expression of apoptosis-related molecules and the increase in the number of apoptotic cells in DM glomeruli as well as in HG-stimulated podocytes were significantly ameliorated by BIO.

**Conclusions:** These findings suggest that enhanced Gsk-3β activity within podocytes under diabetic conditions is associated with podocyte loss in diabetic nephropathy.
in the subrenal nephrectomy (STN) model of CKD and that reestablishing AMPK activity in STN animals via agonist administration normalized kidney function (GFR), metabolic efficiency (oxygen consumption, sodium transport, O2/72mole Na+/mole H2O and sodium flux), improved kidney lesions and fibrosis apparent at 30 days STN. Insulin administration has beneficial effects in CKD, yet would be expected to further decrease activity of the energy sensor AMPK. To investigate this conundrum we evaluated AMPK activity in STN animals administered insulin.

Methods: In order to establish the effects of acute insulin treatment (Aspart, 500mU/kg bolus, followed by iv 5mU/kg/min) in rats subject to STN for 7 days. Protein expressions were evaluated by Northern blotting. All values are relative densitometry units/SEM normalized against alpha-Tubulin.

Results: AMPK activity (p-AMPK T172) total AMPK) decreases from Con (1.26±0.21) to STN (0.94±0.02), yet surprisingly increases markedly with STN+Insulin (1.08±0.25). Evaluating mTOR components reveals mTORC1 activity (via p70S6K), which inhibits insulin sensitivity, expectedly increases from Con (38±3.18) to STN (60±3±017), but decreases when administered STN+Insulin (43±6.8). However, although alpha-SATIK does not increase from Con (3048±430) to STN (3430±116), it does increase with STN+Insulin (4692±177), suggesting a total mTOR increase via mTORC2 in STN+Insulin, which would promote insulin sensitivity. Further, PPAR-g is markedly increased in STN+Insulin (7978±831) animals beyond that of Con (1253±316) or STN (1347±274 animals).

Conclusions: Thus the unconventional induction of a AMPK activity by insulin rather than the prototypical mTORC1 insulin resistance response holds the potential of increasing the renoprotective axis as well as mTORC2 insulin sensitivity axis in the STN model of CKD. Following this line of preliminary data requires further investigation of the components involved.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO133

Regulation of Macrophage Phenotype by M-CSF: GM-CSF Ratio and Its Implication in Diabetic Nephropathy
Satyesh K. Sinha, 1 Susanne B. Nicholas.1, 2
Penn State College of Medicine, Hershey, PA, USA.

Background: Recent studies from our lab have shown that an imbalance in the ratio of the two important isotypes of colony-stimulating factors (CSFs), M-CSF and GM-CSF, may play a role in the development of diabetic nephropathy.

Methods: We have reported that Cell Division Autoantigen 1 (CDA1) plays an important role in DN, which can be potentially retarded by pharmacologically targeting a Novel Enhancer of TGF-β1 or TGF-β2. To investigate the possible role of CDA1, the ApoE KO mice, renal gene expression of TGF-b1, TGF-b2, CTGF, MMP2, VCAN1, collagen III and fibronectin were increased by >2-6 fold in the diabetic group treated with vehicle and this effect of diabetes was blocked by CHA-061. CHA-061 also reduced gene expression of TGF-b type 1 receptor. TGF-α as well as attenuated diabetes associated increases in gene expression of collagens I, IV, MCP1 and ICAM1.

Conclusions: These results demonstrate that pharmacological targeting of CDA1 reduces TGF-b signalling and is potentially effective to retard DN.

Funding: Government Support - Non-U.S.

SA-PO135

RNA Conformational Change Is the Early Marker of Ischemic Tissue Injury
Eikan Mishima, Daisuke Saigusa, Yoichi Takeuchi, Yasutoshi Akiyama, Takehiro Suzuki, Sadayoshi Ito, Yoshihisa Tomioka, Takaaki Abe. Tokohu Univ, Sendai, Japan.

Background: Tissue damage by ischemia and oxidative stress is a major factor in the progression of renal failure. Recently, it has been reported that transfer RNA (tRNA) metabolism is important in response to protect cells. However, it is unclear under these conditions is still unclear.

Methods: We examined the tRNA behavior using a newly generated antibody against tRNA-specific modified nucleoside, 1-methyladenosine (m1A). We also established a measuring system for m1A by LC-MS/MS and for tRNA derivatives by ELISA

Results: Oxidative stress directly generated the conformational change of tRNA structure detected by in vitro immunoprecipitation assay. The conformation change of tRNA was also confirmed in ischemia-reperfusion damaged tissues by IHC. Such conformation change is correlated at earlier phase than DNA damage detected by TUNEL or 8OHdG staining. By ELISA and LC-MS/MS, we next measured the tRNA derivatives in blood under tissue damage conditions. The circulating tRNA derivatives were increased in various animal tissue damage models (renal ischemia-reperfusion, cisplatin nephropathy, and radiation injury). In addition, we also observed increased tissue expression in ischemic renal transplant surgery which renal ischemia is inevitable, the circulating tRNA derivatives were increased after reperfusion procedure. The onset of the increase was earlier than that of urinary KIM-1. Furthermore, we examined serum m1A level in general population (n=103) and their relationship with proteinuria. As a result, the serum level of tRNA metabolites was correlated with mortality suggesting the continuous stress damage in the high level group. In CKD patients (n=29), high level of serum m1A was decreased by statin treatment.

Conclusions: These data suggested that i) under ischemia and other tissue damages, the conformational change of tRNA was induced, ii) following tRNA derivatives release to the blood occurred, iii) resultant circulating levels are correlate with cell damage and mortality. Thus, detection of intracellular tRNA condition and the measurement of circulating tRNA derivatives is important to detect early renal and tissue damages and for intervention.

Funding: Government Support - Non-U.S.

SA-PO136

TGF-β1 and TGF-β2 Synergistically Mediate the Glomerular Endothelial to Mesenchymal Transition Induced by High Glucose through ROCK-1/II, Akt and PI3K Pathways
Eicen Li, Hong Li, Ruilin Jing, Li Guo, Qi Jiang, Zong, Tan-qi Lou. Nephrology, Dept of Medicine, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.

Background: Our previous study found that EndMT occurs in glomeruli of DKD patients. However, the relevance of this change and the mechanism leading to this change remain unclear. In this study, we assessed the co-relationship between permeability of glomerular endothelial cells and EndMT. Additionally, we explored the signaling pathway involved in high glucose induced glomerular EndMT in vitro.

Methods: Rat Glomerular Endothelial Cells (GEnCs), which pre-treated with or without TGF-β1 or TGF-β2 was added into the medium in advanced, respectively. GenC permeability was assessed by TEER. Real-time PCR was used to evaluate the expression of TGF-β1 and TGF-β2, while α-SMA, CD31 and phosphorylation of MYPT1 were determined by western blotting.

Results: High glucose caused EndMT which was associated with increased permeability in cultured GEnCs, which was evidenced by the down-regulation of CD31 and up-regulation of α-SMA. Simultaneously, high glucose stimulated the expression of both TGF-β1 and TGF-β2 that were associated with a significant increase in phosphorylation of MYPT1, reflecting an activation of ROCK. Pre-treatments of LY364947 or Y27632 improved GEnCs permeability and prevented the changes of CD31 and α-SMA stimulated by high glucose; moreover, LY364947 pretreatment blocked the phosphorylation of MYPT1 caused by high glucose. Notably, pre-incubating with antibodies against TGF-β1 or TGF-β2 attenuated the influence of high glucose on α-SMA and CD31, as well as the phosphorylation of MYPT1.

Conclusions: Our study demonstrates that high glucose promotes glomerular EndMT which contribute to increased GEnCs permeability. TGF-β1 and TGF-β2 mediated this response synergistically via ROCK activation.

Funding: Supported by National natural science foundation of China(81170678) and the Fundamental Research Funds for the Central Universities.

Funding: Government Support - Non-U.S.
SA-PO137
Tempol Attenuates Renal Fibrosis in Mice with Unilateral Ureteral Obstruction: The Role of PI3K–Akt–FoxO3a Signaling

Background: Oxidative stress contributes to the pathogenesis of chronic kidney disease. Phosphatidylinoisitol 3-kinase (PI3K), Akt, and Forkhead box O (FoxO) transcription factors control oxidative stress. This study investigated whether temporal, anoxia, and hypoxia on PI3K, Akt, and FoxO signaling against renal injury by using Tempol.

Methods: Mice received unilateral ureteral obstruction (UUO) surgery with or without administration of tempol. We evaluated renal damage and expression of PI3K, Akt, FoxO3a and their target molecules, manganese superoxide dismutase (MnSOD), catalase, Bcl-2, and Bcl-2 in the obstructed kidneys on days 3 and 7.

Results: Collagen deposition and F4/80 macrophage infiltration were significantly lower in tempol-treated mice compared with controls on day 7. The expression of PI3K, phosphorylated Akt, and phosphorylated FoxO3a decreased markedly in tempol-treated mice on days 3 and 7. Tempol increased the expression of MnSOD and catalase on days 3 and 7, and decreased the production of hydrogen peroxide and lipid peroxidation. Significantly less apoptosis, a lower ratio of Bax to Bcl-2 expression, and fewer apoptotic cells in TUNEL staining, was observed in tempol-treated mice compared with controls.

Conclusions: In conclusion, tempol attenuates oxidative stress, inflammation, and fibrosis in the kidneys of mice with UUO, and the modulation of PI3K–Akt–FoxO3a signaling may be involved.

Funding: Government Support - Non-U.S.

SA-PO138
Ethanol Causes Oxidative Stress in Podocytes by Inducing Cytochrome P450 2E1 (CYP2E1)
Ellen T. McCarthy1, Jianping Zhou,2 Tarak Srivastava,1 Ram Sharma,1 Virginia J. Savín,2,3 Mukit Sharma,2,3 Kidney Institute, KUMC, Kansas City, KS,1 Research Service, KC VA Medical Center, Kansas City, MO,1 Nephrology, CHM, UMKC, Kansas City, MO.

Background: Excessive ethanol (EtOH) consumption leads to hypertension while low amounts have beneficial cardiovascular effects. We have shown that low concentrations of EtOH (2μM) increase podocyte expression of CYP isoforms, such as CYP4a12α, that synthesize 20-hydroxyicosatetraenoic acid (20-HETE) and that 20-HETE protects the filtration barrier. High concentrations (10-20 μM) derange the podocyte actin cytoskeleton. EtOH is metabolized by cell-specific cytosolic alcohol dehydrogenase (ADH) and microsomal CYP2E1. Metabolism of EtOH by CYP2E1 produces superoxide. The metabolic consequences of EtOH in podocytes are unknown.

Methods: We examined the effect of EtOH (20 μM) on the expression of ADH and CYP2E1 in immortalized murine podocytes. These concentrations correspond to blood alcohol levels seen in humans. We measured expression of ADH and CYP2E1 using qRT-PCR and Western blotting and examined superoxide generation using the fluorescent probe hydroethidine (HE). We tested the protective effect of 20-HETE (100 nM) in some experiments.

Results: ADH gene and protein expression were detected in all conditions. ADH gene was upregulated by 2 (P<0.001) but not by 10 or 20 μM EtOH. CYP2E1 expression was undetectable in untreated podocytes. EtOH (10 or 20 μM) induced robust expression of CYP2E1 (P<0.001) and increased superoxide generation as indicated by HE fluorescence (P<0.001). Addition of 20-HETE prevented the increase in superoxide (P<0.001).

Conclusions: Low concentrations of EtOH upregulate both CYP4a12α and ADH expression. In contrast, higher concentrations cause oxidative stress through induction of CYP2E1, which also upregulates expression of ADH. This complex pattern of enzyme expression in podocytes is consistent with protection by low-level EtOH consumption via enhanced 20-HETE production. Protection from oxidative injury may be lost during excessive EtOH intake. Further studies are needed to determine the contribution of alcohol consumption to renal disease and progression in humans.

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

SA-PO139
Integrin Linked Kinase (ILK) Regulates AQP2 Independently of cAMP Axis. A New Nephrogenic Diabetes Insipidus Animal Model Jose Luis Cano-pezalver1, Mercedes Grieria,1 Paloma Martin-sánchez1, Ines Mora,2 DlEGO Rodriguez-Puyol,2 Sergio De Frutos Garcia,1 Manuel Rodriguez-Puyol,1 Biologia de Sistemas, Unidad Fisiologia, Universidad de Alcala, Alcala de Henares, Madrid, Spain,1 Fundacion de Investigacion Biomédica, Hospital Universitario Prínipe de Asturias, Alcala de Henares, Madrid, Spain.

Background: AQP2 modifies the tubular water reabsorption through transcriptional and posttranslational content as well as its quick cytoplasm-to-apical membrane trafficking. Phosphorylations by kinases are needed in both short and long-term regulations, including the canonical cAMP-dependent pathway: Vasopressin (AVP) binds to its tubular receptor V2R that activates Adenylate Cyclase (AC), which in turn produce CAMP that activates PKA. We are interested in the extracellular matrix messenger ILK (integrin linked kinase) implication that may lead renal functional changes.

Methods: We previously shown (ASN kidney week 2012) basal poluria in transgenic conditional ILK-deleted adult mice (cKO-ILK) compared with controls (WT). Decreased urine osmolality was due to both AQP2 reduced expression and traffic.

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

SA-PO140
Evaluation of Two Rat Chronic Kidney Disease (CKD) Models to Study Efficacy of Alternative Anemia Treatment Anja Verbals1, Felix W. Funk,2 Patrick C. D’Haese,1 Lab of Pathophysiology, Universiteit, Belgium, 2Vifor(Inter) Ltd, St. Gallen, Switzerland.

Background: Next to erythropoietin (EPO), hepcidin (Hep), by limiting iron (Fe) efflux from enterocytes/macrophages, plays a central role in the development of CKD induced anemia. A lack of Hep clearance and the inflammatory status of CKD patients result in increased plasma Hep levels potentiating anemia upon the reduced renal EPO synthesis in these patients. The present study evaluates the potential use of rat CKD models to study efficacy of alternative anemia treatment.

Methods: Remnant kidney (RK) and C57Bl/6J (B6J) (RK) was induced in 12 rats by 5/6 nephrectomy. Adenine induced CKD (AD) was generated in 12 rats at 7 days by feeding 0.5% adenine for 4 weeks. RK and AD rats were followed up for 11 and 8 weeks respectively. For each model a control (Ctrl) group (n=5) was included. Blood/serum (5) parameters were followed-up: hemocrit (Hct), hematocrit (Hct), Hep and EPO. Liver/spleen Fe content was measured.

Results: EPO treatment was started at week 4 in RK and at week 6 in AD. Hct was already significantly lower in RK rats (80.3±17.6% at week 4 and 75.3±9.3% at week 8, p<0.05) compared to Ctrl rats (91.6±7.9% at week 4 and 86.2±8.8% at week 8, p<0.05). In AD rats, Hct was maximal at week 4 (20.5±6.2nM). In AD, Hct levels were significantly lower (4.5±2.1 vs 14.5±6.9µg/ml at week 8) while unchanged remained in RK rats. Liver Fe was significantly increased in AD (86.7±17.5 vs 74.5±12.3 µg/g w.w, p<0.05) and RK rats (20.5±6.2nM). In RK rats, Hct levels were maximal at week 4 (66.3±17.4 vs 14.8±3.7nM, p<0.05) and returned to normal at week 8 (16.32±6.6nM). SEPO levels of AD rats were sign decreased (8,4±2.1 vs 14.5±6.9µg/ml at week 8) while unchanged remained in RK rats. Liver Fe was sign increased in AD (86.7±17.5 vs 74.5±12.3 µg/g w.w) and RK rats (107.9±30.1 vs 64.2±8.3 µg/g w.w). In AD rats spleen Fe levels were sign increased also (1024.6±160.7 vs 334.3±113.5 µg/g w.w).

Conclusions: In conclusion, AD is a suitable model to study efficacy of anemia treatment since the steep decrease in Hct values goes along with reduced SEPO levels, a substantial rise in Shep, and accumulation of Fe in liver and spleen, the latter pointing to deficient Fe incorporation in hemoglobin.

Funding: Pharmaceutical Company Support - Vifor Pharma

SA-PO141
Urinary Procollagen Type III Aminopropyl Peptide Associates with Anemia Independent of eGFR in Male Pre-Dialysis CKD Patients Akira Suzuki,1 Kodo Tomida,1 Tatsuya Shoji,1 Noriyuki Okada,2 Yoshiharu Tsukibakira,2 Terumasa Hayashi,1 Kidney Disease and Hypertension, Osaka General Medical Center, Osaka, Japan; 1Kidney Complications Research, Osaka Univ Graduate School of Medicine, Suita, Japan.

Background: Tubulointerstitial fibrosis is the common final pathway to the end stage kidney disease. The severity of fibrosis assessed by renal biopsy is correlated with eGFR. Erythropoietin (EPO) is produced by the renal interstitial fibroblasts. In chronic kidney injury, sustained inflammation causes the proliferation and transformation of the fibroblasts to myofibroblasts, which leads to the renal fibrosis. Transformed fibroblasts were reported to be no longer able to produce EPO. Recent studies had demonstrated that the urinary procollagen type III aminopropyl peptide (PHIPN) was correlated significantly with the severity of fibrosis. In this study, the hypothesis was tested that the urinary PHIPN may be associated with the severity of renal anemia in pre-dialysis ESA naïve CKD patients.

Methods: Forty one patients (CKD stage 3-5) were recruited at Osaka General Medical Center. The not treated ESA pathway was studied in 8 patients. The following parameters were measured in each patient, such as urine and serum PHIPN, ferritin, Hb, serum and urine creatinine, serum albumin, urinary protein, and CRP. Correlation between Hb and each one of the parameters were cross-sectionally analysed. Patients with iron deficiency, all liver diseases and lung fibrosis were excluded.

Results: The population included 33 male and 8 female. Since female strongly correlated with low Hb level in this population, the analysis was stratified by sex. In female, any analysis couldn’t be done because of the limited number of patients. In male, univariate analysis indicated that Hb level was correlated with urinary PHIPN (R=0.52956, P=0.0015), but not with any other parameters. In multiple regression analysis including eGFR, urinary PHIPN/Cr was significantly and independently associated with Hb level.

Conclusions: These results suggested that renal fibrosis might be more important for anemia than eGFR in male pre-dialysis CKD patients.

Funding: Private Foundation Support
SA-PO142
Diagnostic Accuracy of Placental Growth Factor in Women with Chronic Kidney Disease/Chronic Hyperpertension and Supersimpered Preeclampsia
Kate Brahman,1 Paul Seel,1 Liz Lightstone,2 Hayley Tarfi,1 Josephine Gill,1 Lucilla Poston,1 Lucy C. Chappell.1 1Div of Women’s Health, King’s College London, London, United Kingdom; 2Imperial College Healthcare NHS Trust Renal and Transplant Centre, Imperial College London, London, United Kingdom.

Background: Women with chronic kidney disease (CKD) and chronic hypertension (CHT) are at increased risk of superimposed pre-eclampsia (SPE). Diagnosis of SPE using blood pressure and proteinuria is challenging because both pre-exist or develop in women with CKD or CHT without SPE. Inaccurate diagnosis may result in unnecessary maternal admission and iatrogenic preterm delivery. Placental growth factor (PIGF) is a secondary marker of associated placental dysfunction in pre-eclampsia (PE), with known low plasma concentrations, but its role in diagnosing SPE in women with CKD or CHT has never been explored.

Methods: Women with CKD or CHT, SPE, PE and low risk controls, were recruited from two tertiary antenatal clinics after 20 weeks gestation. Diagnoses of PE or SPE were made according to International Society of the Study of Hypertension in Pregnancy guidelines. Plasma concentrations of PIGF were measured with Alere Triage® assay. Proportions of women with low PIGF (<100pg/ml) were compared.

Results: Samples from 129 women with CKD or CHT (90 CKD/39 CHT, including 18 with SPE), 24 women with PE and 71 healthy controls were analysed. Proportions of women with low PIGF are shown in Table 1.

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>low PIGF (N, %)</th>
<th>≥200pg/ml (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE: No</td>
<td>6 (24%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>PE: Yes</td>
<td>5 (11%)</td>
<td>27 (61%)</td>
</tr>
<tr>
<td>CHT: No</td>
<td>24 (19%)</td>
<td>115 (91%)</td>
</tr>
<tr>
<td>CHT: Yes</td>
<td>1 (10%)</td>
<td>8 (90%)</td>
</tr>
</tbody>
</table>

Low PIGF for diagnosing PE in low risk women had high sensitivity (95.8%) and NPV (97.6%), but low specificity (56.3%) and PPV (42.6%), and for diagnosing SPE had high sensitivity (83.3%), and NPV (96.5%), but lower specificity (70.3%) and PPV (42.6%).

Conclusions: Low PIGF is the first test to have such high sensitivity and negative predictive values for SPE in women with CKD or CHT. This finding has substantial implications for the future antenatal management of these women and their offspring. Funding: Pharmaceutical Company Support - ALERE

SA-PO143
Adiponectin Receptor 1 Expression in End Stage Renal Disease
Maria P. Martinez Cantarin, Bonita E. Falkner. Medicine, Thomas Jefferson Univ Hospital, Philadelphia, PA.

Background: Adiponectin is an anti-atherogenic, anti-inflammatory and anti-diabetic cytokine mainly produced in adipose tissue whose production is increased in End Stage Renal Disease (ESRD). Adiponectin and its receptors have been well established in non-diabetic chronic kidney disease (CKD). The present study aims to investigate the relationship of insulin resistance (IR) and CVD in non-diabetic CKD patients.

Methods: 25 non-diabetes non-dialysis CKD patients (stage 2-5) were enrolled in this cross-sectional observational study. IR index was assessed by the homeostasis model assessment. They were divided into two groups according to IR index: insulin-resistant group (HOME-IR≥2, N=7) and insulin-sensitive group (HOME-IR<2, N=18). SHP and DBP, left atrium diameter (LAD),interventricular septal thickness (IVST), left ventricular diameter (LVD), left ventricular posterior wall thickness (LVPWT),cardiac output (CO), ejection fraction (EF), E/A, carotid index(CI), carotid artery intima-media thickness (CAIM),HCO3-, serum creatinine, cGFR(calculated by CKD-EPI formula),blood-liquids and urine protein were collected. All data was analyzed by software SPSS 13.0.

Results: Serum creatinine, cGFR, blood-liquids and urine protein were not found significantly different between both groups. Correlation analysis showed that IR was not significantly related to SHP or DBP, LAD, IVST, LVD, LVPWT, CO, EF, E/A, CI, CAIM or HCO3-. Nevertheless, SBP and DBP, LAD,IVST, LVD, LVPWT, CO, EF, E/A and CI were not significant different between both groups. However, insulin-resistant group had significantly thicker left carotid artery intima-media than insulin-sensitive group (1.050±0.129 vs 0.745±0.242, P=0.035) as well as significantly less serum HCO3- (18.329±2.888 vs 21.750±3.453, P=0.03).  

Conclusions: This small-sample pilot study indicated IR may have no apparent correlation with cardiac function or cardiac morphological changes in non-diabetic CKD patients. However, those CKD patients with IR had thicker left carotid artery intima-media than insulin-sensitive patients, which suggested atherosclerosis was more severe in those non-diabetic CKD patients with IR.

SA-PO146
Important Factors Considered in Excluding Patients from Referral for Kidney Transplant – A Survey of Nephrologists’ Views
Ankita Tandon, Jeffrey P. Yourshall, Kevin C. Roe, Nasrolah Ghahramani. Dept of Medicine (Nephrology), Penn State College of Medicine - Hershey Medical Center, Hershey, PA.

Background: Provider perceptions about appropriateness of certain patients for kidney transplant (KT) are potentially important contributors to disparities in KT. We examined nephrologists’ perceptions about factors which they consider important in excluding patients from KT referral and analyzed the association between these perceptions and nephrologists’ demographic and practice characteristics.

Methods: Invitations were sent to 617 nephrologists in the eastern US. 822 expressed interest, and 250 were randomly invited to complete a questionnaire about demographics, practice characteristics, and their perceptions of the importance of various reasons a nephrologist might not refer patients for KT. A total of 216 surveys with complete responses were analyzed. Chi-square and stepwise logistic regression were performed.

Results: The three most common reasons regarded by nephrologists as important for excluding patients were “patient’s inadequate social support” (70% of respondents), “limited understanding of the transplant process due to patient’s inadequate education” (56%), and “patient’s age above 65” (53%). In multivariate analysis, physicians with 2 or fewer transplant centers within a 50 mile radius were more likely to report inadequate social support (OR: 3.15; 95% CI:1.56-6.24; p=0.001) and age greater than 65 years (1.88; 95% CI: 1.01 to 3.49; p=0.04) as reasons to exclude patients from KT referral. Considering limited understanding due to patient’s education, as an important reason to exclude patients for KT evaluation was more likely among nephrologists whose practice includes patients, majority of whom, have not completed high school (OR: 3.31; 95% CI: 1.60-6.86; p=0.001).

Funding: None

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

657A
Conclusions: Patient’s social support, understanding and age are the most common reasons regarded by nephrologists as important for excluding patients from KT referral. Practice location and overall characteristics of the patient population are important determinants of provider perceptions about the importance of these reasons.

Funding: NIDDK Support

SA-PO147

Abstract Withdrawn

SA-PO148

Depression Is Associated with Missed Hemodialysis Treatment
Veeda O. Landera, Michael S. Simonson, Sharon D. Aaron, Marcia R. Silver.
1Medicine, Div of Nephrology and Hypertension, Univ Hospitals Case Medical Center, Cleveland, OH; 2Medicine, Div of Nephrology and Hypertension, MetroHealth Medical Center, Cleveland, OH; 3Social Services, Fresenius Medical Center, Cleveland, OH.

Background: Depression is the most common psychological problem encountered in patients with end-stage renal disease (ESRD). Recent studies demonstrated that psychosocial factors are important predictors of patient outcome. Co-occurrence of depression has been shown to be one of the risk factors of poor prognosis in dialysis patients, partly because it is believed that depressed patients are less likely to adhere to their medication regimen and modify their lifestyle appropriately. Because clinical depression is prevalent among patients with ESRD on hemodialysis, we examined the relationship between clinical depression and missed hemodialysis treatments in an outpatient hemodialysis center.

Methods: We conducted a cross-sectional analysis of 71 outpatient adult hemodialysis patients. Inclusion criteria: age > 18 years and able to take written Beck Depression Inventory (BDI) in English. Exclusion criteria: clinical dementia. Patients scored positive for missed dialysis treatments if they had more than two unexcused absences over 12 months.

Results: Participants were 38% female and 45% African American, and average age was 55. The numerical BDI score correlated positively with missed dialysis treatments (r = 0.248, P=0.037). The correlation between BDI score and missed dialysis remained significant after adjusting for age, race and sex in a logistic regression model.

Conclusions: Higher BDI score, suggesting the presence of depression, was associated with missed hemodialysis treatments in this pilot study. Future studies should include larger number of hemodialysis patients and examine other covariates that might contribute to missed hemodialysis treatments. Also, looking into whether effective intervention, Pharmacological and non-pharmacological, would be at value in this hemodialysis population subset to improve hemodialysis attendance.

Funding: Private Foundation Support

SA-PO149

Perceptions Regarding Genetic Testing in Populations at Risk for Nephropathy
1Wake Forest Sch Med; 2Wake Forest.

Background: Genetic testing will become increasingly available over the next decade. It remains important to determine attitudes toward applying test results.

Methods: Relative to European Americans (EA), African Americans (AA) are at increased risk for ESKD and biologically mediated factors contribute. Concepts regarding acceptability of genetic testing for disease variants associated with common illnesses were explored in a standardized questionnaire administered to 130 individuals (64 AA; 66 EA) at risk for ESKD based on a 1st-degree relative with ESKD. In AA and EA, mean±SD age of surveyed relatives was 45.5±12.8 and 50.5±14.4 yrs, resp. (p=0.04); with similar appearance equally receptive to gathering and applying their genetic test results for common illnesses were surveyed. Recent studies demonstrated that psychosocial factors are important predictors of patient outcome. Co-occurrence of depression has been shown to be one of the risk factors of poor prognosis in dialysis patients, partly because it is believed that depressed patients are less likely to adhere to their medication regimen and modify their lifestyle appropriately. Because clinical depression is prevalent among patients with ESRD on hemodialysis, we examined the relationship between clinical depression and missed hemodialysis treatments in an outpatient hemodialysis center.

Methods: We conducted a cross-sectional analysis of 71 outpatient adult hemodialysis patients. Inclusion criteria: age > 18 years and able to take written Beck Depression Inventory (BDI) in English. Exclusion criteria: clinical dementia. Patients scored positive for missed dialysis treatments if they had more than two unexcused absences over 12 months.

Results: Participants were 38% female and 45% African American, and average age was 55. The numerical BDI score correlated positively with missed dialysis treatments (r = 0.248, P=0.037). The correlation between BDI score and missed dialysis remained significant after adjusting for age, race and sex in a logistic regression model.

Conclusions: Higher BDI score, suggesting the presence of depression, was associated with missed hemodialysis treatments in this pilot study. Future studies should include larger number of hemodialysis patients and examine other covariates that might contribute to missed hemodialysis treatments. Also, looking into whether effective intervention, Pharmacological and non-pharmacological, would be at value in this hemodialysis population subset to improve hemodialysis attendance.

Funding: Private Foundation Support

SA-PO150

Dynamic MRI Assessment of Gastrointestinal Motility in Chronically Kidney Disease Patients
Laura E.A. Harrison, Caroline Louise Head, Luca Marciani, Penny Anne Gowland, Chris W. McIntyre,1,4 Dept of Renal Medicine, Royal Derby Hospital, United Kingdom; 2School of Physics and Astronomy, Univ of Nottingham, United Kingdom; 3Nottingham Digestive Diseases Centre, Univ of Nottingham, United Kingdom; 4Div of Medical Sciences and Graduate Entry Medicine, Univ of Nottingham, Derby, United Kingdom.

Background: Gastrointestinal dysfunction is common in chronic kidney disease (CKD) and associated with nutrient and inflammation. We assessed gastric emptying in Peritoneal Dialysis (PD) and CKD patients as well as Healthy volunteers (HV) utilising Magnetic Resonance Imaging (MRI) based techniques.

Methods: Participants underwent serial MRI fasted and after a mixed liquid/solid meal with measurement of gastric volumes, gastric emptying and motility. Gastric half emptying time (T1/2) was calculated. 32 participants (8 PD, 8 CKD, 16 HV) were recruited. Data collection included demographics, bloods and GI symptom questionnaires.

Results: Gastric volumes immediately post meal (T0) were around 340mls in each group but fell more slowly in PD patients compared to HV. Gastric half emptying time was progressively longer with worsening renal function and slowest in patients on PD. Median GE T1/2 in HV was 69 mins [50-76], CKD 72 mins [70-80], PD 107 mins [66-140], p<0.005. Three hours post meal, 25% of PD patients had over 30% of T0 volume remaining, compared to 0% in CKD and HV groups. PD patients had significantly higher scores than HV on the Gastrointestinal Symptoms Rating Scale (p=0.01).

Conclusions: Gastric emptying is delayed with worsening renal failure and more prolonged in patients receiving peritoneal dialysis, suggesting that dialysis has an additional effect to uraemia related gastric dysmotility. Greater understanding of the factors influencing GI dysfunction is required to address the symptom burden and nutritional challenges these patients are subject to.

Funding: Pharmaceutical Company Support - Baxter Healthcare: Research Grant

SA-PO151

Structural, Physical and Functional Characterization of Soluble Ferric Pyrophosphate (SFP), a Novel Iron Compound for Pharmaceutical Applications
Rameshwar Shukla, Bhoopeesh Mishra, Raymond D. Pratt, Ajay Gupta, Rockwell Medical, Illinois Institute of Technology.

Background: Soluble ferric pyrophosphate (SFP) is the first complex iron salt that does not have a carbohydrate shell for parenteral use. Food grade SFP (FCC-SFP) is a poorly-defined preparation of uncertain composition and is not suitable for pharmaceutical applications. RM-SFP is produced under Good Manufacturing Practice (GMP). RM-SFP has an approximate molecular mass of about 1500 Da and is highly soluble in aqueous solutions. These properties allow its infusion via dialysate (Gupta, Kidney Int. 1999). SFP recently completed Phase III trials in CKD-HD patients.

Methods: We synthesized and characterized a RM-SFP, a water-soluble mixed chelate of iron with pyrophosphate (PPI) and citrate (RM-SFP), comprising 7-11% iron, 14-30% citrate and 10-20% PPI (Rockwell Medical Inc., Michigan, US Patent: US 7816404 B2). Because of the amorphous nature of the compound, structural characterization was carried out using Fe K edge X-ray Absorption Near Edge Structure (XANES) and Extended X-Ray Absorption Fine Structure (EXAFS) Spectroscopy to ascertain differences in the coordination environment of Fe in FCC-SFP vs RM-SFP.

Results: Linear combination fitting of Fe XANES data showed that iron is in the ferric (Fe3+) state and does not complex with sulfate in FCC-SFP or RM-SFP. EXAFS analysis demonstrated that Fe complexation with O in the first coordination sphere (2.02 Å) is similar in both of these molecules. However, significant differences are observed in the coordination environment of Fe with O (3.22 Å) and Fe with P (2.98 Å) binding in the second coordination sphere of Fe in FCC-SFP compared to RM-SFP. With RM-SFP, significantly faster iron transfer to apotransferrin was observed in vitro compared to FCC-SFP.

Conclusions: RM-SFP is significantly more soluble than FCC-SFP. In contrast to IV non-carbohydrate iron complexes, SFP’s fast binding kinetics allows Fe3+ to bind to apotransferrin (in the blood) for direct transport to the erythron, thereby avoiding reticulo-
endothelial processing and storage. RM-SFP is a unique iron compound and a promising new means of providing iron to CKD-HD patients.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

SA-PO154
Subclinical Cardiovascular Disease Is Associated with High Glomerular Filtration Rate in the Non-Diabetic General Population
Bjorn Odvar Erikson,1,2 Kjell Arne Arntzen,1,2 Marit Herder,1 Ulla Dorte Mathisen,2 Toralf Melsom,2 Marit D. Solbu,2 Maja-lisa Lachen.1,2 1Univ of Tromsø, Norway; 2Univ of North Norway, Norway.

Background: Reduced GFR in chronic kidney disease is a risk factor for cardiovascular disease. However, evidence indicates that high normal GFR in apparently healthy persons may also be a cardiovascular risk factor. At present, this issue remains unresolved due to lack of prospective studies and of longitudinal studies on cardiovascular disease with precise GFR measurements. Previous longitudinal studies all used estimates of GFR based on creatinine or cystatin C, which are inaccurate at high levels. Therefore, we performed a cross-sectional study to assess the relationship between high GFR measured as iohexol-clearance and subclinical signs of cardiovascular disease.

Methods: GFR was measured in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6), which consists of a representative sample of middle-aged persons from the general population without prevalent cardiovascular disease. A total of 1521 persons without chronic kidney disease, diabetes, or micro- or macroalbuminuria were investigated with carotid ultrasonography and electrocardiography.

Results: GFR in the highest quartile (>101 ml/min/1.73 m2) was associated with an increased odds ratio of having total carotid plaque area greater than the median of non-zero values (odds ratio 1.56, 95% confidence interval 1.20-2.39) or electrocardiographic signs of left ventricular hypertrophy (odds ratio 1.62, 95% confidence interval 1.10-2.38) compared to the lowest quartile. The analyses were adjusted for cardiovascular risk factors, urinary albumin excretion and fasting serum glucose.

Conclusions: High GFR is associated with carotid atherosclerosis and left ventricular hypertrophy in the general middle-aged population and should be investigated as a possible risk factor for manifest cardiovascular disease in longitudinal studies.

Funding: Government Support - Non-U.S.

SA-PO155
Effects of Low Sodium Intake on the Anti-Proteinuric Efficacy of Olmesartan in Hypertensive Patients with Albuminuria Chun Sook Lim,1 Jin Ho Hwang,2 Ho Jun Chin,3 Sejoong Kim,4 Buon Soon Choi.1 1Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Republic of Korea; 2Dept of Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Kyungki-Do, Republic of Korea; 3Dept of Internal Medicine, Seoul St. Mary’s Hospital, Seoul, Republic of Korea.

Background: Blockade of the renin angiotensin aldosterone system (RAAS) reduces albumin excretion rate. The antiproteinuric effect of RAAS blockade can be magnified by dietary salt restriction. We tried to determine the effect of low salt diet in non-diabetic hypertensive patients with albuminuria on blood pressure and urine protein excretion.

Methods: This study is open label randomized controlled trial. During a run-in period of eight weeks, patients received Olmesartan. And then, patients were divided into two groups. One group was treated for another eight weeks with Olmesartan plus conventional low salt diet (LSD) education and the other group was treated for eight weeks with Olmesartan plus weekly intensive education on LSD. A total of 270 adult recipients were enrolled, and we performed interim analysis with 195 patients.

Results: During a run-in period, daily urinary albumin excretion was significantly decreased by taking Olmesartan for eight weeks (from 928.9 ± (g/day), to 508.6 ± 678.5 mg/day, P<0.001). Recipients with intensive LSD education showed more decreased urinary albumin excretion compared to control group (for Δproteinuria, 146.8 ± vs. -8.3 mg/day, P=0.028). The rate of more than 25% reduction in proteinuria was higher in the recipients with LSD education (61.9% vs. 36.7%, P=0.003). Urinary sodium excretion for 24-hr was decreased 26.0 mEq/day in the intensive education group. With more reduction in 24-hr sodium urinary excretion, there were tendency of more decrease in systolic BP and urinary albumin excretion (for ΔsBP, 10.1 ± vs. 8.5 mmHg, P=0.05; for Δproteinuria, 221.6 ± vs. -20.1 mEq/day, P=0.001).

Conclusions: The reduction in salt intake reduced urine protein excretion and systolic BP in RAAS blockade treated hypertensives. Weekly intensive education on LSD would be a suitable method for clinical practice.

Funding: Pharmaceutical Company Support - Daiichi Sankyo Company

SA-PO156
Urinary Sodium and Kidney Failure in Chronic Kidney Disease Li Fan,1 Hocine Tighiouart,1 Andrew S. Levey,1 Gerald J. Beck,2 Mark J. Sarnak.1 Tufts Medical Center; 2Cleveland Clinic.

Background: Current guidelines recommend less than 2 grams per day sodium intake in individuals with chronic kidney disease (CKD), but there are few data relating sodium intake to long-term outcomes in this population.

Methods: 840 patients with CKD enrolled in the Modification of Diet in Renal Disease (MDRD) Study were used to evaluate the association of mean baseline 24-hr urinary sodium excretion (as a proxy for sodium intake) with kidney failure (defined as need for dialysis or transplantation) using multivariable Cox proportional hazards models.

Results: Mean age was 52 ± 12 years, 60% were men and 85% white. Median proteinuria was 0.32 (IQR, 0.07-1.51) g/day and mean 24-hr urinary sodium excretion 3.46 ± 1.13 g/day. 671 participants developed kidney failure during a median follow-up of 6 (range, 0.25 -18.61) years. A two slope model with a cut-off urine sodium of 3 g/day best
fit the data. In those with urine sodium ≥ 3 g/day there was no association between urine sodium and kidney failure in multivariable models. In those with urine sodium < 3 g/day higher urine sodium was associated with increased risk of kidney failure in those with proteinuria <1 g/day [HR 1.72 (95% CI, 1.31-2.24) per 1 g/day urine sodium higher], and lower risk of kidney failure in those with proteinuria ≥1 g/day [HR 0.61 (95% CI, 0.42-0.89) per 1 g/day urine sodium higher](p < 0.001 for interaction). Results were similar using time-dependent values for urine sodium.

Conclusions: The association of sodium intake with kidney failure depends on the absolute level consumed, as well as the level of proteinuria. These results need to be verified in additional studies and the mechanism explaining them explored.

SA-PO158
Hyponatremia Is Associated with All-Cause Mortality in Chronic Kidney Disease
Diana Chiu, Darren Green, James Ritchie, Smeeta Sinha, Philip A. Kalra. Salford Vascular Research Group, Univ of Manchester, MAHSC, Manchester, United Kingdom.

Background: Hyponatremia is one of the commonest electrolyte abnormalities encountered in hospitalized patients. Few studies have investigated the association between hyponatremia and all-cause mortality in Chronic Kidney Disease (CKD).

Methods: A cross-sectional analysis of data from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS), a prospective observational study of outcome in patients with all-cause CKD stages 3-5, managed in secondary care, was carried out. Hyponatremia was defined as baseline serum sodium<135mmol/l. Predictors of all-cause mortality were selected from forward stepwise cox regression (including potential confounders: age, gender, smoking status, systolic and diastolic blood pressure, history of heart failure, previous myocardial infarction, diuretic use, renin angiotensin blocker use, eGFR, albumin, hemoglobin).

Results: From 2093 patients (mean eGFR 33±16 ml/min/1.73m²), there were 1311 (63%) men, 660 (32%) diabetics, 346 (17%) had a history of heart failure, and 1002 (47.9%) had hypertension. Mean eGFR was 33±16 ml/min/1.73 m². Predictors of all-cause mortality were selected from forward stepwise cox regression (including potential confounders: age, gender, smoking status, systolic and diastolic blood pressure, history of heart failure, previous myocardial infarction, diuretic use, renin angiotensin blocker use, eGFR, albumin, hemoglobin).

Conclusions: There is an association between hyponatremia with all-cause mortality in CKD. It is uncertain whether this is a reflection of the adverse effects of hyponatremia or it is a surrogate marker of existing comorbidities. Further studies are needed to elucidate the cause.

SA-PO159
Association of Food Insecurity and End Stage Renal Disease (ESRD) among a National Cohort of Low-Income Adults with Chronic Kidney Disease (CKD)
Tanushree Banerjee, Donald E. Wesson, 1Sai Hussirh Dharmarajan, 2Rajiv Saran, 3Sharon Saydah, 4Nilka Rios Burrows, 5Deidra C. Crews, 2Neil R. Powe. 1UCSF; 2UM; 3Texas A&M College of Medicine; 4UM; 5CDC.

Background: Poor access to food among low income adults has been recognized as a risk factor for CKD, but there is little data on the impact of food insecurity on development of ESRD. We hypothesized that food insecurity would be independently associated with developing ESRD, that food insecurity would be associated with dietary acid intake and dietary acid intake would modify associations between food insecurity and development of ESRD.

Methods: We conducted a national, longitudinal cohort study of 1,451 adult (>20 years) with CKD enrolled in NHANES 2001-2004 with a household income ≤400% of the federal poverty level (FPL). Food insecurity was defined as ≥3 affirmative responses to (CRISIS), a prospective observational study of outcome in patients with all-cause CKD stages 3-5, managed in secondary care, was carried out. Hyponatremia was defined as baseline serum sodium<135mmol/l. Predictors of all-cause mortality were selected from forward stepwise cox regression (including potential confounders: age, gender, smoking status, systolic and diastolic blood pressure, history of heart failure, previous myocardial infarction, diuretic use, renin angiotensin blocker use, eGFR, albumin, hemoglobin).

Results: From 2093 patients (mean eGFR 33±16 ml/min/1.73m²), there were 1311 (63%) men, 660 (32%) diabetics, 346 (17%) had a history of heart failure, and 1002 (47.9%) had hypertension. Mean eGFR was 33±16 ml/min/1.73 m². Predictors of all-cause mortality were selected from forward stepwise cox regression (including potential confounders: age, gender, smoking status, systolic and diastolic blood pressure, history of heart failure, previous myocardial infarction, diuretic use, renin angiotensin blocker use, eGFR, albumin, hemoglobin).

Conclusions: There is an association between hyponatremia with all-cause mortality in CKD. It is uncertain whether this is a reflection of the adverse effects of hyponatremia or it is a surrogate marker of existing comorbidities. Further studies are needed to elucidate the cause.

SA-PO158
The Effects of Cigarette Smoking in Patients with Chronic Kidney Disease (CKD): Results from the Study of Heart and Renal Protection (SHARP)
Natalie Staplin. On Behalf of the SHARP Collaborative Group, Clinical Trial Service Unit & Epidemiological Studies Unit, Univ of Oxford, United Kingdom.

Background: Smoking tobacco is a major cause of vascular and non-vascular morbidity and mortality in the general population, but its absolute and relative importance in people with CKD, particularly its relevance to renal progression, is uncertain.

Methods: The SHARP study was a randomized trial of LDL cholesterol lowering with ezetimibe/simvastatin in 9270 patients with CKD followed for a median of 4.9 years. The relative risks of particular outcomes associated with baseline smoking status were estimated by Cox regression. Analyses were adjusted for age, sex, ethnicity, country, education and prior disease (vascular disease or diabetes mellitus).

Results: At screening, 1243 patients (13%) were current cigarette smokers (median consumption 10 per day), 3272 (35%) were former smokers and 4755 (51%) were never smokers. Compared with never smokers, vascular event risk was 36% higher among current smokers (adjusted hazard ratio 1.36, 95% CI 1.19-1.54) reflecting a 49% increase in atherosclerotic (1.49, 1.26-1.75) and a 25% increase in non-atherosclerotic (1.25, 1.05-1.49) events. All-cause mortality was 48% higher among current smokers than never smokers (HR 1.48, 95% CI 1.29-1.69), with significant increases seen for both vascular (1.35, 1.07-1.69) and non-vascular (1.59, 1.33-1.90) causes of death. Among 6247 patients not on dialysis at randomization, rates of end-stage renal disease (initiation of dialysis or renal transplantation) were similar among current and never smokers (HR 1.02, 95% CI 0.89-1.16) as were (the statistically more sensitive) estimates of annual rates of change in eGFR (ml/min/1.73m²/year: current smokers -2.10 [SE 0.18], former smokers -2.04 [0.11], never smokers -1.97 [0.09]).

Conclusions: While smoking does not seem to accelerate renal progression in patients with CKD, it increases vascular morbidity and both vascular and non-vascular mortality to a similar proportional extent as is seen in other populations. The absolute excess risks attributable to smoking in this high risk population are therefore large, and the potential benefits of cessation substantial.

Funding: Pharmaceutical Company Support - The SHARP study was funded mainly by Merck/Schering-Plough Pharmaceuticals (North Wales, PA, USA), Government Support - Non-U.S.
on the 18-item questionnaire. Net Acid Excretion (NAE) was determined by the dietary recall questionnaire (24 hrs) using a model by Remer and Manz. Development of ESRD was ascertained over an average of 5.4 years of follow-up via linkage to Medicare ESRD Registry. We used a Fine-Gray competing risk model to estimate hazard ratio (HR) for ESRD associated with food insecurity after adjusting for demographics, socio-economic position, diabetes, hypertension, eGFR, urinal albumin:creatinine ratio, daily caloric intake, and NAE.

Results: 125 (8.6%) adults with CKD were food insecure. Median NAE in the food secure vs food insecure group was 48.4 mEq/day vs 52.8 mEq/day (p<0.04). Food insecure individuals were more likely to be males (41.6%), black (30.4%), have diabetes (41.6%), or have albuminuria (74.4%) compared to their counterparts (p<0.05). Food insecure adults were far more likely to develop ESRD (HR [95% CI]: 5.5 [5.3-5.6]) compared to food secure adults after adjustment for potential confounders. NAE did not appear to be a mediator of the association between food insecurity and ESRD.

Conclusions: Among persons with CKD with a household income ≤400% of the FPL, food insecurity is strongly and independently associated with development of ESRD. Innovative approaches to address food insecurity among CKD patients may be warranted. Funding: Other U.S. Government Support

SA-PO160
The FRIENDS Study: Familiarization of Research Regarding Satisfaction with Life and Ways of Coping amongst Chronic Kidney Disease Patients at a Canadian Center
Sassan Ghazan-Shahi, Karen E. Yeates. Medicine, Queen’s Univ, Kingston, Canada.

Background: The patients with moderate to advanced chronic kidney disease (CKD) are perceived to struggle with high co-morbidity burden related to living with chronic disease. It is the perception that patients may suffer from higher depressive symptoms and poor satisfaction with life and may lack coping mechanisms. The main objectives of this study were to determine the severity of reported depressive symptoms by the subjects and identify the self-perception of satisfaction with life and investigate the existence and frequency of coping strategies.

Methods: A cross-sectional observational study of Stage III-V CKD patients enrolled in the multidisciplinary CKD clinic at Kingston General Hospital, Queen’s University. The measures used in this study evaluate emotional health and coping through the use of following scales. Emotional health: § Well-being Satisfaction with Life Scale (SWLS); § Depression: Beck Depression Index (BDI); Coping: § Strategy identification: Ways of Coping Questionnaire (WOQC). Data collection was via self-administered questionnaires and interviews.

Results: Total of 192 patients fully completed our questionnaires including demographic data and the study measures. 107 patients (55.7%) were male. Mean age ± Standard deviation (Min, Max):70.8±12.5 (28.4, 94.9).

62% of patients described minimal depressive symptoms, and 8% described severe symptoms. 30% were satisfied with their lives while 18% were dissatisfied. In the Ways of Coping, 16% of subjects coped with stressors by distancing themselves and 17% sought social support.

Conclusions: Despite having chronic kidney disease, a large proportion of subjects described relatively good satisfaction with life and lower than expected depressive symptoms. Further adjustment with subject co-morbidity and degree of renal insufficiency may yield more specific correlation with these results.

SA-PO161
Neighborhood Poverty: A Surprisingly Poor Predictor of Lack of Pre-End-Stage Renal Disease Care at U.S. Dialysis Facilities
Laura Plantinga, Min Kim, Margarethe Goetz, Rachel E. Patzer. Emory Univ, Atlanta, GA.

Background: Receipt of nephrology care prior to end-stage renal disease (ESRD) is a strong predictor of improved ESRD outcomes, but 34% of U.S. ESRD patients begin dialysis having never seen a nephrologist. Because pre-ESRD care varies geographically, we examined whether neighborhood poverty was associated with lack of pre-ESRD care at facilities.

Methods: Geospatially linked data from the 2007-2010 Dialysis Facility Report and 2006-2010 American Community Survey were used in hierarchical mixed-effects models to assess the association of neighborhood poverty (≥20% of households in census tracts living below poverty) with facility-level lack of pre-ESRD care (% of patients at a facility with no nephrology care prior to dialysis start), adjusting for facility and neighborhood confounders and allowing for neighborhood and network random effects.

Results: Among 5244 facilities, 1799 (34.3%) were located in a poverty area. With adjustment, facility location within a poverty area was not associated with lack of pre-ESRD care: the absolute increase in percentage of patients at a facility with no pre-ESRD care associated with facility location in a poverty area vs. other neighborhood was only 0.1% (95% CI: -13.2%, 14.7%; P=0.9). When poverty was examined continuously, potential effect modification by Gini index of income inequality was detected, such that the effect of poverty at a lower, but not higher, level of income inequality was modest but statistically significant.

Conclusions: Despite previously reported detrimental effects of neighborhood poverty on health, it appears to have no substantial effect on facility-level lack of pre-ESRD care in this multi-level, ecological study. However, the observed statistical interaction with Gini index suggests that homogeneity of neighborhood poverty as a predictor of lack of pre-ESRD care may warrant further investigation.

Funding: Other NIH Support - NIMHD

SA-PO162
Perceived Racism and Discrimination in Health Care and Medical Mistrust Predict Poorer Health Related Quality of Life in End-Stage Kidney Disease Patients
Michael A. Freeman,1 John R. Pleis,2 Ron Shapiro,1 Larissa Myaskovsky,3 1School of Medicine, Univ of Pittsburgh; 2School of Public Health, Univ of Pittsburgh; 3VA Pittsburgh Healthcare System.

Background: Health-related quality of life (QOL) is a multi-dimensional concept which measures a patient’s subjective experience of their physical, mental, emotional and social well-being. Although many non-medical factors (i.e. financial stress, crime) that influence QOL are beyond the scope of the medical community to address, factors such as experiences of discrimination, racism, and mistrust in health care occur within the medical setting and may be influenced during the course of medical care. Within medicine there has been a renewed focus on a holistic, patient-centered approach to patient care, rather than solely focusing on physiologic markers of health and disease. Given the potential for non-medical factors to affect a patient’s QOL, it is important that practitioners be aware of these effects in order to optimize patient care.

Methods: Our group is prospectively following a large cohort of end-stage kidney disease (ESKD) patients as they proceed through the kidney transplant (KT) evaluation. In this subsample, 590 patients completed 2 structured interviews: 1 at the time of initial transplant evaluation (T1), and another when transplant evaluation is completed (T2). Perceived racism, experiences of race-based discrimination, medical mistrust and trust in physician were assessed as predictors at T1. QOL was assessed as an outcome at T2 using the KDQOL-SF.

Results: Preliminary results indicate that more experiences of discrimination in healthcare, greater medical mistrust and lower trust in one’s physician significantly predict poorer QOL across all 9 subscales of the KDQOL-SF (p<0.05). Greater perceived racism in health care predicted poorer QOL on the symptom, effects on daily life, work status and cognitive function subscales of the KDQOL (p<0.05).

Conclusions: These data indicate the injurious effect that discrimination and mistrust in health care may have on our patients, and indicate areas for patient-, provider-, and system-level focused interventions.

Funding: NIDDK Support
SA-PO163
Clinical usefulness of KDIGO 2012 CKD classification in an HIV population: A multicenter study in Japan
Naoki Yanagisawa,1,2 Minoru Ando,1 Ken Tsuchiya,1 Kosakata Nitta.1 1Dept IV of Internal Medicine, Tokyo Women’s Medical Univ; Tokyo, Japan; 2Div of Infectious Diseases, Dept of Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan.

Background: Chronic kidney disease (CKD) is epidemic among HIV-infected populations, and a determinant of their prognosis. The 2012 KDIGO CKD classification elaborated on how to identify patients at high risk for adverse outcomes. Methods: Distribution of CKD in 1947 HIV-infected subjects (1829 men, 118 women, mean age: 44.9 ± 11.5 years) who regularly visited one of the 5 tertiary hospitals was studied, based on the 2012 KDIGO CKD classification. In addition, prevalence of HIV infection was studied in 176,839 chronic HD patients, according to the questionnaire survey in 1,951 dialysis facilities. Among 1947 pre-diagnosed HIV subjects, 66 were prospectively followed up for 3.5 years to determine incidence of composite outcomes, including all-cause mortality, cardiovascular disease and a decline over 25% from baseline in eGFR. Few risk categories were constructed using the combination of 5 stages of eGFR and 3 grades of albuminuria. The cumulative incidence of the outcomes was analyzed with Kaplan-Meier method, and hazard risk (HR) for the outcome incidence was calculated using multivariable proportional hazards regression, adjusted for some known risk factors.

Results: The frequency of each category was shown in Table. The prevalence of HIV infection was 0.024% in the chronic HD patients. The Kaplan-Meier estimates were significantly increased over time in the risk categories 2 and 3, compared with the risk categories 0 and 1. The HR for risk categories 2 and 3 was 2-fold greater (HR = 2.00; its 95% confidence interval, 1.08 – 3.57; P = 0.0277), as compared to the other.

Conclusions: The new KDIGO classification may facilitate targeting of high-risk CKD in the HIV-infected population as well as in the general population.

Funding: Government Support - Non-U.S.

SA-PO164
Early start: co-morbidities account for the lack of benefit independently of the vascular access type

Background: When and how to initiate Hemodialysis (HD) is still controversial. An early start (ES) on HD seems to show a lack of benefit. “Lead time bias” and co-morbidities have been associated with different outcomes in ES groups. However, it is well accepted the impact that vascular access (VA) type has on patient survival (PS). Our aim was correlate PS with ES vs. late start (LS) on HD, taking into account the VA used.

Methods: Between 1995 and 2012, 322 incidental patients (Pts) initiated HD at CEMIC. eGFR was estimated by the MDRD-EPI equation. Co-morbid conditions were assessed using the Khan index (KI) and Pts were stratified in 3 grades: 0, 1, 2, 3. The mean age: 44.9 ± 11.5 years) who regularly visited one of the 5 tertiary hospitals was studied, based on the 2012 KDIGO CKD classification. Among 1947 pre-diagnosed HIV subjects, 66 were prospectively followed up for 3.5 years to determine incidence of composite outcomes, including all-cause mortality, cardiovascular disease and a decline over 25% from baseline in eGFR. Few risk categories were constructed using the combination of 5 stages of eGFR and 3 grades of albuminuria. The cumulative incidence of the outcomes was analyzed with Kaplan-Meier method, and hazard risk (HR) for the outcome incidence was calculated using multivariable proportional hazards regression, adjusted for some known risk factors.

Results: The frequency of each category was shown in Table. The prevalence of HIV infection was 0.024% in the chronic HD patients. The Kaplan-Meier estimates were significantly increased over time in the risk categories 2 and 3, compared with the risk categories 0 and 1. The HR for risk categories 2 and 3 was 2-fold greater (HR = 2.00; its 95% confidence interval, 1.08 – 3.57; P = 0.0277), as compared to the other.

Conclusions: The new KDIGO classification may facilitate targeting of high-risk CKD in the HIV-infected population as well as in the general population.

Funding: Government Support - Non-U.S.

SA-PO165
Carbamylated Albumin Is Better Correlated with Time Averaged Urea Levels in Chronic Kidney Disease Than in End-Stage Renal Disease
Tammy Hod, David J. Friedman, S. Ananth Karumanchi, Anders H. Berg. BIDMC.

Background: Urea carbamylates proteins and amino acids, and carbamyalted proteins contribute to atherosclerosis. Deficiencies of free amino acid scavengers promote protein carbamylation. Amino acid stores are depleted in HD patients due to amino acid loss into the dialysate, in contrast to HD patients in whom protein stores are preserved even when protein intake is decreased. We previously showed that increased urea and decreased amino acid concentrations were independently correlated with protein carbamylation in ESRD patients. Furthermore, the correlation between urea and carbamyalted albumin (C-Alb) was significantly stronger in CKD patients as opposed to two ESRD cohorts. We hypothesized that serum levels of C-Alb better represent time-averaged urea concentrations in CKD patients compared to ESRD patients, and that carbamylation in CKD patients is less dependent upon serum amino acid levels.

Methods: Serum from 124 subjects with stage 3 or 4 chronic kidney disease were analyzed for carbamyalted albumin (C-Alb) and free amino acids using LC-MS/MS. Blood urea nitrogen concentrations were measured using a clinical assay method. Associations between C-Alb, amino acids, and blood urea nitrogen were analyzed using Spearman correlations and partial correlations adjusted for amino acid levels.

Results: There was a strong correlation between carbamyalted albumin and blood urea nitrogen concentrations among our CKD cohort which was not significantly altered when adjusted for differences in amino acid concentrations (r=0.75, P<0.001). Furthermore, the correlations between carbamyalted albumin and serum amino acids were much weaker in these CKD subjects compared to our previously published analysis of ESRD patients.

Conclusions: Serum %C-Alb represents a clearer index of average urea concentrations in CKD patients compared to ESRD patients and may serve as an indicator of time-averaged urea levels similar to HbA1C in diabetes.

SA-PO166
Has the Prevalence of Hypertension, Diabetes, Obesity Changed Among Adults with Chronic Kidney Disease in the U.S. from 1999 to 2010? Sharan D’Sah,1 Edward Gragge,2 Media F. Pavkov,3 Nilka Rios Burrous,3 Neil R. Powe,2 Rajiv Saran,3 Yi Li,3 Desmond Williams.1 1C/D, 2UCSF, 3UMich.

Background: Hypertension and obesity are risk factors for progression of chronic kidney disease. Whether the prevalence of hypertension, diabetes and obesity has changed in the past decade among adults with CKD in the U.S. is unknown.

Methods: Data from the 1999-2010 National Health and Nutrition Examination Surveys in 4 year periods were analyzed to examine trends among adults with CKD (n = 22,879). CKD was defined as eGFR < 60 ml/min/1.73 m2 or ACR ≥ 30 mg/g. Total diabetes (DM) was defined as self report or undiagnosed (undi) DM (A1c ≥ 6.5%). Hypertension (HTYN) was defined self reported HTYN treatment or undx HTYN (blood pressure ≥ 140/90 mmHg). Overweight was body mass index (BMI) 25 to 30 kg/m2 and obese was a BMI ≥ 30 kg/m2. Estimates age, sex and race/ethnicity adjusted.

Results: Trends and 95% CI in the prevalence of DM, HTYN and obesity among persons with CKD are shown table.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>1999-2002</th>
<th>2003-2006</th>
<th>2007-2010</th>
<th>Adjusted % change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total diabetes</td>
<td>26.1 (22.8, 29.7)</td>
<td>26.6 (23.2, 30.4)</td>
<td>29.6 (27.0, 32.4)</td>
<td>3.5 (-0.8, 7.9)</td>
</tr>
<tr>
<td>Total hypertension</td>
<td>66.2 (62.9, 69.5)</td>
<td>67.9 (64.6, 71.3)</td>
<td>71.9 (69.0, 74.8)</td>
<td>4.5 (1.6, 7.4)</td>
</tr>
<tr>
<td>Obesity</td>
<td>38.7 (33.8, 43.8)</td>
<td>40.1 (36.8, 43.5)</td>
<td>42.6 (39.7, 45.6)</td>
<td>3.9 (-1.8, 9.6)</td>
</tr>
</tbody>
</table>

The prevalence of undx HTYN decreased by 7.8 percentage points in the past decade.

Conclusions: The prevalence of risk factors for CKD progression is high among adults with CKD. While there has been no significant change in the prevalence of DM, HTYN and obesity among adults with CKD in the past decade, the prevalence of undx HTYN decreased.

SA-PO167
Natural experiment with Bosnian immigrants who settled Croatian endemic area – Final epidemiological evidence Ivana Vukovic-Lela, Sandra Karanovic,1 Zivka Dika,1 Jelena Kos,1 Ante Cvetkovic,1 Marica Miletic-medved,3 Karen Edwards,2 Arthur P. Grollman,2 Bojan Jelakovic.1 1Dept of Nephrology, Arterial Hypertension, Dialysis and Transplantation, Univ Hospital Zagreb, Zagreb, Croatia, Croatia; 2Dept of Pharmacological Science, State Univ of New York at Stony Brook, New York, NY; 3Institute for Public Health Slavonski Brod, Slavonski Brod, Croatia; Univ of Washington, Seattle, WA, Croatia.

Background: Endemic nephropathy(EN) represents a form of aristolochic acid nephropathy(AAN) where AA was ingested via contaminated bread. Improvement in agriculture that occurred in EN area 25 years ago significantly decreased contamination of flour with AA. A group of immigrants from Bosnian non-EN area settled Croatian EN area 30 years ago(AA EN). This is considered as period long enough for intake of cumulative toxic AA dose. However, due to mentioned improvement it can be supposed that they were no longer exposed to AA. To test this hypothesis we analyzed proximal tubule damage(PTD),an early hallmark of EN, and renal function in BoEN.

<table>
<thead>
<tr>
<th>AAN prevalence</th>
<th>Final Epidemiological Evidence</th>
<th>2002-2004</th>
<th>2005-2007</th>
<th>2008-2010</th>
<th>Adjusted % change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD: Epidemiology, Outcomes - III</td>
<td>662A</td>
<td>Poster/Saturday</td>
<td>Underline represents presenting author/disclosure.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Method: A cross-sectional study of 42 children and young adults with CKD stage 3-5. CIROC was measured using a computerized neurocognitive battery comprised of 14 tests assessed on accuracy and speed: executive-control (abstraction/mental flexibility, attention, working memory), episodic memory (verbal, facial, spatial), complex cognition (language and nonverbal reasoning, spatial processing), social cognition (emotion identification, emotion empathy, differentiation, age differentiation), and sensorimotor and motor speed. Scores for CKD subjects were transformed to T-scores using the mean and SDs of the control group as comparison.

Conclusions: Symptom burden was high in this US cohort with CKD stage 3-5. Certain symptoms were associated with mortality; others with ESRD. The significantly lower frequency of symptom documentation in clinic charts points to a potential practice improvement opportunity to identify high risk CKD patients.

SA-PO169

Cognitive Performance on a Computerized Neurocognitive Battery in Children and Young Adults with CKD

Divya Ganeshmurthy Moodalbail,1 Nina Laney,2 Ruben C. Gur,3 Allison M. Mott,1 Stephen R. Hooper,3 Jerilyn Radcliffe,1 Abbas F. Jawad,2 Kosha Ruparel,1 Susan L. Furth.1

Background: Deficits in IQ, memory, attention and executive function have been reported in children with CKD, which may contribute to poor adherence to complex medical regimens and high rates of morbidity and mortality.

Methods: Cross sectional observational study of 42 children and young adults with CKD (eGFR ≤ 90 ml/min/1.73m2) and 25 healthy controls, ages 8-25 years. Cognitive performance was assessed using a cognitive neuroscience-based computerized battery comprised of 14 tests scored on Accuracy and Speed: executive-control (abstraction/mental flexibility, attention, working memory), episodic memory (verbal, facial, spatial), complex cognition (language and nonverbal reasoning, spatial processing), social cognition (emotion identification, emotion empathy, differentiation, age differentiation), and sensorimotor and motor speed. Scores for CKD subjects were transformed to T-scores using the mean and SDs of the control group as comparison.

Conclusions: We observed a statistically significant independent relationship of high exposure to particulate matter and albuminuria in this cohort after controlling for pertinent risk factors. This novel finding paves the way for future studies of environmental exposures and inflammation in the pathogenesis of albuminuria.

Funding: Other U.S. Government Support
SA-PO171

Skin Autofluorescence: A Non-Invasive Test to Improve Mortality Risk Prediction in Chronic Kidney Disease Stage 3

Maarten W. Taal,1 Simon D.S. Fraser,2 Paul J. Roderick,2 Scott Harris,2 Natasha J. McIntyre,1 Richard J. Fluck,1 Chris W. McIntyre.1 
1Royal Derby Hospital; 2Univ of Southampton.

Background: Novel markers are needed to improve risk prediction in CKD. One potential candidate is tissue advanced glycation end product (AGE) accumulation, a marker of cumulative metabolic stress that can be assessed non-invasively by measurement of skin autofluorescence (SAF). SAF correlates with higher risk of cardiovascular (CV) events in people with diabetes and people requiring renal replacement therapy. We aimed to investigate SAF as a predictor of all-cause mortality in a large cohort of people with CKD stage 3.

Methods: People with eGFR <60 ml/min/1.73m² on 2 occasions prior to inclusion were recruited from Primary Care. Medical history was obtained and participants underwent clinical assessment as well as urine and serum biochemistry tests. SAF was measured using an AGE Reader® (DiagnOptics, Groningen, The Netherlands). The UK Health and Social Care Information Service provided date and cause of all deaths.

Results: Mean age was 72.9±9 years and baseline eGFR 52.2±10.4ml/min/1.73m². After a median of 3.6 years 179 of 1707 (10.5%) had died. The most common cause of death was CV disease (41%). Kaplan-Meier plots showed a progressive increase in all-cause mortality with higher SAF in tertiles. Cox proportional hazards models identified SAF as an independent predictor of all-cause mortality (Table).

<table>
<thead>
<tr>
<th>SAF tertiles</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.25 (1.06-1.47)</td>
<td>0.007</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1.41 (1.10-1.80)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Conclusions: We have identified SAF as a simple, non-invasive test that predicts of all-cause mortality independent of several other well-established risk factors in a cohort of predominantly older people with CKD stage 3. Further research should focus on how best to incorporate SAF into risk prediction models and on interventions that may reduce AGE accumulation and the associated risk.

Funding: Pharmaceutical Company Support - Roche Products PLC; Sanofi, Private Foundation Support

SA-PO173

Kidney Magnetic Resonance Imaging Reveals Structural Abnormalities That Are Associated with Kidney Function and Risk Factors for Adverse Outcomes in an Older Community-Based Cohort

Todd Woodward,1 Sigurdur Sigurdsson,2 John D. GotaI,1 Alyssa A. Torjesen,1 Lesley Inker,3 Thor Aspelund,1 Gudny Eiriksdottir,2 Vilmundur Gudnason,3 Tamara Harris,3 Lenore J. Launer,4 Andrew S. Levey,5 Gary F. Mitchell,1 
1Cardiovascular Engineering Inc; 2Icelandic Heart Association; 3Tufts Medical Center; 4National Institute on Aging.

Background: Because of the ability of the kidney to autoregulate perfusion and filtration, estimated glomerular filtration rate (eGFR) may underestimate early structural damage such as fibrosis, which contributes to disease progression and may be detectable by kidney imaging.

Methods: We performed dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) with rapid 3D imaging of the kidneys for 5 minutes following injection of 1 mmol of Gd in 514 participants (79±4 years old, 57% women) in the AGES-Reykjavik Study. After tracing the kidney contour (excluding large cysts), custom software automatically segmented kidney tissue into 6 types: cortex, medulla, pelvis, fat, fibrosis or none of the above based on template matching of intensity-time data for each voxel. Fibrosis was defined empirically as voxels with persistently low signal intensity during DCE-MRI. A stepwise multiple regression model that entered age, sex, body surface area (BSA) and eGFR was used to examine relations between fibrosis and potential correlates of adverse outcomes.

Results: Mean total kidney volume was 335±82 ml, eGFR was 67±15 ml/min/1.73m² and fibrosis was 8.2±5.0% of total kidney volume. Higher fibrosis % (model R²=0.49, P<0.001) was related to male sex (P=0.002), higher BSA (P<0.001), lower eGFR (P<0.001), higher cardiac output (P<0.001), higher heart rate (P=0.006), lower hematocrit (P<0.001), lower augmentation index (P=0.023) and treated hypertension (P=0.034).

Conclusions: In a community-based cohort of older people, modest kidney fibrosis detected by DCE-MRI was associated with reduced eGFR and other potential risk factors for adverse outcomes. The association of fibrosis with higher cardiac output and heart rate suggests that sympathetic nervous system activation may be a mechanism by which fibrosis detected by DCE-MRI contributes to chronic kidney disease.

Funding: NIDDK Support, Other NIH Support – NIA; NHLBI, Government Support - Non-U.S.

SA-PO174

The Prognostic Value of a Combined Renal Artery Patency Score in Atherosclerotic Renal Artery Stenosis

James Ritchie, Darren Green, Philip A. Kalra, Salford Royal Hospital.

Background: Atherosclerotic renovascular disease (ARVD) is often diagnosed by non-invasive plane angiography. Most studies define significant disease by the minimum percentage stenosis (MPS) to the most affected artery and consider bilateral disease in sub-group analyses. We hypothesized that considering both renal arteries (Sareth et al, NDT 2000) may better reflect the systemic impact of ARVD.

Methods: We compared MPS with a combined renal artery patency score (CPS). CPS is defined as [200 – combined luminal loss to both kidneys] such that a score of 200 represents bilateral 0% stenosis and a score of 0 represents bilateral 100% stenosis. 615 patients with ARVD diagnosed using CT or MRI angiography were assessed. Separate CPS were adjusted for age, sex, diabetes, blood pressure and proteinuria) were constructed to consider prognostic associations of MPS and CPS in relation to death, cardiovascular event (CVE) and progression to dialysis.

Results: Baseline age was 70±9 years; eGFR 32 [21-45] ml/min/1.73m²; follow-up of 1.8±6 years. As a continuous variable CPS significantly associated with risk for death and CVE, MPS did not. When considering bilateral disease, CPS associated more significantly with risk for death than MPS but CPS associated significantly with risk for CVE. Neither measure associated with risk for dialysis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Death</th>
<th>CVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>0% vs. &gt;70%</td>
<td>0.05 [1.01-1.06]**</td>
<td>0.03 [1.01-1.06]**</td>
</tr>
<tr>
<td>70% vs. &gt;90%</td>
<td>0.04 [0.9-1]</td>
<td>0.03 [0.9-1]</td>
</tr>
<tr>
<td>MPS</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>0% vs. &gt;70%</td>
<td>0.04 [1.01-1.04]**</td>
<td>0.03 [1.01-1.04]**</td>
</tr>
<tr>
<td>70% vs. &gt;90%</td>
<td>0.04 [0.9-1]</td>
<td>0.03 [0.9-1]</td>
</tr>
</tbody>
</table>

Conclusions: Defining patients by CPS and MPS appears to have differing prognostic associations in ARVD. Both methods are limited by their inability to consider cross sectional flow.

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

SA-PO175

Functional Status Associates with All-Cause Mortality in CKD

James Ritchie, Helen Alderson, Darren Green, Diana Chiu, Smeeta Sinha, Philip A. Kalra, Salford Royal Hospital.

Background: Global health assessments allow effects of multiple co-morbidities to be compared between patients. Measurements of functional status act as independent predictors of risk for death in the general and dialysis populations, but have not been assessed in a CKD cohort. One commonly used measure is the Karnofsky performance score (KPS).

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

Underline represents presenting author/disclosure.
Methods: Patients were selected from the Chronic Renal Insufficiency Standards Implementation Study (CRISSIS), a prospective observational study of outcome in patients with CKD 3-5 managed in secondary care. Differences in rate of change in eGFR between groups of KPS were assessed in a mixed effects model.

Results: 1515 patients with a median follow-up of 3.2 [1.5-5.0] years were included in this analysis (584 [39%] KPS 100; 648 [42%] KPS 80; 283 [19%] KPS ≤80). Patients with a higher KPS were younger, had higher eGFR and hemoglobin values and fewer previous macrovascular events. In multivariate analysis (adjusted for age, gender, eGFR, hemoglobin, albumin, diabetes, macrovascular events and diabetes), an association was observed between reductions in KPS at time of recruitment and risk for death. KPS 90 HR 1.2 [0.9-1.5] p<0.1; KPS 80 HR 1.8 [1.4-2.4] p<0.001. In a mixed effects model correlating proteinuria, diabetes, hemoglobin and blood pressure, annual reduction in eGFR in patients with KPS >80 was 3%, and 5% in patients with KPS ≤80 p<0.008.

Conclusions: This analysis suggests in a secondary care CKD cohort, reduced KPS predicts risk for death independently of renal function and vascular co-morbidities. This increased risk is associated with faster rates of eGFR loss in patients with lower KPS scores.

SA-PO176

The Marshfield Epidemiologic Study Area (MESA) Study on Urolithiasis and Their Impact on Chronic Kidney Disease

Radmila Mikan Savcic-kos, Jingbo Huang, Matthew R. D’costa, Hong Liang, Andrew D. Rule, Narayana S. Murali. Dept of Nephrology & Hypertension, Marshfield Clinic, Marshfield, WI; Dept of Nephrology, Mayo Clinic, Marshfield, WI.

Background: Epidemiological evidence exists that stone formers are at increased risk for ESRD. It is unclear if urological intervention impacts prevention or progression of CKD. The MESA database, established in 1991, performs an automated daily review of all computerized databases of the Marshfield Clinic, finds and follows all residents, 90% of whom receive all care at the Marshfield Clinic or its affiliated centers and hospitals in a 24 zip code area that includes 89,291 patients.

Methods: We conducted a retrospective observational cohort study of the patients in MESA between Jan. 1991 and May 2007, where 1340 stone formers were matched by age, gender, and index date with 2712 control subjects. Cox proportional Hazards models adjusted for age, gender, and comorbidities using comorbidity propensity score were performed to evaluate the risk for incident Chronic Kidney Disease (CKD), elevated Serum Creatinine and any-cause mortality. Of the 1340 stone formers, 446 had urological procedures. Stone formers with procedures were compared to those without procedures.

Results: Stone formers with a mean of 9.1 yr of follow-up were at increased risk for elevated Scr (HR [95% CI] = 1.30 [1.16-1.52]) and for CKD (HR [95% CI] = 1.30 [1.03-1.63]). Stone formers had higher rate of any cause mortality (16.2% vs. 25.6% in control group) (HR (95% CI) = 0.49 (0.40-0.59)). Stone formers had lower rate of any cause mortality (16.2% vs. 25.6% in control group) (HR (95% CI) = 0.49 (0.40-0.59)).

Conclusions: Stone formers are at increased risk for elevated Creatinine and for CKD but urological procedures per se (e.g., lithotripsy) do not appear to impact prevalence of CKD.

Funding: Private Foundation Support
Serum Cystatin C, Markers of Chronic Kidney Disease and Retinopathy in Indians without Diabetes


Background: Serum cystatin C, a novel marker for chronic kidney disease (CKD) has been shown to be superior to serum creatinine in predicting the onset of diabetes and its complications including nephropathy. Small clinical studies have shown correlations between cystatin C levels and diabetic retinopathy. However, it not clear if cystatin C is associated with retinopathy in subjects without diabetes.

Methods: We examined 1,757 Indian adults, aged 40-80 years who participated in the Singapore Indian Eye Study (2007-09) and were free of diabetes mellitus. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 determined from serum cystatin C (eGFRcys) and serum creatinine (eGFRcr). Retinopathy was assessed from digital fundus photographs of both eyes. The associations of CKD-eGFRcys (n=200), CKD-eGFRcr, (n=81) and confirmed CKD (eGFRcys <60 and eGFRcr <60, n= 58) with retinopathy were examined using logistic regression models adjusted for potential confounding factors including pre-existing cardiovascular disease and albuminuria.

Results: The prevalence of retinopathy among those with CKD-eGFRcys and CKD-eGFRcr, were 8.5% and 9.9%. In separate models, CKD-eGFRcys showed a significant association with odds ratio (OR, 95% Confidence interval [CI]) of 1.98 (1.06-3.72) while CKD-eGFRcr did not show a significant association with retinopathy 2.22 (0.96-13.13). In models including both markers, compared to optimal kidney function (eGFRcys >60, eGFRcr >60), confirmed CKD was associated with a three-fold odds of having retinopathy (OR [95% CI] = 3.10 [1.20-8.00]).

Conclusions: Further studies are warranted to validate the mechanistic and prognostic significance of these nucleoside markers by simultaneous assessment in plasma and urine from a larger cohort of CKD patients.

Funding: Government Support - Non-U.S.
Results: The mean age was 14.5 years, 50% female, 63% white, 15% black, 13% Mexican-American, 78% active or involuntary tobacco smoke exposure, 35% overweight/obese, 40% diabetic. The median total urinary arsenic concentration and DMA (IQR, interquartile range) was 6.7 μg/L (IQR 3.8 – 12.1) and 3.6 μg/L (IQR 2.1 – 5.5), respectively. Higher quartiles of total arsenic and DMA were associated with higher eGFRs compared to the lowest quartile (Table).

<table>
<thead>
<tr>
<th>Difference in estimated GFR associated with urinary total arsenic and DMA</th>
<th>μg/L</th>
<th>p-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2-4)</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>1.43 (1.7)</td>
<td>1.4 (2.2)</td>
<td></td>
</tr>
<tr>
<td>1 (1.2-3.9)</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>1.2 (2.4-9)</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Higher total urinary arsenic and DMA levels were associated with higher eGFR. This relationship could be explained by glomerular hyperfiltration induced by arsenic. Alternatively, among this population of adolescents with eGFR in the normal range, relatively higher eGFRs may be associated with greater urinary arsenic excretion, with implications for exposure assessment using urinary biomarkers.

Funding: NIDDK Support

SA-PO184

Genetic Polymorphism of Transportsors and Protein in Renal Tubules and Urinary Excretion of Uric Acid in the Japanese General Population: The Takahata Study

Kazuko Suzuki, Kei Kamei, Hiroko Sato, Kosuke Kudo, Kazunobu Ichikawa, Tsuneo Konta, Isao Kubota. Dept of Cardiology, Pulmonology, and Nephrology, Yamagata Univ School of Medicine, Yamagata, Japan.

Background: A cluster of transportsors and proteins expressed in renal tubules play a role in the metabolism of uric acid and the function of these molecules are genetically modified. To examine how the polymorphism of genes related with the metabolism of uric acid affect renal excretion of uric acid, we conducted a cross-sectional study in participants of community-based health checkup.

Methods: We genotyped the SNPs of 7 uric acid-related genes, including 5 transportsors (URAT1, GLUT9, ABCG2, SLC17A3 and SLC22A4) and 2 proteins (UMOD and ALDH2) in 1001 Japanese subjects. Urinary fractional excretion of uric acid (FEUA) was determined from morning spot sample and the association between FEUA and genotypes of these genes were examined.

Results: In total subjects, the analysis of variance (ANOVA) showed that FEUA was significantly different between the genotypes of rs505802 in URAT1, rs4293393 in UMOD and rs671 in ALDH2. Multiple regression analysis with adjustment for potential confounders showed that the genotypes of URAT1 and UMOD were independently associated with FEUA, in addition to male gender, systolic blood pressure, body mass index (BMI), salt intake and estimated GFR. The genotypes of ALDH2 was an independent factor of FEUA, not in total subjects, but in the subjects with renal insufficiency and BMI <25 kg/m².

Conclusions: This study revealed that the genotypes of URAT1, UMOD and ALDH2 were independently associated with FEUA. This indicates that genetic background of renal transportsors and protein might affect renal excretion of uric acid in the Japanese general population.

SA-PO185

Factors Associated with Vasopressin Concentration in a General Population Cohort

Mariane Van Gastel,1 Esther Meijer,1 Lieneke E. Scheven,1 Joachim Struck,1 Stephan J.J. Bakker,2 Ron T. Gansevoort.1

1Dept Nephrology, UMC, Utrecht, Netherlands; 2Nephrology, Tokyo Medico Intl.

Background: Vasopressin (AVP) plays an important role in maintaining volume homeostasis. Recent studies, however, show that AVP also plays a detrimental role in progressions of chronic kidney disease. It is therefore of interest to identify factors that influence AVP concentration, particularly modifiable ones, because intervention on these factors may have beneficial renal effects.

Methods: This study was performed in a large, general population based cohort study (PREVEND Study, Groningen, the Netherlands). Copeptin (pro-AVP) was measured in 6,821 available plasma samples as surrogate for AVP. Associations of patient related factors with copeptin concentration were assessed in uni- and multivariable linear regression analyses.

Results: Median copeptin concentration was 4.70 pmol/L (IQR 2.94-7.62). We found a reverse association between copeptin concentration and eGFR (p<0.001) and a positive association with albuminuria (p<0.001) when analyzed univariable and when adjusted for age and gender. The final stepwise backward model (adjusted for age and gender) revealed that associations with higher copeptin concentration for, in order of the strength of their association, lower fluid intake (p<0.001), higher sodium intake (p<0.001), higher blood pressure (SBP, p<0.001), current smoking (p<0.001), higher alcohol use (p<0.001), higher serum glucose (p<0.001), higher BMI (p<0.001), use of diuretics (p<0.001) and use of antidiabetic (p<0.005). No associations with copeptin concentration were found to be related to protein intake, C-reactive protein and use of non-diuretic antihypertensives.

Conclusions: In a large, biracial, population-based study, higher baseline levels of FGF-23 were associated with an increased risk of FEUA and other risk factors.

Funding: NIDDK Support, Other NIH Support - The Atherosclerosis Risk in Communities Study is carried out as a collaborative drive study supported by National Heart, Lung and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). Additional support was provided by R01HL103706 from the National Heart, Lung and Blood Institute, R01DK089174 from the National Institute of Diabetes and Digestive and Kidney Diseases, and U10DK085689 from the National Institute of Diabetes and Digestive and Kidney Diseases (CKD Biomarkers Consortium). Dr. Rebholz is supported in part by the National Heart, Lung and Blood Institute Cardiovascular Epidemiology training grant T32HL070724.

SA-PO187

Temoporal Trends in Area-Level Poverty and End-Stage Renal Disease (ESRD) Incidence

Bridget Garrity,1 Holly J. Kramer,1 Kavitha Vellanki,1 David J. Leechey,1 David A. Shoham,1 Medicine, Loyola Medical Center; 2Public Health Sciences, Loyola Medical Center.

Background: Poverty is associated with end-stage renal disease (ESRD). The economic downturn in the U.S population which started during years 2007-2008 may have impacted ESRD incidence.

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

Underline represents presenting author/disclosure.

667A
Methods: We examined ESRD incidence using data from the United States Renal Data System (USRDS). Analysis included adults aged ≥18 years who initiated dialysis during years 1995-2010 (n=1,253,541). Data were then linked with the 2000 and 2010 U.S. Census data. Negative-binomial regression was used to analyze temporal trends in the association between ESRD incidence and living in a poverty area defined by ZIP code with ≥20% of the population in that ZIP code living below the US federal poverty line. The numerator for each rate was the number of incident ESRD cases in a given race-ethnicity/sex/age group for a given period for each ZIP code. Analyses were stratified by time period (pre and post recession). Time period 1 was defined as January 1, 1995 - December 31, 2004 (pre-recession). Period 2 was defined as January 1, 2005 - December 31, 2010 (recession and post recession). Rates were calculated per million population per year.

Results: Between January 1, 1995 and December 31, 2010, there were 1,253,541 incident cases of ESRD in the USRDs network. Of these, 697,279 observations were in Period 1 and 556,262 observations were in Period 2. During period 1 (1995-2004), individuals living in a poverty area (17.4% of incident cases) had 24% higher ESRD incidence compared to those not living in a poverty area (95% CI 1.22, 1.25). During period 2 (2005-2010), a greater proportion of incident cases came from a poverty area (23.8%), and the association between poverty area and ESRD incidence was significantly stronger (p<0.001), with an incidence rate ratio of 1.28 (95% CI: 1.27, 1.30).

Conclusions: The influence of area-level poverty on ESRD incidence is increasing over time. Future surveillance and interventions for CKD prevention should target high poverty areas.

Funding: Clinical Revenue Support

SA-PO188

Low Income, Community Poverty and Risk of End Stage Renal Disease

Deidra C. Crews,1 Orlando M. Gutierrez,2 Suzanne E. Judd,2 David G. Warnock,2 William M. McClellan.1 Johns Hopkins Univ; 1Univ of Alabama, Birmingham; 2Emory Univ

Background: The risk of ESRD is increased among poor individuals and in low income communities. We examined the associations of individual and community measures of socioeconomic status with incident ESRD.

Methods: In the population-based Reasons for Geographic and Racial Differences in Stroke (REGARDS) study of 23,314 U.S. adults aged 45 years and older, we used ANOVA and chi-square tests to assess participant differences across geospatially-linked categories of county poverty (outlier poverty, extremely high poverty, very high poverty, high poverty, neither (reference), high affluence and outlier affluence defined using data obtained from the 2000 US Census). We used multivariable Cox proportional hazards models to examine the independent association of annual family income and county poverty measures with incident ESRD. Confounders included age, sex, race and region of residence (stroke belt, stroke buckle, other regions), and education.

Results: Participants residing in impoverished counties were more likely to be female and/or black, and were less likely to have completed high school than those in affluent counties (P<0.05 for all). There were 158 cases of ESRD per 100,000 person-years (10.5 events/100,000 person-years) in Period 1 and 556,262 observations were in Period 2. During period 1 (1995-2004), a greater proportion of incident cases came from a poverty area (23.8%), and the association between poverty area and ESRD incidence was significantly stronger (p<0.001), with an incidence rate ratio of 1.28 (95% CI: 1.27, 1.30).

Conclusions: The influence of area-level poverty on ESRD incidence is increasing over time. Future surveillance and interventions for CKD prevention should target high poverty areas.

Funding: Clinical Revenue Support

SA-PO189

Testing the Validity of a New Quantitative Image Analysis Technique to Measure Severity of Abdominal Aortic Calcification on Lateral Lumbar Radiographs

Mark D. Grant,1 Rachel M. Holden,2 Michael A. Adams.1 Queen’s Univ; Canada; 2Kingston General Hospital, Canada.

Background: Vascular calcification represents a serious complication of chronic kidney disease. Lateral lumbar radiographs images are inexpensive and prominently display abdominal aortic calcification (AAC); however, to date, there remains no fully quantitative method to report severity of calcification. The present study focuses on testing the reliability of a new quantitative image analysis technique compared to the previously validated semi-quantitative technique (AAC-24) when measuring severity of AAC on a lateral lumbar radiograph.

Methods: The quantitative image analysis technique was developed using Image Pro 6.0 and Microsoft Excel software. One hundred and ninety three subjects were selected from the Kingston cohort of the Canadian Multicenter Osteoporosis Study (CaMOS) based on availability of radiographic data. Subjects were sorted according to bone mineral density values and compared within standard deviation groups. Inter-observer reliability was assessed by having two readers analyze the same fifty images for severity of AAC using both the semi-quantitative technique, and the quantitative technique in proposal. Additionally, one reader analyzed the same set of fifty images twice, using both techniques previously mentinoed, to assess inter-observer reliabilities. Two scores were generated for each technique: L2-L4 and L3-L4 Sum.

Results: For the L2-L4 Sum, the intra- and inter-class correlation coefficients for the quantitative and semi-quantitative techniques were 0.975, 0.962 and 0.917, 0.892, respectively (n=35). For the L3-L4 Sum, the intra- and inter-class correlation coefficients for the quantitative and semi-quantitative techniques were 0.982, 0.964 and 0.899, 0.762, respectively (n=50).

Conclusions: The quantitative technique in proposal is a more reliable method to assess severity of AAC than the semi-quantitative technique. In addition to improved reliability, it is also a more informative assessment of AAC in the regions adjacent later L2, L3, and L4 vertebrae. This quantitative method demonstrates promise for future application in clinical and epidemiological studies.

SA-PO190

The Characteristics of Advanced Aged IgA Nephropathy

Yasuiko Oshima, Takahito Moriyama, Chihiro Iwasaki, Kayu Tanaka, Kosaku Nitta. Medicine, Tokyo Women’s Medical Univ; Tokyo, Japan.

Background: The susceptible age for IgA nephropathy (IgAN) is younger. However, IgAN is sometimes developed in the advanced age, and its characteristics remains unknown.

Methods: We selected 600 IgAN patients, observed at least half a year and aged over 20 years old. We divided them into three groups as advanced aged group (AAG, n=31, aged over 50 years old), middle aged group (MAG, n=163, aged between 30 and 49 years old), and young aged group (YAG, n=407, aged between 20 and 39 years old). We analyzed clinical and histological background, renal outcomes, and risk for progression.

Results: In AAG, mean arterial pressure (MAP) was significantly higher than YAG (97.0 ± 8.5 mmHg P<0.0004). In the clinical findings, total protein, serum albumin, and estimated glomerular filtration rate (eGFR) were significantly lower, and blood urea nitrogen, the amount of proteinuria (U-Prot) and N-acetyl-β-D-glucosaminidase (NAG) were significantly higher in AAG than in MAG and YAG [eGFR; 42.3 vs. 59.4 and 79.3 ml/min (P<0.001, P<0.001), U-Prot; 2.04 vs. 0.80 and 0.66 g/day (P=0.021, P=0.003), NAG; 10.6 vs. 5.8 and 4.5 U/l (P=0.003, P=0.004), in AAG vs. MAG and YAG, respectively]. In the histological and clinical findings analyzed by Oxford classification, interstitial fibrosis/tubular atrophy was severe in AAG than YAG (TO/T1/T2; 40.7±29.7/9.4% in AAG vs. 76.9±29.0/4.1% in YAG, P<0.001). Also arteriolar sclerosis was severe in AAG than MAG and YAG [grade as none/mild/middle/severe: 9.5/19.0/35.7/11.9 % in AAG vs. 20.6/47.5/24.5/7.5 % in MAG and 61.7/40.8/6.1/2.2 % in YAG (P=0.014, P=0.0001)]. Renal survival rate analyzed by Kaplan Meyer Method was significantly lower in AAG (27.2 % / 17.5 year in AAG vs. 69.2 and 84.9 % / 20 year in MAG and YAG, P=0.0001). The patients advanced to end stage renal disease (ESRD) in AAG were higher MAP and severe U-Prot than non-advanced patients [MAP; 103.5 vs. 92.5 mmHg (P=0.019), U-Prot; 3.02 vs. 1.57 g/day (P=0.036)].

Conclusions: The characteristics of IgAN in advanced age were higher blood pressure, lower renal function, severe proteinuria, severe interstitial change, and arteriolar sclerosis. The prognosis was very severe and over 70% was developed to ESRD within 20 years.

Funding: Clinical Revenue Support

SA-PO191

Effect of Hematuria on the Outcome of IgA Nephropathy with Moderate Proteinuria

Chihiro Iwasaki, Takahito Moriyama, Kayu Tanaka, Yasuko Oshima, Kosaku Nitta. Medicine, Tokyo Women’s Medical Univ; Tokyo, Japan.

Background: Recently, hematuria has been recognized to be excreted from the active inflammatory lesion of glomerular capillaries in IgA nephropathy (IgAN). However, the relationship between hematuria and histological lesion, and the effect of hematuria on the renal function and proteinuria, severe interstitial change, and arteriolar sclerosis. The prognosis was very severe and over 70% was developed to ESRD within 20 years.

Methods: We examined 80 IgAN patients with proteinuria greater than 1g/day and were treated with predonisolone (0.8mg/kgBW). We divided them into two groups: low urinary red blood cells (U-RBC) group (L group, n=30, U-RBC < 40 counts/high-power field [HPF]), and high U-RBC group (H group, n=50, U-RBC ≥ 40 counts/HPF). We analyzed the clinical and histological background, the relationship between hematuria and histological lesion, renal outcome, and the risk factors for progression.

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

Underline represents presenting author/disclosure.
**SA-PO192**

**Obesity as a Risk Factor for Chronic Kidney Disease: Health Survey for England 2010**

_Helen L. MacLaughlin, 1,2 Wendy L. Hall, 1 Iain C. Macdougall, 1_  
1King’s College Hospital, London, United Kingdom; 2King’s College London, United Kingdom.

**Background:** Observational studies in North America, Europe, & Asia indicate that obesity is a risk factor for CKD, yet there is no similar study of a nationally representative sample in the United Kingdom (UK). The aim of this study was to determine if overweight and obesity are independently associated with the prevalence of CKD in the Health Survey for England (HSE) 2010 cross-sectional cohort.

**Methods:** CKD was defined as estimated glomerular filtration rate (eGFR) <60ml/min/1.73m² using the CKD-EPI formula. Multivariable logistic regression models were developed to estimate CKD risk by BMI in 5 categories (reference category 18.5–24.9 kg/m²), and were repeated with eGFR calculated using the 4-variable MDRD study equation for comparison with previous studies.

**Results:** The analytic cohort consisted of 3, 463 men & women (mean age 51y; SD 17y). The prevalence of CKD in the HSE was 5.9%. The prevalence of obesity was 43% in the CKD group vs 26% in the non-CKD group (p < 0.001). Those with CKD were older, had more diabetes & hypertension, & a higher mean BMI than those without CKD. The risk of CKD was over 2.5 times higher in obese participants, but not under- or overweight participants compared with BMI ≥30. After adjustment for age, sex, and baseline genetic ethnicity, smoking, diabetes & hypertension: BMI <18.5 kg/m² adjusted OR 2.08 (95% CI 2.07 to 15.74 NS), BMI 25.0-29.9 kg/m² adjusted OR 1.47 (95% CI 0.94 to 2.31 NS), BMI 30.0-39.9 kg/m² adjusted OR 2.78 (95% CI 1.75 to 4.43, p < 0.001), & BMI ≥40.0 kg/m² adjusted OR 2.68 (95% CI 1.05 to 6.85, p = 0.035). Results were similar, although attenuated, using the MDRD equation to define CKD status: BMI <18.5 kg/m² adjusted OR 1.73 (95% CI 0.32 to 9.47 NS), BMI 25.0-29.9 kg/m² adjusted OR 1.37 (95% CI 0.95 to 1.99 NS), BMI 30.0-39.9 kg/m² adjusted OR 2.02 (95% CI 1.37 to 2.97, p < 0.001) & BMI ≥40.0 kg/m² adjusted OR 2.31 (95% CI 0.89 to 5.44, NS).

**Conclusions:** The risk for CKD increases with obesity in the UK population, supporting findings from previous epidemiological studies. Future delivery service planning should account for increasing CKD risk in the years following an epidemiic rise in obesity population rates.  

_Funding: Government Support - Non-U.S._

**SA-PO193**

**The Impact of Initial and Subsequent Blood Pressure Control on Renal Outcome in Moderate to Severe Chronic Kidney Disease**

_Ping-min Chen, Tai-shuan Lai, Wen-Chih Chiang, Shuei-Liong Lin._  

**Background:** Blood pressure (BP) is an important risk factor of end stage renal disease. The protective effect of BP control is well known in early stage chronic kidney disease (CKD). Limited data is available in late stage CKD. This study is to examine the impact of baseline and subsequent BP control on renal outcome in late stage CKD patients.

**Methods:** This is a retrospective single-center study, enrolling total 1210 stage 3B-5 CKD patients (age 18~80). The baseline BP when enrolling and in the first year were collected. The primary outcome was initiation of long-term renal replacement therapy (RRT). The outcome was compared between different baseline BP groups. Good BP was defined as BP <130/80 mmHg, otherwise high BP. Patients were then stratified into four groups according to the baseline BP and subsequent BP control in the first year, if they were followed-up for more than one year. Survival analysis of the four groups was performed. Multivariate cox regression model was used to evaluate the effect of risk factors, baseline BP, and subsequent BP on renal outcome. Subgroup analysis according to the baseline urine protein/creatinine ratio (UPCR) was performed.

**Results:** High baseline BP was a risk factor of RRT (HR 1.487, p < 0.001). Those with baseline high BP and subsequent good BP control (Group 1) showed the best renal survival, followed by those with baseline high BP and subsequent good BP control (Group 2). Group 3 (good baseline BP but high subsequent BP) and Group 4 (high baseline and subsequent BP) patients had the worst outcome. Comparing group 2 and group 4, subsequent good BP control was associated with less risk of RRT (HR 0.515, p = 0.009). This renal protective effect of subsequent BP control was more prominent for patients with higher proteinuria (UPCR ≥ 1 g/g, HR 0.485, p = 0.012).

**Conclusions:** Baseline high BP is a risk factor for CKD progression. Patients with subsequent good BP control had lower risk of RRT even baseline BP is high. This study showed the beneficial role of good BP control in slowing CKD progression in late stage CKD patients.

**SA-PO194**

**Gastrointestinal Bleeding in End-Stage Renal Disease**

_Juliana F. Yang, Aniko Szabo, Hartiprasad S. Trivedi._  

_Medical College of Wisconsin.

**Background:** We investigated the epidemiology of serious gastrointestinal bleeding (GIB) in end-stage renal disease (ESRD) subjects receiving dialysis.

**Methods:** Serious GIB was defined as GIB requiring hospitalization or during hospitalization for inter-current illness. The United States Renal Data System database was used to identify patients with non-HMO Medicare as payer and first service date between January 1, 1996 and December 31, 2005. The patients were followed 90 days after the first service date to the first occurrence of death, transplant, loss of Medicare, or December 31, 2006. Analysis of predictors of GIB incidence was performed using underspersed Poisson regression. A Cox regression model with time-dependent predictors was used to evaluate the effect of GIB on survival. The process of recurrent GIB was modeled using a partially conditional Cox regression model.

**Results:** A total of 395,717 patients were followed for 841,192 person-years during which 66,679 GIB events (79/1000 person-years) were identified. The incidence of GIB was relatively stable from 1996 to about 2000, with an increasing trend thereafter. In 2006 the relative risk (RR) was 1.37 as compared to 1996 (95% CI 1.23-1.53). Females (vs. males), blacks (vs. whites), those with hypertension as cause of ESRD (vs. diabetes), and persons ≥ 49 years of age (progressively in each age decile) had a higher RR of GIB. The incidence of GIB increased the hazard of death by about 2-fold (hazard ratio [HR] 1.91, 95% CI 1.88-1.95); each additional episode of GIB further increased the hazard by about 3% (HR 1.029, 95% CI 1.02-1.04). Having had a previous episode of GIB increased the hazard of recurrence substantially (HR 3.21, 95% CI 3.07-3.37), and each further episode kept increasing the hazard (HR 1.22, 95% CI 1.19-1.26).

**Conclusions:** In patients new to long-term dialysis the risk of serious gastrointestinal bleeding has increased by about 37% over a 10-year period and is associated with a higher risk of death.  

_Notice: The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government._

_Funding: Other NIH Support - Supported in part by grant 1UL1RR031973 from the Clinical and Translational Science Award (CTSA) program of the National Center for Research Resources, National Institutes of Health, Clinical Research Support._

**SA-PO195**

**Genetic Influence on the Variation in Serum Uric Acid Levels in Western Alaska Natives**

_V. Saroja Voruganti,1 Shelley A. Cole,1 Karin Haack,1 Jessica L. Laston,1 Sven O.E. Ebbesson,2 Jean W. Maccluer,1 Anthony Comuzzie,1 Jason G. Umanas3_  
1Genetics, Texas Biomedical Research Institute, San Antonio, TX; 2Norton Sound Health Corporation, Nome, AK; 3Medstar Health Research Institute, Hyattsville, MD.

**Background:** Serum uric acid (SUA) levels are heritable and are correlated not only with renal urate transporters but with adiposity and inflammation.

**Methods:** We assessed genetic contributions to the variation in SUA in both phases of the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study, having previously reported that SUA was independently associated with prevalent CKD and hyperuricemia. In addition, we investigated the relationship between SUA and cardio-metabolic disease risk factors in a unique Alaska Native population. We investigated the following risk factors in SUA: triglyceride (TG), high density lipoprotein cholesterol (HDL-C), body mass index (BMI), total cholesterol (TC), age, female, hypertension, diabetes, and smoking.

**Results:** We used an extended pedigree linkage approach to test for linkage using the GENESIS program for X-chromosome (X), autosomes (A), and mitochondrial DNA (M) for a total of 10 linked intervals. No linkage was found for any of the chromosomes tested at significance thresholds of p < 0.05 and p < 0.01.

**Conclusions:** We investigated the relationship between SUA and cardio-metabolic disease risk factors in a unique Alaska Native population. No linkage was found for any of the chromosomes tested at significance thresholds of p < 0.05 and p < 0.01.

_Funding: Other NIH Support - Supported in part by grant 1UL1RR031973 from the Clinical and Translational Science Award (CTSA) program of the National Center for Research Resources, National Institutes of Health, Clinical Research Support._

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

_Underline represents presenting author/disclosure._
SA-PO196

Association between Osteoprotegerin, Baseline and Change in Arterial Stiffness in CKD
Helen Alderson, James Ritchie, Philip A. Kalra. Salford Royal Hospital.

Background: Osteoprotegerin (OPG) is elevated in CKD and has been associated with vascular calcification and aortic stiffness. We sought to investigate the relationship between OPG and rate of change in arterial stiffness in a CKD population.

Methods: Patients were selected from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS), a prospective observational study of outcome in patients with CKD 3-5. OPG was measured in stored baseline sera from 140 patients who had a contemporaneous and follow-up measurement of arterial stiffness. Arterial stiffness was assessed using augmentation index corrected for heart rate (AIx) measured with a Sphygmocor device. Patients were grouped by quartiles of OPG.

Results: At baseline, mean age was 63±13 years, eGFR 31±12ml/min/1.73m², OPG 6.9 (5.5-9.2) pmol/L. 75% of follow up measure of AIx were performed at 12-months and 25% at 24-months. Baseline AIx was not significantly correlated with OPG level (r 0.09 p=0.3), no significant difference in AIx existed between quartiles of OPG. No significant correlation between OPG level and rate of change in AIx existed (r 0.12 p=0.2). When quartiles of OPG were compared, only patients in the highest quartile had a mean increase in vascular stiffness, with a significant difference observed between the highest and lowest quartiles (-1.5±4 vs 1.0±7.7 p=0.03). Similarly when change in AIx was considered as a binary variable (increased / decreased), a greater proportion of patients in the highest OPG quartile had an increase in AIx.

Conclusions: Any relationship between OPG level and rate of change in vascular stiffness appears to be non-linear, with patients who have the highest OPG levels at the greatest risk. Further work should include a larger sample size and consider possible confounding effects of renal function and other bone-mineral parameters.

SA-PO197

Association of Cystatin C and Urine Albumin to Creatinine Ratio with Change in Ankle Brachial Index: The Multi-Ethnic Study of Atherosclerosis
Kimberly Miyaguni, 1, 2 Renita Silsicki, 1 Sarah Mays, 10, 11 Elke Schaeffer, 12 Christoph Wanner, 13 Kai-Uwe Eckardt.

Background: Low ankle brachial index (ABI), a reflection of atherosclerotic ed vessels, are both measures of subclinical cardiovascular disease (CVD). The association of serum cystatin C and albumin-creatinine ratio (ACR) with development of either high or low ABI is unknown.

Methods: We investigated the longitudinal associations of cystatin C and ACR with development of low (ABI 0.9-1.4 to ABI < 0.9), and high ABI (0.9-1.4 to > 1.4) over 10 years in 5,591 MESA (Multi-Ethnic Study of Atherosclerosis) participants with follow-up ABI values using multilevel regression.

Results: Mean (SD) age was 61 (10) years, 57% were women and 27% were blacks. Mean (SD) cystatin C was 0.88 (0.2) mg/L and median (IQR) ACR was 5.1 (3.2-10.0) mg/gm. Higher cystatin C was associated with progression to both low and high ABI in univariate, but not multivariable analyses (p<0.05). Elevated levels of ACR were significantly associated with progression to both low and high ABI in univariate and multivariable analyses.

Conclusions: Elevated levels of ACR are significantly associated with risk of progression to both low and high ABI.

SA-PO198

Prognostic Value of Red Cell Distribution Width in Advanced Chronic Kidney Disease
Pablo Marcos Braillard Poccard, Cesar Garcia-cantion, Noemi Esparza, Celia Lopez, Ana Ramgrz Puga, Elvira Bosch, Rita Guerra, Eduardo Baamonde, Dolores Checa. Nephrology, Hospital Universitario Insular, Las Palmas, Gran Canaria, Spain.

Background: Increased red cell distribution width (RDW) is related to oxidative stress and pro-inflammatory states and is associated with higher mortality risk in the general population and in patients with cardiovascular diseases.

Our objective was to evaluate the association between RDW and mortality risk in a population with advanced Chronic Kidney Disease (CKD) and to describe the possible relationship with other prognostic factors.

Methods: Prospective observational cohort study of incident advanced CKD patients, who attended our clinic between January 2008 and December 2012 and were followed-up until March 30th 2013. The relationship between RDW and the rest of prognostic variables was studied. A survival analysis based on RDW tertiles was conducted by using the Kaplan Meier method and the Cox proportional hazards model.

Results: The study included 533 patients aged 67.5 years, 55.9% male, 67.4% diabetic. Subjects were classified into RDW tertiles. Median follow-up times were: 16.7 months tertile 1 (T1), 17.6 months tertile 2 (T2), 17.9 months tertile 3 (T3). Mortality was 8.2%, 14.2% and 30.2% for T1, T2 and T3 respectively p<0.001. Tertile groups were different in age, %diabetes,%cardiovascular disease, hemoglobin, albumin, cholesterol T and CRP. and no differences were shown in gender, uric acid, phosphorus, GF MDRD, proteinuria or triglycerides. In a binary logistic regression model for mortality, RDW tertiles remained significant with OR of T3 against T1 2.929 (CI95% 1.498 - 5.727) independently of the rest of variables. Kaplan-Meier survival curves for RDW tertiles showed survival means of 50.6m T1, 47.7m T2 and 37.8m T3; p<0.001. The Cox proportional hazards model showed a relative mortality risk of 2.325 for T3 against T1 (CI95% 1.266-4.271) adjusted for the rest of variables.

Conclusions: In this study, RDW appeared to be a marker for mortality risk independent of other known markers in CKD. The pathophysiological meaning and prognostic value of this finding for advanced CKD patients should be verified in further studies.

SA-PO199

Prevalence and Control of High Blood Pressure in a German Cohort with Chronic Kidney Disease: Cross-Sectional Data from the German Chronic Kidney Disease (GCKD) Study

Background: We assessed blood pressure control in a large german cohort of chronic kidney disease (CKD) patients in nephrology specialist care.

Methods: The German Chronic Kidney Disease (GCKD) study is a prospective observational cohort study which enrolled 5217 german patients with CKD of various aetologies, who are under nephrology specialist care. Inclusion criteria were an estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73 m² or overt proteinuria in the presence of an eGFR<60 mL/min/1.73 m². Office blood pressure measured according to WHO criteria by trained study nurses was available from 5181 participants. Hypertension was defined as systolic >140 mm Hg or diastolic >90 mm Hg or intake of antihypertensive medications. Blood pressure was considered as controlled if systolic <=140 and diastolic <=90 mm Hg.

Results: Office blood pressure (mean±SD) of 5181 participants was 139±20.4 / 79.3 ±11.7 mm Hg; no less than 4958 (95 %) of the patients were hypertensive. The remaining 51 % exhibited a blood pressure of 156.3 ± 15.3 / 85.3 ± 11.7 mm Hg. Among patients with diabetes (35 % of the cohort), office blood pressure was 142.2 ± 21.4 / 76.3 ± 11.9 mm, 98 % were hypertensive, and 52 % of the latter were controlled. Blood pressure in uncontrolled diabetic patients was 158.2 ± 15.3 / 81.6 ± 11.6 mm Hg.

Conclusions: Blood pressure control of CKD patients in Germany is less than optimal, even in nephrology specialist care. Identifying potential reasons will require further analyses of e.g. medication patterns. Improving blood pressure control provides an opportunity to ameliorate progression of CKD and prevent some of its complications.

Funding: Private Foundation Support, Government Support - Non-U.S.
SA-PO200
Self-Reported Cardiovascular Disease and Long Term Renal Outcomes in Chronic Kidney Disease (CKD) – A Report from the Chronic Renal Insufficiency Cohort (CRIC) Study
Mahboob Rahman,1 Dawei Xie,2 Harold I. Feldman,3 Alan S. Go,3 Jiang He,4 John W. Kusek,5 James P. Lash,5 Akinoluto O. Ojo,1 Stephen L. Seliger,6 Susan P. Steigerwalt,7 Valerie L. Teai,8 Raymond R. Townsend,9 Case Western Reserve Univ; 1Univ of Pennsylvania; 2Kaiser Permanente; 3Talune Univ; 4NIDDK; 5Univ of Illinois; 6Univ of Michigan; 7Univ of Maryland; 8St. Johns Health System.

Background: Although CKD and cardiovascular disease (CVD) are commonly observed together, it is unclear whether CVD increases risk of progression of CKD, we evaluated whether CVD is an independent risk factor for progression of kidney disease among a cohort individuals with CKD.

Methods: A prospective study of 3939 participants with CKD enrolled in the CRIC Study between June 2003 and June 2008. Self-reported cardiovascular disease (myocardial infarction/revascularization, chronic heart failure (CHF), stroke or peripheral arterial disease) was ascertained by questionnaire at study entry. Our primary endpoint was a composite of end-stage renal disease or a decline in glomerular filtration rate (GFR) to one-half from baseline.

Results: Mean GFR at baseline was 42.8 ml/min/1.73m2. One third (33.4%) of the study participants reported a history of cardiovascular disease, and 10.7 % reported a history of chronic heart failure. Over a median follow up of 3.3 years, 779 (19.8%) participants experienced a renal endpoint. In multivariable models, a composite of any prevalent CVD at baseline was not an independent predictor a renal endpoint (HR 1.08; 95% CI: 0.92 - 1.28). However, self-reported history of CHF was independently associated with a 32% higher relative rate of the endpoint (HR 1.32; 95% CI: 1.05 - 1.66). This relationship was consistent across subgroups defined by age, race, gender and diabetes status.

Conclusions: Although overall prevalent CVD was not an independent predictor of decline in kidney function, self-reported history of CHF was a strong predictor of CKD progression. Future work is needed to investigate mechanisms for this association.

Funding: NIDDK Support

SA-PO201
Renal Function and Outcome in Thrombolysed Stroke Patients
Hardi Hasan,1 Azim Majeez,2 David Sandler,2 Don Sim,3 Shahid A. Khanur,1 Indranil Dasgupta.1

1Geriatric Dept - Stroke Unit, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom; 2Stroke Unit and Nephrology Dept, Birmingham Heartlands Hospital, Birmingham, United Kingdom; 3Geriatric Dept - Stroke Unit, Sandwell and City Hospitals Birmingham, Birmingham, United Kingdom.

Background: Stroke and renal impairment are common with ageing. Thrombolysis in stroke is offered to acute stroke patients aiming at significant reduction in disability after stroke. Little is known about the effects of eGFR on disability after stroke thrombolysis. This study tries to find any possible association between the baseline impaired renal function and disability in thrombolysed stroke patients.

Methods: A retrospective study analyzing the data from a group of thrombolysed stroke patients in three teaching hospitals in the West Midlands UK, between October 2008 and December 2012. Patients were categorized into two groups; group-1 with eGFR less than 60, and group-2 with eGFR more than 60. The outcomes studied were the admission National Institutes of Health Stroke Scale (NIHSS) as an indicator of severity of the stroke, discharge Modified Rankin Scale (mRS) as a general disability measure, and length of stay in hospital. We also looked at the discharge destinations for the two groups.

Results: Data from 263 patients were analysed. Among these, 68 patients belonged to group-1, and 195 to group-2. The mean age was significantly different (group-1 76 vs group-2 64, p =0.0001). The mean for admission NIHSS was 15.4 for group-1 vs 13 for group-2 (p = 0.0014). Group-1 were more disabled on discharge with mean mRS of 2.7 vs 1.9 for group-2 (p = 0.0001). The mean length of stay was 23 and 13 for group-1 and 2 respectively (p = 0.0061).

Mortality among group-1 patients was 16% compared to 6% in group-2, and more patients among group-2 went home compared to group-1 (75% vs 53% respectively) and less ended in institutional care (4% compared to 10% respectively).

Conclusions: This study shows that patients with impaired renal function are older, have more severe stroke and have poorer outcome following thrombolysis. These patients have longer length of stay in hospital, higher mortality,more disability, and increased risk of institutionalization.
Conclusions: Higher ESA doses are associated with worse outcomes in CKD. Given randomized trials in which targeting higher Hb with ESA resulted in worse outcomes, our study suggests high ESA dose itself may be harmful. Focusing on ESA dose instead of Hb level should be considered in anemia management.

Funding: NIH Support, Private Foundation Support

SA-PO205

Change in Serum Phosphorus Level over Time and Mortality in Hemodialysis Patients

Jongha Park,1 Elani Streja,2 Csaba P. Kovesdy,3 Kamyar Kalantar-Zadeh.1

Background: Previous studies have found an association of hyperphosphatemia with mortality in maintenance hemodialysis (MHD) patients. However, an association between change in serum P over time and mortality has been insufficiently explored.

Methods: A total of 66,684 MHD patients treated from (6/2001 to 6/2006) in the US were analyzed. Patients were stratified by baseline serum P values (≥3.5, 3.5 to <5.5 and ≥5.5 mg/dL), then were divided into 3 groups in within each stratum based on mean level during the 3rd calendar quarter. Cox proportional hazard models were used with adjustments for casemix and malnutrition inflammation complex markers.

Results: Compared with patients whose serum P level was sustained greater than 5.5 mg/dL, survival benefit was revealed in patients with decrease in serum P level from ≥5.5 mg/dL to 3.5–<5.5 mg/dL. In the same vein, increase in serum P level from 3.5–<5.5 mg/dL to ≥5.5 mg/dL tended to be associated with higher mortality compared with no change in serum P level within 3.5–<5.5 mg/dL. In contrast, decrease to low level (<3.5 mg/dL) was paradoxically associated with increased mortality in comparison with no change in each baseline serum P stratum.

Conclusions: Decrease in serum P level may be associated with better survival. However, decrease in serum P level below normal range seems to be associated with increased mortality, in which low serum P may be a proxy of poor nutritional state.

Funding: NIH Support, Private Foundation Support

SA-PO206

Trends in Key Clinical Parameters before and after Initiation of Dialysis: The Renal Research Institute (RRI)-CKD Extension Study

Aleksandar Milovanovic,1 Anca Tilia,2 Brenda W. Gillespie,1 Michael Heung,1 Peter Kotanko,3 Rajiv Saran.1 Univ of MI; 2Renal Research Inst.

Background: There is a paucity of studies examining the critical transition and continuum through advanced stages of CKD through initiation of dialysis and beyond.

Methods: We conducted a follow-up study of CKD patients at University of Michigan (UM), one of the sites in the RRI-CKD study (a 4-center prospective cohort), using electronic chart review among patients where follow-up had previously ended at or prior to ESRD. Electronic records were abstracted to track clinical events and outcomes 1year pre- and post-dialysis (hemodialysis-HD or peritoneal dialysis-PD).Spline regression examined trends in clinically relevant parameters in the period before and after initiation of dialysis, stratified by HD/PD.

Results: 74 of 280 UM patients were identified in the dialysis database.Mean age at dialysis initiation was 57 yrs, 83% were white, 56% male; 95% had hypertension and 40% were diabetic.52% were on HD and 39% on PD; 21 subjects had died. Comparative trajectories of key clinical parameters are shown in the Figure by dialysis type.Among HD patients, BMLBP and serum albumin were relatively stable pre- and post-dialysis. For PD patients, BMI steadily decreased and serum albumin showed a significant dip at 6 months pre- and post-dialysis, while systolic BP increased by an average of 22mmHg after initiation of dialysis.Serum potassium levels showed a dip for both dialysis types 3-months around the time of initiation of dialysis.However, PD patients on average had higher serum potassium levels than those on HD.

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

Underline represents presenting author/disclosure.
Conclusions: Healthcare use was high among CKD patients both during the late CKD and early ESRD. AVF use as first vascular access was associated with lower number of days in hospital compared with AVG or catheter.

SA-PO208
Association of Race-Ethnicity with Mortality in Incident Peritoneal Dialysis Patients Chunyang Li,1 Elani Streja,1 Connie Rhee,1 Wei Ling Lau,1 Miklos Zsolt Molnar,1 Csaba P. Kovesdy,2 Rajnish Mehrotra,2 Kamyar Kalantar-Zadeh,1 1Harold Simmons Center, UCI, Orange, CA; 2Dept of Epidemiology, Fielding School of Public Health, UCLA, Los Angeles, CA; 3DaVita, Needham, MA; 4Dept of Statistics, Univ of Michigan, Ann Arbor, MI; 5Univ of Ulsan College of Medicine, Ulsan, Korea; 6Memphis Veterans Affairs Medical Center, Memphis, VA; 7Univ New Mexico, Albuquerque, NM.

Background: It has been previously reported that African-American and Hispanic dialysis patients have greater survival than whites (“African-American Paradox”). Survival advantage has also been reported in Hispanics despite lower socioeconomic status and faster chronic kidney disease progression to dialysis dependency (“CKD Hispanic Paradox within Paradox”). However the association between race and mortality peritoneal dialysis (PD) patients is still unclear.

Methods: We examined 8-year (7/2001-6/2009) all-cause mortality for a cohort of 5,067 DaVita incident (< 90 days dialysis vintage days at the time of entry into cohort) PD patients including 1,052 African-Americans, 765 Hispanic, and 3,250 Whites using Cox proportional hazard models adjusted for case-mix and malnutrition-inflammation complex syndrome (MICS) covariates.

Results: Among African-Americans, Hispanics, and whites the mean age (mean ± SD) was 52±14, 53±16, and 59±15 yrs old and included 55%, 48% and 42% women; and 46%, 57% and 48% diabetics, respectively. Compared to Whites, African-Americans and Hispanics have a lower risk of mortality; even after adjusting for case mix and MICS markers: HRs (95%CI) 0.77 (0.68-0.88) and 0.64 (0.56- 0.74), respectively. Compared to African-Americans, Hispanics had slightly lower risk of mortality.

Conclusions: Incident African-American and Hispanic PD patients have greater survival in comparison to white PD patients. Further studies are needed to examine these racial-ethnic differences.

Funding: NIDDK Support, Private Foundation Support

SA-PO209
Hemodialysis Dose and Survival: A Marginal Structural Model Analysis Paungpaga Lertdumrongluk,1 Elani Streja,1 Onyebuchi A. Arah,1 Jongha Park,3 Csaba P. Kovesdy,3 Connie Rhee,1 Steven M. Brunelli,2 Daniel L. Gillen,3 Kamyar Kalantar-Zadeh,1 Mark L. Unruh,1 1Harold Simmons Center, UCI, Orange, CA; 2Dept of Epidemiology, Fielding School of Public Health, UCLA, Los Angeles, CA; 3DaVita, Needham, MA; 4Dept of Statistics, Univ of California, Irvine, Irvine, CA; 5Univ of Ulsan College of Medicine, Ulsan, Korea; 6Memphis Veterans Affairs Medical Center, Memphis, VA; 7Univ New Mexico, Albuquerque, NM.

Background: Observational studies have consistently demonstrated the survival benefits of greater dialysis dose, whereas randomized controlled trials show conflicting results. The causal analysis of the impact of dialysis dose on mortality requires investigation with novel statistical methods such as marginal structural models (MSM) that account for time-varying confounding.

Methods: We quantified the effect of delivered dose of hemodialysis (spKt/V) on mortality in a 2001-2005 cohort of 68,060 patients undergoing thrice-weekly hemodialysis (HD). We compared conventional Cox regression and MSM analyses, accounting for time-varying confounding by applying longitudinally modeled inverse-probability-of-dialysis-dose weights.

Results: In Cox models, baseline spKt/V showed a weak negative association with mortality, while higher time-averaged spKt/V was strongly associated with lower mortality risk. In MSM analyses, a spKt/V <1.2 was associated with increased mortality (HR [95% CI] 1.77 [1.64-1.92], whereas lower mortality risk was observed with spKt/V values >1.4 (ref: spKt/V 1.2>1.4): HRs (95%CI) 0.72(0.69-0.76), 0.62(0.58-0.65), 0.55(0.51-0.59), and 0.55(0.51-0.60) for spKt/V ranges of 1.4<1.6, 1.6<1.8, 1.8<2.0, and ≥2.0, respectively.

Conclusions: Among African-Americans, Hispanics, and whites the mean age (mean ± SD) was 52±14, 53±16, and 59±15 yrs old and included 55%, 48% and 42% women; and 46%, 57% and 48% diabetics, respectively. Compared to Whites, African-Americans and Hispanics have a lower risk of mortality; even after adjusting for case mix and MICS markers: HRs (95%CI) 0.77 (0.68-0.88) and 0.64 (0.56- 0.74), respectively. Compared to African-Americans, Hispanics had slightly lower risk of mortality.
Conclusions: The data suggest higher dosing of hemodialysis is robustly associated with greater survival in MSM analyses that more completely account for time-varying confounding.

Funding: NIDDK Support, Private Foundation Support

SA-PO210
Comparative Effectiveness of Laboratory Measures for One-Year Survival Prediction in Maintenance Hemodialysis Patients

Lan Bai,1 Elani Streja,2 Miklos Zsolt Molnar,2 Csaba P. Kovesdy,1 Kamyar Kalantar-Zadeh,3 Daniel L. Gillen.1

Abstract Withdrawn

SA-PO211
Abstract Withdrawn

SA-PO212
Patients with Primary Glomerulonephritis on Renal Replacement Therapy May Be Cured: Data from the Veneto Dialysis and Transplantation Registry

Maurizio Nordio, Nicola Tessitore, Cataldo Abaterusso, Barbara Rossi, Giovambattista Virga, Francesco Antonucci. Veneto Dialysis and Transplantation Registry, Padua, Italy.

Background: Survival on RRT is affected by the primary renal disease (PRD). By using relative survival analysis (patients’ mortality is compared with the general population) we observed that patients on RRT with primary glomerulonephritis (PGN) had the best survival. After ten years of RRT, patients with PGN experience the same mortality rate as the general population, indicating the effectiveness of RRT modalities in controlling uraemia. Moreover, it underlines the relevance of comorbidities, because of their independent effect on survival rates. Our findings suggest that the tendency of considering RRT as a unique condition may be misleading.

Funding: Government Support - Non-U.S.

SA-PO213
Comparative Effectiveness of Iron Formulation and Dosing Practices on Health-Related Quality of Life in Patients on Hemodialysis

Miklos Zsolt Molnar,1 Csaba P. Kovesdy,1 Kamyar Kalantar-Zadeh,3 Daniel L. Gillen.1

Background: We used rigorous prediction model building methods to identify 14 potentially modifiable biomarkers that influence survival at one year among new hemodialysis patients. Identification of these factors provides targets for treatment among new hemodialysis patients.

Funding: NIDDK Support, Private Foundation Support

SA-PO214
Proteinuria with High Serum Level of Hepcidin-25 Indicates a Bad Prognosis in Non-Hodgkin’s Lymphoma Patients

Masaki Hara1 Minoru Ando,1 Ken Tsuchiya,2 Kosaku Nitta.2 Renal Div, Dept of Medicine, Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Tokyo, Japan; 2Dept IV of Internal Medicine, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan.

Background: Serum hepcidin-25 level increases in the state of chronic inflammation including kidney disease and cancers; however, its clinical impact on disease prognosis has not fully understood.

Methods: One-year prospective study was conducted to ascertain an impact of serum hepcidin-25 on mortality in non-Hodgkin’s lymphoma (NHL) patients with CKD. The cohort comprised 50 NHL patients receiving chemotherapy (mean age, 66 years). Serum hepcidin-25 level was measured by liquid chromatography-mass spectrometry. Proteinuria, a simple sign of kidney disease, was determined as a dipstick test ≥1+, persistent in three consecutive examinations. Cumulative survival curves were drawn with Kaplan-Meier method, which were stratified into 4 groups by both presence or absence of proteinuria and presence or absence of elevation in serum hepcidin-25 more than the mean value. Multivariable proportional hazards regression analysis was used to calculate hazard ratio (HR) with its 95% confidence interval (CI) for mortality.

Results: Prevalence of proteinuria was 14%. Mean serum hepcidin-25 level was 65.4 ± 60.9 ng/ml (the healthy reference: 22.2 ± 12.3 ng/ml). Distribution of the 4 groups was as follows: non-proteinuria with lower hepcidin-25 (58%), non-proteinuria with higher hepcidin-25 (25%), proteinuria with lower hepcidin-25 (6%), and proteinuria with higher hepcidin-25 (14%). Therapy initiated due to elevated risk (HR>0.7) in the group of proteinuria with higher hepcidin-25 among all. The HR (95% CI) of this group was 7.98 (2.20–29.5), as compared with the group of non-proteinuria with lower hepcidin-25 levels.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
and 17% were non-adherent. 49% of patients were overweight (BMI ≥30% prenatally or in the 1st year of life). Adherence was documented in 63% of patients followed within 1 year of clinic transition to con

cancer.

Conclusions: Proteinuria accompanied by serum hepcidin-25 elevation may predict poor outcome in NHL patients.

SA-PO216 Renoprotective Effectiveness of Third Generation Calcium Channels Blockers  Ricardo M. Heguilen, Amelia Rita Bernasconi.  Nephrology, Hospital Juan A Fernandez, Buenos Aires, Argentina.

Background: Angiotensin converting enzyme inhibitors (ACEis) and angiotensin 2 receptor blockers (ARBs) have widely recognized renoprotective properties. Third generation dihydropyridine calcium channel blockers (3dhpCCBs), acting on L as well as T-type calcium activated channels, would reduce intraglomerular pressure (P-GC) and urine protein excretion, improving renal function in patients with chronic kidney disease (CKD). We evaluated whether the addition of 3dhpCCB lecarnidipine (LER) has similar renoprotective effect to ENL plus LOS.

Methods: We assessed 33 IgA nephropathy patients. Pathologist reviewed biopsy slide was not over 6 years according to the Oxford classification. All patients had been maintained ARB or ACEi. 17 Patients were treated with 500 mg intravenous MP every 2 weeks for 6 months to improve renal function. The efficacy of MP pulse was analyzed by comparing the slopes of eGFR/ml/min/1.73m² and log transformed serum albumin/creatinine ratios before, during, and after therapy using linear regression coefficients. We compare outcome between 17 steroid pulse groups (Group1) and 16 untreated groups (Group2).

Results: Median duration between biopsy and pulse therapy is 1 month (range 0–73 months). In group1, the rate of decline of eGFR increased in both group (p = 0.02). According to the Oxford classification 1/17 patient was M1, 2/17 were E1, 14/17 were S1, 6/17 were T0, 10/17 were T1, 1 patient was T2 in group1. Using χ² test, we found no significant differences in Oxford classification of histological grade between group 1 and 2. Mean eGFR for group1 was 41.3 ± 15.7. Linear regression analysis showed improvement of decline of eGFR after steroid pulse in 9 of 14 group1 patients with initial GFR ≥30. After steroid pulse, the rate of monthly decline of eGFR decreased in group1 (p = 0.04 vs. 0.34 vs 0.35, p = 0.08). There was no improvement of urine albumin/creatinine ratio in group1. As the grade of T increased, the rate of decline of eGFR increased in both group (p = 0.02). Other parameters in Oxford classification were not a significant variable.

Conclusions: Steroid pulse therapy could improve the decline of eGFR in IgA nephropathy. Among the Oxford classification, only T grade affects the change of eGFR irrespective of steroid pulse therapy.

SA-PO215 Outcomes of Pediatric-Onset CKD Patients Who Underwent Health Care Transition Preparation  Maria E. Ferris, Nicole M. Fenton, Gerald A. Hladik, Abhijit V. Kshirsagar.  UNC Kidney Center, Univ of North Carolina at Chapel Hill.

Background: The impact of health care transition preparation (HCTP) in pediatric-onset CKD patients transitioning from pediatric to adult-focused providers needs to be characterized.

Methods: We conducted an IRB approved cross-sectional study of adult nephrology patients who received at least one HCTP session at the UNC pediatric nephrology clinic between July ’07 to May ’13 (intervention). Disease self-management/readiness to transition therapy was assessed by the provider-administered UNC TRxANSITION Scale and the self-administered STARx Survey. Adherence was ascertained based on health provider notes.

Results: We included 405 NHANES participants aged >20 yrs with eGFR <60 ml/min/1.73m². There were 154 deaths over 1190 years of follow-up. Table 1 summarizes the definitions and duration of PA levels of each min/hr of SA with each of PA levels

Results: The mean ± SD age was 69.3 ± 11.8 yrs. 39% were men and 6% were black. There were 154 deaths over 1190 years of follow-up. Table 1 summarizes the definitions and duration of PA levels

Results: Sixty four (44 men) 48 – 79 years old Ps, receiving ENL (10-25 mg/d) were included. LOS (50 mg/d) was added in 31 while LER (10 mg/d) was added in 33. The addition of LOS or LER produced no changes in BP. Serum creatinine decreased in both group. (LOS 1.48 ± 0.28 and LER 1.44 ± 0.29 mg/dL) and CoC (LOS 46.2 ± 5.8 and LER 45.1 ± 8.7 ml/min/1.73 m²) remained stable (p: NS) at 2.5 years.

Conclusions: The addition of LER to the standard therapy with ENL has similar renoprotective effect to ENL plus LOS.

SA-PO217 Effect of Steroid Pulse Therapy in Patients with IgA Nephropathy According to the Oxford Classification  Kyeong Woo Nho, Wonsok Yang, Su-Kil Park.

Div of Nephrology, Dept of Internal MedicineCollege of Medicine, Univ of Ulsan, Asan Medical Center.

Background: Steroids have been shown to reduce proteinuria and preserve renal function. We investigated the effect of steroid pulse therapy in patients with IgA nephropathy according to the Oxford classification.

Methods: We assessed 33 IgA nephropathy patients. Pathologist reviewed biopsy slide was not over 6 years according to the Oxford classification. All patients had been maintained ARB or ACEi. 17 Patients were treated with 500 mg intravenous MP every 2 weeks for 6 months to improve renal function. The efficacy of MP pulse was analyzed by comparing the slopes of eGFR/ml/min/1.73m² and log transformed serum albumin/creatinine ratios before, during, and after therapy using linear regression coefficients. We compare outcome between 17 steroid pulse groups (Group1) and 16 untreated groups (Group2).

Results: Median duration between biopsy and pulse therapy is 1 month (range 0–73 months). In group1, the rate of decline of eGFR increased in both group (p = 0.02). According to the Oxford classification 1/17 patient was M1, 2/17 were E1, 14/17 were S1, 6/17 were T0, 10/17 were T1, 1 patient was T2 in group1. Using χ² test, we found no significant differences in Oxford classification of histological grade between group 1 and 2. Mean eGFR for group1 was 41.3 ± 15.7. Linear regression analysis showed improvement of decline of eGFR after steroid pulse in 9 of 14 group1 patients with initial GFR ≥30. After steroid pulse, the rate of monthly decline of eGFR decreased in group1 (p = 0.04 vs. 0.34 vs 0.35, p = 0.08). There was no improvement of urine albumin/creatinine ratio in group1. As the grade of T increased, the rate of decline of eGFR increased in both group (p = 0.02). Other parameters in Oxford classification were not a significant variable.

Conclusions: Steroid pulse therapy could improve the decline of eGFR in IgA nephropathy. Among the Oxford classification, only T grade affects the change of eGFR irrespective of steroid pulse therapy.

SA-PO218 Sedentary Activity Is Associated with Increased Mortality and Light Intensity Activity Is Associated with Decreased Mortality in CKD  Ricardo Filipevic1, G. Wei, R. Marcus, Michel Chonchol,1 Tom Greene,1 Srinivasan Beddhru.1 U of Utah; 2U of Colorado.

Background: Sedentary activity (SA) is emerging as a major risk factor for mortality in the general population. However, the association of SA and physical activity (PA) intensity levels with mortality has not been studied in CKD. Therefore, we examined the associations of objectively measured SA and PA intensity levels with mortality in CKD using 2003-2004 National Health & Nutrition Examination Survey (NHANES) data.

Methods: PA levels were measured with Actigraph 7164 accelerometer in NHANES. Mortality data until Dec 31, 2006 were obtained by NHANES. For the current analyses, we included 405 NHANES participants aged ≥20 yrs with eGFR <60 ml/min/1.73m² & valid accelerometer data (wore the device ≥10 hr/day & ≥4 days). Cox regression models adjusted for age, gender, race, education, smoking, alcohol use, lung disease and mobility limitations were used to examine the associations of PA levels with mortality.

Results: The mean ± SD age was 69.3 ± 11.8 yrs. 39% were men and 6% were black. There were 154 deaths over 1190 years of follow-up. Table 1 summarizes the definitions and duration of PA levels

Results: The mean ± SD age was 69.3 ± 11.8 yrs. 39% were men and 6% were black. There were 154 deaths over 1190 years of follow-up. Table 1 summarizes the definitions and duration of PA levels

Conclusions: The impact of health care transition preparation (HCTP) in pediatric-onset CKD patients transitioning from pediatric to adult-focused providers needs to be characterized.

Methods: We conducted an IRB approved cross-sectional study of adult nephrology patients who received at least one HCTP session at the UNC pediatric nephrology clinic between July ’07 to May ’13 (intervention). Disease self-management/readiness to transition therapy was assessed by the provider-administered UNC TRxANSITION Scale and the self-administered STARx Survey. Adherence was ascertained based on health provider notes.

Results: We included 90 participants (66 intervention, 24 controls) with the following characteristics: 36 (40%) male; mean age of diagnosis 10.7 ± 5.67 years; 46% African American, 35% White, 8% Hispanic and 11% other race; 48% had private insurance and 50% came from a two-parent household. Currently, 25% of patients receive anti-depressants, 2% ADHD treatment and only 30% reported school attendance/employment. There was one death. Glomerular disease was reported in 59% of patients, transplant 34%, with a mean eGFR 66 ± 33 ml/min/1.73m² (range 5-110); 50% were diagnosed at ≥30 kg/m²), and 31% were obese (≥30 kg/m²). The BMI of patients with glomerular disease was higher than the BMI of patients with transplant/patient with transplant (p=0.02) and adherence (p=0.05). There was no improvement of urine albumin/creatinine ratio in group1. As the grade of T increased, the rate of decline of eGFR increased in both group (p=0.02). Other parameters in Oxford classification were not a significant variable.

Conclusions: Steroid pulse therapy could improve the decline of eGFR in IgA nephropathy. Among the Oxford classification, only T grade affects the change of eGFR irrespective of steroid pulse therapy.
These data suggest that trade off of SA with light PA is significantly associated with ↓ mortality while MV might also confer a lower mortality.

Conclusions: SA is associated with increased mortality in CKD and replacing SA with light or MV activities are likely to reduce mortality.

Funding: NIDDK Support

SA-PO219

Comparative Survival Predictability of Phosphorus and Albumin-Adjusted Calcium in HD and PD Patients

Methods: Among a 2001-2006 cohort of 129,604 dialysis (10,066 on PD and 118,998 on HD at study entry) patients with Ca and P data. Time-averaged Cox models were examined to assess the comparative survival predictability of P and albumin-corrected Ca in HD vs PD patients.

Results: Risk for death was higher for HD patients with albumin-corrected Ca>9.1mg/dl or >9.5mg/dl, but was lower in all sub-groups of PD patients with Ca<9.9 mg/dl (ref: HD patients with Ca 9.4–9.95mg/dl). Risk for death was higher for individuals undergoing HD with P>4.5 mg/dl or >5.4 mg/dl (ref: HD patients with P 4.5–5.4mg/dl), and PD patients with P>6.4 mg/dl. The risk for death for HD was higher than for PD patients at all levels of P and across all causes of death.

Conclusion: The associations between Ca and P with mortality are disparate between HD and PD patients. Low P level is associated with poor outcomes in HD, whereas high P levels predict mortality for patients with either modality, with the threshold above which risk is increased being higher in PD patients. Further studies exploring differences in the association of death risk of mineral metabolism parameters in HD vs. PD patients are warranted.

Funding: NIDDK Support, Private Foundation Support

SA-PO220

Effect of Cigarette Smoking on Renal Function in Healthy Subjects

Methods: This cross-sectional study was conducted on healthy male subjects in the age group of 31-40 years. The study consisted of 40 subjects in each of the two groups: non-smokers and smokers (cigarettes only). The claimed smoking status of study subjects was verified using smokercyfer. Various laboratory investigations included assessment of renal function (eGFR) using CKD-EPI and MDRD equations, and urine albumin creatinine ratio (ACR).

Results: Using EPI equation, mean eGFR was 110.7±9.6 mL/min/1.73m² (non-smokers) and 110.7±9.4 mL/min/1.73m² (smokers) (p=0.999). Using MDRD formula, mean eGFR was 109.0±16.3 mL/min/1.73m² (non-smokers) and 110.1±15.7 mL/min/1.73m² (smokers) (p=0.750). Mean urine ACR was significantly (p=0.001) higher in smokers (14.55±8.08 mg/g) as compared to non-smokers (7.96±2.86 mg/g) as shown in Figure 1. Further within smokers, pack years of cigarette smoking showed a significant positive correlation with urine ACR levels (p=0.001) (r=0.858). In smokers urine ACR based on number of pack years of smoking was: 7.97±2.74 mg/g (for ≤1 pack year) 17.73±7.90 mg/g (for >1 pack year) (p=0.001).

Conclusions: In healthy young males, cigarette smoking was associated with significantly higher urine ACR even within normal limits of albumin excretion rates. Higher degrees of cigarette smoking was associated with increasing urine ACR levels; however, there was no significant effect of smoking on eGFR in our cross sectional study.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author/disclosure.

676A
SA-PO222

Model Analysis. Megha Mahendra Doshi,1 Elani Streja,1 Connie Rhee,1 Wei Ling Lau,1 Allen R. Nissen,2 Csaba P. Kovesdy,1 Kamyar Kalantar-Zadeh.1

Background: Prior studies have found an inverse association between body mass index (BMI) and mortality for hemodialysis (HD) patients (obesity paradox). It has been suggested that these observations are a result of biases such as selection bias and that studies are needed to investigate the association between BMI and mortality accounting for time-dependent confounders using marginal structural modeling (MSM) and inverse probability of censoring weights. We hypothesize that even after applying these novel methods, the inverse association between BMI and mortality in HD patients is robust.

Methods: We examined the associations between BMI with all-cause mortality among a 2001-2006 cohort of 127,324 adult HD patients using 11 categories of BMI. We examined baseline, time-averaged, and time-varying BMI using multivariable adjusted Cox models, as well as an MSM considering time-varying BMI and time-dependent confounders.

Results: In all four models, BMI showed a linear incremental inverse association with all cause-mortality. In MSM analyses, compared to a BMI of 25-27.5, BMI<18 was associated with a 83% higher risk of mortality (HR 1.83, 95% CI 1.48-2.26), whereas the mortality risks were significantly lower with higher BMI: HRs (95%CI) 0.84(0.72-0.98), 0.80(0.69-0.93), 0.71(0.58-0.87), 0.56(0.40-0.78), and 0.55(0.36-0.81) for BMI ranges of 27.5–<30, 30–<35, 35–<40, 40–<45, and ≥45, respectively. The greatest survival advantage of higher BMI was observed with a BMI range of 40–<45 in MSM.

Conclusions: The linear inverse relationship between BMI and all-cause mortality is robust across models including MSM analyses that more completely account for time-dependent confounding and potential selection biases.

Funding: NIDDK Support, Private Foundation Support

SA-PO223

Association of Cholesterol and Mortality in Hemodialysis Patients: A Joint Model Analysis. Megha Mahendra Doshi,1 Elani Streja,1 Connie Rhee,1 Allen R. Nissen,2 Csaba P. Kovesdy,1 Kamyar Kalantar-Zadeh.1

Background: Earlier data has shown a paradoxical linear inverse association with cholesterol levels and mortality in hemodialysis (HD). However, these data did not account for the random effects variance covariance matrix. All models were adjusted for case-mix and malnutrition and inflammation (MICS) covariates.

Results: Baseline cholesterol showed a linear inverse association with mortality. When examining a time-dependent or time-averaged model, the pattern of association reverses direction. In joint model analyses, we observed a decreasing linear trajectory 0.98 for cholesterol over time, and an 18% mortality increase.

Conclusions: The linear relationship between cholesterol and mortality is no longer inverse after accounting for cholesterol time variations. Further studies are needed to examine the relationship between change in cholesterol and mortality over time.

Funding: NIDDK Support, Private Foundation Support

SA-PO224

Age and Gender Variations in the Management of Renal Disease in South India: An Epidemiological Experience from State Sponsored Insurance Programme. Devaraju Sree Bhushan Rau, Nephrology, Nizams Institute of Medical Sciences, Hyderabad, Andhra Pradesh, India.

Background: There is no major epidemiological study done in India based on insurance data especially among those with various kidney diseases. The government of Andhra Pradesh has sponsored a free, cash less Health Insurance programme called Aarogyasri (AS) to cover all the people below the poverty line in the state.

We aim to study the Nephrology services provided under this programme especially the age and gender variations in them.

Methods: We analysed all the patients admitted under AS for Renal disease like Acute Kidney Injury (AKI; n=9083), Chronic Kidney Disease stage V (CKD; n=14146), Nephrotic syndrome (NS; n=2951), Rapidly progressive Renal failure (RPRF; n=1785), maintenance hemodialysis (MHD; n=11158) and renal transplantation (Tx; n=737) was between April 2007 to July 2012.

Results: Younger patients (<40yrs) constitute nearly 40% Patients of AKI, CKD and MHD were majorly between 40-60 yrs. RPRF was common between 20—40 yrs of age. NS was seen predominantly before 20 yrs (45%). Tx was not a preferable choice for many and majority continued on MHD. Nearly 70% of the patients of Tx group were less than 40 yrs. Less than 10% of patients on MHD were > 60 yrs. Only one third of patients in AKI, CKD and MHD groups were females. Tx was opted for males only and 80% of the Tx patients were males.

Conclusions: 40% of patients with kidney disease were young (<40 yrs) and is male preponderant. MHD was the preferred modality and Tx was not opted by many. Further analysis of this largest epidemiological study on renal diseases would help in planning preventive and treatment strategies at national level.

Funding: Government Support - Non-U.S.
Methods: To describe longitudinal outcomes of patients with CKD managed in a metropolitan Australian Renal Unit through a registry of all consenting patients in public renal care in G retired. At 10,180, CKD among the public eligible cohort was 10%. CKD 6.5% outcomes were documented for the patients who was followed renal clinic at the RBBW over the first year after their recruitment to the CKD.QLD registry. This analysis 46.7% of prevalent CKD patients at RBBW had consented and 612 were enrolled for at least 12 months.

Results: After ≥12 months, of these 612 patients, 32 had started RRT (5.4%), 14 had died (2.3%), all prior to start of RRT (if planned), and 12 had been discharged or transferred. Cause of death was ESRD (4%), cardiovascular (5), malignancy (5), other/unknown (2).

29% of these 612 patients (47%) had at least one complication, with a range of diagnosis from 1 to 25 episodes, and a median of 2. They had a total of 919 hospital episodes, with length of stay (LOS) ranging 1 to 95 days, mean LOS of 10.9 days and total LOS of 3110 days. Admitting units were renal (26.7%), general medical (22%), surgical (18.1%), specialist medical (12.1%), urology (17.9%), vascular (3.3%) and “others” (9.9%).

29% of hospitalised CKD patients, (13.6% of the total eligible cohort) generated 65% of admissions, LOS and costs. This group of 83 frequent and heavy users accounted for 602 admissions, 2035 bed days and AUD$1,523,130.51 of costs over the 1 year period. Their mean age was 65.9 years, 50% were female and they most commonly CKD Stage 4 (33.7%). A higher proportion had CKD Stage 5 (18% vs 8.5%) and diabetic nephropathy (12% vs 5.7%). A higher proportion had CKD Stage 5 (18% vs 8.5%) and diabetic nephropathy (12% vs 5.7%).

Discussion: The hospitalisations and costs are considered with most generated by a subset of frequent heavy users. Further definition of this subset is required.

Funding: Government Support - Non-U.S.

SA-PO228

N-Terminal Pro-Brain Natriuretic Peptide Is A Novel Valuable Biomarker For Progression of CKD Patients: A Longitudinal Follow-Up Study

Yoshiko Shirahama, 1 Koji Hidetoshi, 1 Kyoko Taniyama, 1 Yoshinori Inoue, 1 Yoshinori Iinagiuchi, 1 Masayuki Ishihara, 1 Taro Horino, 1 Kenji Yuasa, 2 Shigeko Yamanaka, 3 Tetsuro Sugiyara, 1 Yoshio Terada. 1 Endocrinology, Matabolism and Nephrology, Kochi Medical School; 2Kochi-Takasu-Hospital; 3Laboratory Medicine, Kochi Medical School.

Background: N-terminal pro-brain natriuretic peptide (NTpro-BNP) is known as a diagnostic and prognostic biomarker of cardiac events. Recent report showed that cardiac-renal interaction is an important problem in chronic kidney disease (CKD) patients. However, few longitudinal follow-up studies have been reported to evaluate NTpro-BNP as a biomarker for renal progression. Accordingly, we elucidated the relationship between NTpro-BNP and renal function in CKD patients.

Methods: Alongitudinal follow-up study for 24 months was performed in 318 consecutive CKD patients in Kochi medical school. The patients classified into 6 groups: CKD stages 1-4, Stage 5 for those still not on or initiated hemodialysis for ≥3 months, Stage 5D for patients undergoing hemodialysis for ≤3 months. Prediction of NT-proBNP was positively correlated to creatinine (P=0.001: r=0.437), age (P=0.05: r=0.136), uric acid (P=0.05: r=−0.170) and phosphorus (P=0.001: r=0.379) and negatively to estimated glomerular filtration rate (eGFR) (P=0.001: r=−0.306), hemoglobin (P=0.01: r=−0.380) and albumin (P=0.001: r=0.280). NTpro-BNP level in patients with heart failure was higher than those without (P<0.001).

Conclusion: We approved by the Kochi Medical School review board. All patients provided written informed consent.

Results: The serum level of NTpro-BNP was positively correlated to creatinine (P=0.001: r=0.437), age (P=0.05: r=0.136), uric acid (P=0.05: r=−0.170) and phosphorus (P=0.001: r=0.379) and negatively to estimated glomerular filtration rate (eGFR) (P=0.001: r=−0.306), hemoglobin (P=0.01: r=−0.380) and albumin (P=0.001: r=0.280).

Conclusion: In our study, NT-proBNP showed a positive correlation with the decline rate of eGFR. Thus, NT-proBNP might be an useful biomarker to predict the progression of CKD patients.

SA-PO229

Hyperuricemia Is a Risk Factor for the Progression to ESRD in Biopsy-Proven Benign Nephrosclerosis

Hiroaki Suzuki, 1 Tomomi Endo, 1 Tatsuo Tsukamoto, 2 Eri Muso. 1 Dept of Nephrology and Dialysis, Tazuke Kofukai Medical Research Institute Kitano Hospital, Osaka, Japan; 2Graduate School of Medicine, Kyoto Univ.

Background: End stage renal disease due to benign nephrosclerosis is increasing in Japan. Diagnosis of benign nephrosclerosis is usually made based on existence of hypertensive organ damages (hypertensive retinopathy, cardiac hypertrophy etc) without renal biopsy. However, little is known about clinical characteristics and prognostic factors in biopsy-proven benign nephrosclerosis.

Methods: We selected 42 cases which were diagnosed by renal biopsy as having benign nephrosclerosis. Clinical and histological parameters and prognostic factors were investigated retrospectively.

Results: Clinical characteristics at renal biopsy were male to female ratio: 76.1%, age: 59.8±10.6 years, BMI: 24.9±5.0kg/m², hypertensives: 80.9%, hypercholesterolemia: 50%, diabetes: 14.2%, hyperuricemia: 73.8%, and smoker: 52.5%. Laboratory data were urine protein excretion: 0.57±1.2g/day, occult blood: 26.1%, serum creatinine: 1.25±0.5mg/dl, and uric acid: 6.93±1.6 mg/dl. Among these patients, 22 cases (male 168.1%) who could be followed more than 2 years (mean observation period, 3.2 years) were analyzed. Mean decline of eGFR in these patients was -2.95±4.4 ml/min/yr. Four patients showed more than -5ml/min/yr (rapid decline) and 1 patient reached end stage renal disease in 5 years. Existence of occult blood and hypertension were related to rapid decline (RR 2.7, 95%CI:1.060, 6.880 and RR 2.0, 95%CI:1.260, 3.174, respectively). Blood pressure and urinary protein excretion trended to be higher in rapid decline but not significant (149.5±17.8/5.6±12 vs 121.5±34/7.2±22 mmHg p=0.069 and 2.5±3.5 vs 0.4±0.5 g/day p=0.323, respectively). Histological examination indicated that adhesion of glomerular tuft to Bowman’s capsule was related to rapid decline (p=0.042), but rate of global sclerosis was not significant (p=0.095).

Conclusions: Hyperuricemia, occult blood, and adhesion were related to rapid decline of eGFR in biopsy-proven benign nephrosclerosis patients. There might be a possibility that hyperuricemia was related to formation of adhesion.

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

Underline represents presenting author/disclosure.
SA-PO230

Inter Study and Inter-Operator Variabilities of CMR-Derived LV Mass Measurements in CKD Patients Ketan Kanji Vekaria,1 Nihit Chitalia,2 Debashis Banerjee,3 David Goldsmith.1 3School of Medicine, King’s College London, London, United Kingdom; 1Nephrology, Guy’s and St. Thomas’ NHS Foundation Trust, London, United Kingdom; 2Nephrology, St. George’s Healthcare NHS Trust, London, United Kingdom.

Background: Patients with CKD have increased risk of mortality from Cardiovascular Disease (CVD). We are conducting the SCVitaminD RCT with LVM cardiac remodelling as an endpoint. To validate the use of a small study population - ideal for a complex intervention such as this - we needed to use a cardiac imaging technique that was precise and accurate.

Methods: Subjects were imaged on a 1.5T Philips Intera MRI Scanner with 32 channel cardiac coil to obtain short axis stack (30 cardiac phases). Analysis was carried out on a Viewforum workstation (Philips Healthcare) by delineating the diastolic LV endocardial and epicardial borders. (a)5 patients were scanned twice using the same CMR protocol. Patients were scanned and then re-scanned again 10 mins later. Analysis was performed by the same observer twice. (b)16 patients on the SCVitaminD study were analysed for LV mass using the same CMR analysis protocol by 2 independent observers.

Results:

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean SD LVM</th>
<th>Mean SD LVM 2</th>
<th>Difference of mean (g)</th>
<th>Standard Deviation of mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter study</td>
<td>120.40±18.1</td>
<td>133.12±17.6</td>
<td>12.72</td>
<td>18.06</td>
</tr>
<tr>
<td>Inter operator</td>
<td>115.45±18.0</td>
<td>130.14±17.5</td>
<td>14.69</td>
<td>20.01</td>
</tr>
</tbody>
</table>

Conclusions: The average discrepancy between the two LVM measurements was 7.43g, which is both small, and below the threshold of clinical significance for this study. These data validate our choice of CMR over echocardiography as the imaging technique for our study.

SA-PO231

Screening for Kidney Disease among Pre-Term and Low Birth Weight Children in Jalisco, Mexico Jose Raul Reyna Raygoza,1 Ricardo Martinez,2 Laura Lopez,3 Katia Valenzuela,1 Alfonso Gutierrez Padilla,1 Eusebio Angulo,2 Susan M. Samuel,1 Guillermo G. Garcia.1 1Div of Nephrology, Hospital Civil de Guadalajara, Mexico; 2Univ of Calgary, Canada; 3Dept of Pediatrics, Hospital Civil de Guadalajara, Mexico.

Background: Pre-term infants (<37 weeks gestation) or low birth weight infants (<2500 grams) are at risk of developing hypertension and chronic kidney disease later in life. We sought to examine the prevalence of hypertension, albuminuria and either reduced estimated glomerular filtration rate (eGFR) or hyperfiltration among low birth weight or pre-term infants born in Jalisco, Mexico.

Methods: We evaluated records of all patients born at the Guadalajara Civil Hospital and those hospitalized in the Neonatal Intensive Care Unit during 1995-2010 with biopsy proven MN. Enrolled patients were followed up for a median of 38.35 (32.98, 44.76) months. A logrank test indicated that segmental glomerulosclerosis is associated with the poor outcome of these patients (P=0.01).

Results: A COX regression model indicated that segmental glomerulosclerosis increased the risk of chronic renal injury by 6.39 times (95% CI, 1.28, 31.95). The other parameters did not correlate to clinical outcomes.

Conclusions: This cohort study suggested that segmental glomerulosclerosis in Oxford IgAN classification is associated with the poor outcome of IgAN patients.

SA-PO232

Segmental Glomerulosclerosis in Oxford IgAN Classification Is Associated with the Poor Outcome of IgAN Patients: A Cohort Study of 240 Cases Pin Zhou,1 Yongjun Wang,2 Yi Lin,2 Hongyu Chen.1 Dept of Nephrology, Hangzhou Hospital of Traditional Chinese Medicine (Guangxing Hospital), Zhejiang Chinese Medical Univ, Hangzhou, Zhejiang, China.

Background: To investigate the parameters in Oxford IgAN classification associated with the outcome in a cohort of 240 Chinese patients. A total of 240 patients with biopsy proven IgAN and CKD stage I-4 were enrolled. Renal clinical and histopathologic parameters according to Oxford IgAN classification were assessed. A Kaplan-Meier survival analysis was performed to compare the survival rate. A Cox proportional hazard model was adopted to test the independent prognostic value of clinical parameters and pathological parameters. The primary outcome of chronic renal injury was defined as the serum creatinine increased to 1.5 times of baseline.

Results: Enrolled patients were followed up for a median of 38.35 (32.98, 44.76) months. A logrank test indicated that segmental glomerulosclerosis is associated with the poor outcome of these patients (P=0.01).

Conclusions: This cohort study suggested that segmental glomerulosclerosis in Oxford IgAN classification is associated with the poor outcome of IgAN patients.

SA-PO233

Outcome of Renal Biopsy Proven Membranous Nephropathy Receiving Immunosuppressive Therapy: Muhammad Akhtar,1 Ibrahim Sharp,2 Katie Ht Wong,2 Mona Wahba.1 1Dept of Renal Medicine, St. Helier Hospital, Surrey, United Kingdom; 2Dept of Medicine, St. Peter Hospital, Surrey, United Kingdom.

Background: Membranous Nephropathy (MN) is the commonest cause of nephrotic syndrome in adults. Previous studies looked at progression of MN in patients having immunosuppressive therapy versus no immunosuppressive therapy.

Methods: Single centre retrospective study from 1995-2010 with biopsy proven MN. Data points of urine protein creatinine ratio (UPCR in mg/mmol), baseline eGFR at 2, 5 and 10 years following the initial renal replacement therapy (RRT) and patient survival. Immunosuppression regimens were: Prednisolone alone (P) and/or Cyclophosphamide (P+CYP). Those on Modified ponticelli were included in the P+CYP group. Those on maintenance therapy were on a combination of P+ Azathioprine(AZA) or P+ Mycophenolate mofetil(MMF).

Results: 48/125 were immunosuppressed. 18/48 were given P, 22/48 P+CYP, 4 P+MMF, 3 P+AZA, 1 MMF. All patients received angiotensin converting enzyme inhibitors (ACEI) or Angiotensin 2 receptor blockers (ARB) and a statin. 27 male, 22 female with median age of 60 years in P and 54.5 years in P+CYP group. UPCR was significantly lower at 5 years from baseline with P therapy (p<0.01), contrary to those in the P+CYP who showed no significant difference in UPCR at 2 and 5 years (p=0.05, p=0.01, respectively).

Conclusions: There is no difference in Cr or eGFR over time in either group. A trend in declining eGFR was seen over 10 years with P. The improvement in albumin from baseline continued over 2, 5 and 10 years (p<0.05) with no difference between the two groups following the initial significant decline in cholesterol from baseline. Those treated with P show a significant improvement in Albumin at 2 and 5 years (p<0.01) with a greater level of significance in
Quo Vadis? Plasma Exchange and Intravenous or Oral Cyclophosphamide in Dialysis-Dependent ANCA-Associated Vasculitis

Wladimir M. Szpir,1 Elizabeth Krausz,2 Martin Eggli.1 *Nephrology, Rigshospitalet, Denmark. †Nephrology, Herlev Hospital, Univ of Copenhagen, Copenhagen, Denmark.

Background: Salama et al. published in JASN (2013,Nov 15) results on 41 ANCA Associated Vasculitis (AAV) patients (pts) requiring dialysis on admission, who were treated with Plasma Exchange (PLEX), standard prednisolone 1 mg/kg/day (STOCs), IV CYC (IVCYC) (6-10 pulses given over 13 weeks; 7.5 - 12.5 mg/kg depending on age). Their mortality and dialysis dependency at 3 and 12 months were superior to and compared with MPEXP oral CYC (ORCYC) arm (2.5 mg/kg daily). The total doses of IVCYC given were 2.96-7.38 g, whereas MEPEXP pts. received up to 15-16 g in cumulative CYC dose. Their mortality and dialysis dependency at 3 and 12 months were superior to and compared with MEPEXP oral CYC (ORCYC) arm (2.5 mg/kg daily). The total doses of IVCYC given were 2.96-7.38 g, whereas MEPEXP pts. received up to 15-16 g in cumulative CYC dose.

Methods: We analysed this report in connection to a subgroup of 39 HD pts -out of 132 AAV pts referred to our centre between 2000-2010 and treated in 105 pts by 7 PLEX sessions, low ORCYC regimen (1.5 mg/kg/day < 65 years, 0.75 mg/kg/day > 65 years) and 39 STOCs. Totally our pts received a estimated cumulative CYC dose of 4.75 g for older and 9.5 g for younger pts. Azathioprine or mycophenolate mofetil was given for maintenance of remission after 4 months.

Results: At 3 months of IV CYC treated and 3 pts in our low ORCYC cohort died, 12 pts were dialysis dependent compared to our 8 low ORCYC pts. At 1 year 13 IVCYC pts remained dialysis dependent, whereas 13 in of 39 our pts were on dialysis at 12 months. Patient survival in ORCYC cohort at 3 years was 72% (95% in no HD group) and 53% (95% in no HD group). Kidney survival in IVCYC cohort was 53% at 3 years (95% in no HD) and 40% (80% in no HD group) at 5 years. 11 were 2.96-7.38 g, whereas MEPEXP pts. received up to 15-16 g in cumulative CYC dose. 11 were 2.96-7.38 g, whereas MEPEXP pts. received up to 15-16 g in cumulative CYC dose. 11 were 2.96-7.38 g, whereas MEPEXP pts. received up to 15-16 g in cumulative CYC dose.

Conclusions: In our opinion low oral CYC induction regimen is not inferior to IV CYC in HD dependent AAV pts, when combined with PLEX and STOCs.

Epidemiology of Cardiovascular Mortality in Patients with Chronic Kidney Disease and Cardiac Disease: A Retrospective Cohort Study

Navneet Kumar,1 Peter A. McCullough.2 *Cardiology, St. John Providence Health System, Novi, MI. †Nephrology, Herlev Hospital, Univ of Copenhagen, Copenhagen, Denmark.

Background: Chronic kidney disease (CKD) patients, particularly end-stage renal disease (ESRD) have higher mortality than those without renal dysfunction. Estimated glomerular filtration rate (eGFR) and mortality have an inverse relationship. ESRD patients have 50% higher mortality at 1 year and 40% at 5 years.

Methods: We obtained data on 106 consecutive stroke cases from the hospital in-patient stroke portal. Demographic information, RRS components, presenting creatinine & eGFR were collected. RRS calculated as follows: Age (years) + 5 (if female) + 5 (if diabetic) + 10 (if using insulin) + (10 if history of hypertension). The diagnostic value of RRS for predicting the presence of CKD was measured using sensitivity, specificity, and receiver operator characteristic (ROC) curves. Statistical analysis performed with SPSS Version20.

Results: Data from N=101 (45 male) patients were analysed. Average age: 70.02 years. 92/101 (91%) patients had acute ischaemic events, 8/101 (7.9%) were haemorrhagic. Average RRS: 81.28 (30-113). The prevalence of moderate (CKD stage ≥3) and severe (CKD 4&5) renal impairment was 31.68% and 3.96% respectively. Using a ROC curve the diagnostic value of an RRS as a tool to predict CKD ≥3 or greater was AUROC 0.738 (p<0.0001). A cut-off value of 82.5 maximum sensitivity (84.5%) and specificity (75%). In a subgroup analysis of CKD≥5 patients, a RRS score >82.5 was associated with a sensitivity and specificity of 75% and 45.8% respectively.

Conclusions: Moderate to severe renal impairment is common in this population. The RRS is a useful tool in assessing for this at initial presentation. A cut-off score of >82.5 was most useful in our study population.

The Use of a Previously Validated Renal Risk Score in an Irish Cohort of Stroke Patients

Caitriona M. McEvoy,1 Sean Murphy,2 *Nephrology Dept, Mater Misericordiae Univ Hospital, Dublin, Ireland; †Stroke Dept, Mater Misericordiae Univ Hospital, Dublin, Ireland.

Background: Patients presenting with a suspected cerebrovascular accident undergo emergency CT scanning to identify those suitable for thrombolysis. Imaging often involves administration of iodinated contrast, incurring the risk of contrast induced nephropathy (CIN) in those with underlying renal dysfunction. Scans are performed emergently, frequently without knowledge of the patient’s renal function. A 5-point Individual Renal Risk Score (RRS), aiming to identify patients with acute stroke at highest risk of CIN, in the absence of an available estimated glomerular filtration rate eGFR) was recently described (Vergouwen et al). We examined the potential of the RRS to identify significant renal impairment in these CKD patients who are not on dialysis.

Methods: We obtained data on 106 consecutive stroke cases from the hospital in-patient stroke portal. Demographic information, RRS components, presenting creatinine & eGFR were collected. RRS calculated as follows: Age (years) + 5 (if female) + 5 (if diabetic) + 10 (if using insulin) + (10 if history of hypertension). The diagnostic value of RRS for predicting the presence of CKD was measured using sensitivity, specificity, and receiver operator characteristic (ROC) curves. Statistical analysis performed with SPSS Version20.

Results: Data from N=101 (45 male) patients were analysed. Average age: 70.02 years. 92/101 (91%) patients had acute ischaemic events, 8/101 (7.9%) were haemorrhagic. Average RRS: 81.28 (30-113). The prevalence of moderate (CKD stage ≥3) and severe (CKD 4&5) renal impairment was 31.68% and 3.96% respectively. Using a ROC curve the diagnostic value of an RRS as a tool to predict CKD ≥3 or greater was AUROC 0.738 (p<0.0001). A cut-off value of 82.5 maximum sensitivity (84.5%) and specificity (75%). In a subgroup analysis of CKD≥5 patients, a RRS score >82.5 was associated with a sensitivity and specificity of 75% and 45.8% respectively.

Conclusions: Moderate to severe renal impairment is common in this population. The RRS is a useful tool in assessing for this at initial presentation. A cut-off score of >82.5 was most useful in our study population.

Serum Cystatin c (CyC) Has a Significant and Negative Correlation with Kidney Function in Patients with Chronic Kidney Disease (CKD)

Patients Hirotsugu Iwata,1 Yusuke Sakaguchi, Hiroaki Kawabata, Ryohei Yamamoto, Hiromi Rakugi, Yoshitaka Isaka. Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

Background: Serum creatinine (Cr) is a marker of renal function, but is affected by muscle volume or renal tubular excretion. Unlike Cr, CyC has been reported to be an excellent marker of renal glomerular filtration rate (GFR). Although serum CyC has been regarded as a mere marker of GFR, CyC has a physiological activity of cytokine protease inhibitor and, therefore, potentially affects antigen presentation in antigen presenting cells such as dendritic cells. It is also well known that immune function is impaired in patients with decreased GFR. We assessed an association between CyC and lymphocyte count in patients with CKD in the predialysis stage.

Methods: The present cross-sectional study included 71 hospitalized CKD patients in the department of nephrology in Osaka University Hospital between April 2012 and May 2013. Because of its skewed distribution, lymphocyte count was normalized by logarithmic transformation. Associations between lymphocyte count (log10 n/ml) and CyC (Cr or gGFR) were assessed in multivariate linear regression models adjusting for clinically relevant factors, including age, sex, and total cholesterol.

Results: In univariate models lymphocyte count were significantly associated with consecutive stroke patients at our institution.

P+CYP treatment produced a significantly sustained reduction in UPCR and improving albumin over 10 years.

SA-P0234

SA-P0235

SA-P0236

SA-P0237

SA-P0238

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

Underline represents presenting author/disclosure.
SA-PO239

**GFR Decline as an Alternative Endpoint for Clinical Trials in CKD – A Meta-Analysis of Individual Associations from Randomized Trials: Report of an NKF-FDA Workshop**

Hiddo Jan Lambers Heerspink,1 Hocine Tighiouart,2 Yingying Sang,1 Shoshana Ballew,1 Kunihiro Matsushita,3 Josef Coresh,1 Andrew S. Levey,2 Lesley Inker,2 Andrew S. Levey,2

1UMC Groningen, Netherlands; 2Tufts Medical Center, Boston; 3Johns Hopkins, Baltimore.

Background: ESRD and doubling of serum creatinine (2XScr) are established clinical endpoints for CKD progression. However, a Scr doubling (57% decline in eGFR) is generally a late event in CKD. Alternative endpoints defined by lesser eGFR declines may reduce trial duration and increase feasibility of trial conduct. As part of an evaluation of these endpoints, we describe the associations of a GFR decline with subsequent development of clinical endpoints.

Methods: Using a pooled dataset of 12821 patients from 43 clinical trials, we assessed the association between a 20%, 30%, and 40% decline in eGFR from baseline to month 12 with subsequent development of an established endpoint (EE) of dialysis, GFR <15 or 2XScr. Cox analyses were performed within study, followed by random effects meta-analyses, and were adjusted for age, sex, race, baseline eGFR, proteinuria, and blood pressure, and diabetes. Meta-regression was used to explore baseline eGFR, proteinuria, and intervention treatment as potential source of heterogeneity.

Results: Over a median follow-up of 2.0 [IQR 1.2–3.1] years, 2661 EE were observed after the 1-year baseline period. A strong linear association was observed between eGFR decline and subsequent EE (Figure 1). Hazard ratios of EE for 20%, 30%, or 40% decrease in eGFR were 4.5, 9.6, and 20.3, resp. The associations were consistent regardless of baseline eGFR, proteinuria, disease aetiologies, and treatments.

Conclusions: These analyses provide some support that changes in eGFR lesser than 57% can be used as alternative endpoints for trials of CKD progression.

SA-PO240

**Association of Urinary Biomarkers of Kidney Injury with All-Cause Mortality and Cardiovascular Events: The Health Aging and Body Composition (Health ABC) Study**

Mark J. Sarnak,1 Ronit Katz,2 Anne B. Newman,3 Tamara Harris,4 Carmen A. Peralta,5 Prasad Devarajan,6 Michael R. Bennett,6 Linda F. Fried,7 Joachim H. Ix,8 Suzanne Satterfield,9 Eleanor Marie Simonsick,1 Chirag R. Parikh,9 Michael Shlipak,9 Tufts Medical Center,1 Univ of Washington,2 Univ of Pittsburgh,3 NIA,4 UCSF,5 Univ of Cincinnati,6 UCSD,7 Univ of Tennessee,8 Yale Univ.

Background: Kidney damage is a common sequel of several chronic pathologic conditions. Whether biomarkers of different forms of kidney damage are prognostic for cardiovascular disease (CVD) and all-cause mortality is unknown.

Methods: We measured three urinary biomarkers, kidney injury molecule (KIM) 1, IL-18, and urinary albumin in 3010 individuals enrolled in the Health ABC. KIM-1, IL-18 and albuminuria were all standardized to urine creatinine. Cox proportional hazards were used to investigate the associations of quartiles of urinary KIM-1/cr, IL-18/cr and albumin/cr (ACR) with all cause mortality and CVD. Multivariable models adjusted for demographics, traditional CVD risk factors, and estimated glomerular filtration rate.

Results: Mean age was 74 years, 49% were men, and 41% black. There were 1450 deaths and 797 CVD outcomes during a median follow up of 12.4 years. KIM-1/cr had a modest association with mortality, while the association of ACR with mortality was stronger and more linear. In similar analyses only ACR showed an association with CVD.

Conclusions: Urinary KIM-1 had a modest, independent association with all-cause mortality but not CVD, while urinary IL-18 showed no association. In contrast, albuminuria was strongly and independently associated with all cause mortality and CVD. Future studies should evaluate reasons for differences in the prognostic importance among kidney injury markers.
SA-PO242

State Variation in Awareness of Chronic Kidney Disease in the United States
Sai Hurrish Dharmarajan,1 Hal Morgenstern,1 Neil R. Powe,2 Delphine S. Tuot,2 Rajiv Saran.1 1Univ of Michigan, Ann Arbor, MI; 2Univ of California San Francisco, San Francisco, CA.

Background: Although low awareness of chronic kidney disease (CKD) in the US has been reported, the extent of geospatial variation in CKD awareness is unknown. We estimated state-level awareness and examined variation across the continental US.

Methods: Using 2011 Behavioral Risk Factor Surveillance System (BRFSS) data, we identified adults who reported being told they have “kidney disease”. Although the BRFSS provides state-level data on self-reported CKD, there is no clinical/lab information to serve as the “gold standard” for identifying who actually has CKD. To deal with that limitation, we estimated CKD awareness in each state indirectly by comparing—as a ratio—the observed prevalence of self-reported CKD in the BRFSS sample to the prevalence predicted from clinical data in the 2005-06 National Health and Nutrition Examination Survey (NHANES), using a logistic model adjusting for age, sex, race/ethnicity, hypertension status, and diabetes status. CKD in NHANES was defined as MDRD eGFR <60 mL/min/1.73m2 or urinary albumin:creatinine ratio >30mg/g. We also compared estimated CKD awareness by category of age, race/ethnicity, sex, hypertension, and diabetes status.

Results: The state-specific prevalence of self-reported CKD ranged from 2% in Iowa to 24% in Arizona. The predicted prevalence of CKD ranged from 4% in Arkansas to 9% in Florida. Estimated CKD awareness in the US was 34%, and it ranged from 17% in Iowa to 61% in Arkansas. Overall CKD awareness in the US was higher in adults with self-reported diabetes (40%), non-Hispanic blacks (64%) and adults less than 65 years of age (96%).

Conclusions: The prevalence of self-reported CKD is low throughout the US, reflecting a low level of awareness that appears to vary appreciably across states and by category of major CKD risk factors. A method for indirectly estimating CKD awareness, perhaps improved by incorporating state variation, could be applicable in CKD surveillance programs to study CKD awareness.

Funding: Other U.S. Government Support

SA-PO243

Quality of Care of Chronic Kidney Disease in a Community Practice
Pradeep Arora,1 Brian M. Murray,1 Cheston H. Fox,2 Robert N. Anderson,2 Rocco C. Venuto.1 Medicine, VAMC, Buffalo, NY; 2Medicine, Univ of Buffalo, Buffalo, NY; 3Computer Task Group, Buffalo, NY.

Background: Chronic kidney disease (CKD) is a major public health problem in the United States. There is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. Kidney disease is the ninth leading cause of death in United States. Data from United States Renal Data System (USRDS) indicates that there has been a 104% increase in the prevalence of chronic renal failure (CRF) between the years 1990-2002. There is an even higher prevalence of earlier stages of CKD. We aimed to study the prevalence and resource utilization of CKD in Western NY.

Methods: We analyzed data collected from 4.8 million claim records which included claims on >30,000 CKD patients from local payers and providers between 2006 and 2010. Patient demographics (age, gender), lab data and outcomes (hospitalization, ESRD, cardiovascular events and death) were captured from this data base. CKD was defined as per NKF-KDOQI guidelines.

Results: Mean age of the patients was 69.2±15.3 SD, 50.4% were male, 54% were above age of 70 years. 94% of patients with CKD had hypertension, and 55% had diabetes. Urine albumin/creatinine, in-morning available in only 25% of the patients with CKD. As per diagnostic code for CKD,7028 had stage 3, 1592 stage 4, 244 stage 5 and 1428 were ESRD. The remainder were coded as CKD without stage.17% of patients with advanced CKD (stage 4 and 5) were not seen by a nephrologist. Only 5.7% of patients had AV fistula prior to initiation of dialysis and 22% required extensive hospital initiated dialysis.

Conclusions: More than 3/4 of patients with stage 4 CKD were seen by nephrologist. However AV fistula rate prior to start of dialysis was dismal. These data allows specific focus on regional deficiencies in CKD care that could be addressed and improve outcomes. The success of quality improvement programs can be evaluated by analysis of future claim based data.

SA-PO244

Enhancing ESRD Risk Prediction Using Age Based Risk Calculation in Stage 4 CKD
Shayan Shirazian, Candace D. Grant, Joseph Mattana. Medicine, Winthrop Univ Hospital, Mineola, NY.

Background: Accurate ESRD risk prediction is essential in identifying patients who will require preparation for renal replacement therapy as well as low risk patients who are unlikely to reach ESRD in whom such preparation should be avoided. Stage based risk classification may overestimate risk especially in some older patients. In this study we applied a validated risk calculator, which incorporates age, to determine the frequency with which ESRD risk may be overestimated in a CKD-4 population.

Methods: In this cross-sectional study, the electronic health records of patients with CKD-4 seen in our nephrology practice were reviewed. Variables necessary for ESRD risk prediction were extracted, including age, sex, glomerular filtration rate (GFR), spot urine albumin to creatinine ratio, calcium, phosphorus, albumin, and bicarbonate. All CKD-4 patients are designated as very high risk according to KDIGO guidelines. Two year estimated risk of progression to ESRD was calculated using a risk calculator developed and validated by Tangri et al (JAMA 2011;305(15):1533-9). Patients were considered to be low risk to for progression to ESRD if their 2 year calculated risk was <10%.

Results: Two hundred and four records were reviewed and 85 patients met study criteria. The average age was 69.8 years, 61% were male, 74% were white and the average GFR was 22 mL/min/1.73m2. The average 2 year calculated ESRD risk was 19%. Despite their all being deemed very high risk based on stage, 41% of patients were found to be low risk using the risk calculator. Further analysis of the low risk subgroup revealed a mean age of 78±13,which was significantly older compared to the remainder of the population (65.1±15.4, p< 0.01). Other variables including age, gender and race were not significantly different between the groups.

Conclusions: Using an age-based calculator, a substantial proportion of patients with CKD-4 were found to be at low risk for progression to ESRD over 2 years. These patients were at least 2 drinks/day of soft drink is associated with incidence of diabetes (40%), non-Hispanic blacks (64%) and adults less than 65 years of age (96%).

SA-PO245

Traditional Risk Factors Predict Renal Outcomes in Cancer Patients with Chronic Kidney Disease

Background: Cancer patients have a high prevalence of chronic kidney disease (CKD). The aim of this study was to assess prognostic factors for kidney failure and CKD progression.

Methods: Among 350 outpatients with cancer referred to nephrology evaluation (2009-12) 173 had CKD according KDIGO definitions and at least 3 months of follow up. Clinical and biochemical data were retrieved from patient medical records. The primary endpoint was defined as kidney failure (eGFR < 15 mL/min/1.73m2, CKD-EPI formula). Rapid CKD progression (sustained decline in eGFR of more than 5mL/min/1.73 m2/yr) was defined as the secondary endpoint.

Results: Patients baseline characteristics and outcomes data are shown in Table 1. Results are expressed as mean±SD and percentage.

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

682A
SA-PO247

RAS Blockade in Diabetic Patients with Renal Dysfunction in China
Chuanming Hao,1 Qionghong Xie,1 Dayi Hu,2 Dani Zhang.3
1Div of Nephrology, Huashan Hospital. Fudan Univ, Shanghai, China; 2Peking Univ People's Hospital; 3Ytalstrategic, Research Institute.

Background: It is well documented that RAS blockade is associated with improved outcome in patients with diabetic kidney disease. This study examined the usage of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in type 2 diabetes patients (2-DM) with or without chronic kidney disease (CKD) in China.

Methods: Data from the China Cardiometabolic Registries on blood pressure, blood lipid and blood glucose in 2-DM patients (CCMR-3B Study) were used to analyze ACEI/ARB use in this population. Outpatients who had been diagnosed of 2-DM for > 6 months were recruited to this non-interventional, observational, cross-sectional study. CKD was defined as having urine albumin creatinine ratio (ACR) > 30mg/g or eGFR < 60 ml/min.

Results: A total of 25,454 outpatients from 6 regions in China (north, south, east, west, northeast and central China) were enrolled. The mean age was 63.0±11.9 yrs, 47.0% were male, 55.1% with HbA1C >7%, 63.8% with cholesterol >4.5mmol/L and 59.8% with hypertension (SBP > 130 mmHg, DBP> 80mmHg). Serum creatinine data was available in 22,628 patients, and 2258 (10.0%) had an eGFR<60ml/min. ACR was measured in 6,383 patients, and 3,231 (50.6%) of them had ACR > 30mg/g. Among hypertensive patients, 73.0% were on antihypertensive medications, and 39.7% were on ACEI/ARBs. A total of 2151 patients with hypertension had positive albuminuria, 1040 (48.3%) of them used ACEI/ARB, 22.9% used CCBs without ACEI/ARB, 7.7% used other antihypertensives and 21.1% not treated. In the non-hypertensive patients with or without albuminuria, ACEI/ARB utilizations were < 1%.

Conclusions: In diabetic patients with hypertension and albuminuria in CCMR-3B population, more than half of the patients were not treated with ACEI/ARB. This real world evidence suggest that the current treatment for diabetes with hypertension and albuminuria is sub-optimal.

SA-PO248

Classification Tree Method Analysis Related Factors of Early Renal Damage by Type 2 Diabetes Mellitus
Wenbo Zhao,1 Lin Wei,1 Hui Peng,1 Xin Liu,1 Jia-ling Rao,1 Tan-qi Lou.1
1Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ; Guangzhou, Guangdong, China; 2Neurology, The Guangdong Province Traditional Chinese Medical Hospital, Guangzhou, Guangdong, China.

Background: To explore the factors influencing classification T2DM early nephropathy by the tree model, in order to provide evidence for prevention and treatment.

Methods: The 1040 hospital patients from January 2011 to January 2013, according to eGFR and the urine albumin, divided into T2-DM group (755 cases) and early diabeto-crenalin impairment group (285 cases ). to analyze the main factors to developed to microalbuminuria by Exhaustive CHAID classification tree.

Results: Classification tree model screened Fib, retinopathy, SBP, DPVD, gender from 34 candidate variables, related to the early renal impairment. Elevated Fib was the main influencing factor. The incidence of Fib>4.34 was 52.9%, higher than the Fib ≤ 3.30 (14.9%). Fib between 3.30 and 3.85 group (26.0%) and between 3.85 and 4.34 group (41.5%), Fib>4.34 group was high-risk group. Influencing factors screened with different fibrogen were not same, SBP, DR. Gender and DR dividedly. Fib>4.34 group with DR were higher risk, 75.0%, comparing no DR, 43.9%, Fib≤3.85 and≤4.34group, correlated with gender, the female was higher risk than male. Fib>3.30 and≤3.85 group with DR, had a higher risk; A history of DR, had a higher risk. Female without DPVD had a mean higher risk. Female without DPVD was lower risk. Fib≤3.30 group screened influence factors were SBP, Respectively the three groups were 6.5%, 18.1% and 42.5% with SBP increasing. SBP 127 to 161mmHg group, the main influencing factor was retinopathy. Compared with no retinopathy team, the incidence was higher.

SA-PO246

Prognostic Factors for Death or Palliative Care in Patients with Cancer and Chronic Kidney Disease
Elerson Costalongo, Veronica T. Costa e Silva, James Hung, Luis Yu, Emmanuel A. Burdmann. Nephrology, Cancer Institute of Sao Paulo, Brazil.

Background: Cancer patients have a high prevalence of chronic kidney disease (CKD). The aim of this study was to assess prognostic factors for death or palliative care in cancer patients with CKD.

Methods: Among 350 outpatients with cancer referred to nephrology evaluation (2009-12) 173 had CKD according KDIGO definitions and at least 3 months of follow up. Clinical and biochemical data were retrieved from patient medical records. The primary endpoints were defined as death or palliative care.

Results: After a follow-up of 17±8 m, 27% of the patients reached the endpoints. Their baseline features are shown in Table 1.

Conclusions: Traditional risk factors as baseline eGFR and albuminuria can predicted renal outcomes in cancer patients with CKD.
and markers of elevated LV filling pressure were closely related with the presence of carotid atherosclerosis. According to multivariate analysis, age, hs-CRP levels, and the ratio of early peak transmitral inflow velocity (E) to early diastolic mitral annular velocity (E') were significant determinants of carotid atherosclerosis. During the study period of 28.8 ± 16.1 months, 23 cases of adverse CV events occurred. Patients with carotid atherosclerosis showed significantly higher rates of annual cardiac event rates than those without (8.6% vs 1.5%, p < 0.001). Smoking (OR 3.13, 95% CI 1.10-9.09), increased E/E' ratio (OR 1.10, 95% CI 1.01-1.21), and the presence of carotid plaque (OR 7.80, 95% CI 1.45-45.97) were independent predictors for adverse CV events.

Conclusions: Subclinical carotid atherosclerosis was closely associated with poor prognosis in non-diabetic CKD patients. Increased age, hs-CRP, and E/E' ratio may be useful indicators suggesting the presence of subclinical carotid atherosclerosis.

SA-PO251
Clinical Significance of Subclinical Carotid Atherosclerosis and Its Relationship with Echocardiographic Parameters in Non-Diabetic Chronic Kidney Disease Patients Jwa-kyung Kim, Sun Ryoung Choi, Jong-woo Yoon, Jung-woo Noh, Sung Gyun Kim. Internal Medicine, Hallym Univ Sacred Heart Hospital, Kidney Research Institute, Korea.

Background: Risk stratification of chronic kidney disease (CKD) patients is of particular interest and the presence of subclinical carotid atherosclerosis may be a good indicator of high-risk group. We investigated long-term outcomes of subclinical carotid atherosclerosis in non-diabetic CKD patients and tried to find echocardiographic parameters suggesting the presence of subclinical carotid atherosclerosis.

Methods: As a prospective design, a total of 182 patients underwent carotid ultrasonography and Doppler echocardiography at the time of CKD diagnosis. Carotid atherosclerosis was defined as carotid intima-media thickness >1.0 mm and/or the presence of plaque.

Results: Subclinical carotid atherosclerosis was found in 99 (54.4%) patients and they were significantly older and had a higher prevalence of hypertension, increased pulse pressure, and serum high-sensitivity C-reactive protein (hs-CRP) levels than those without carotid atherosclerosis. Regarding echocardiographic results, left ventricular hypertrophy and markers of elevated LV filling pressure were closely related with the presence of carotid atherosclerosis. During the study period of 58.9 months of follow up, 1,840 (1.3%) participants were dead. Interestingly, the mortality rate of hyperfiltration group was higher than normofiltration group in both men (3.8% vs 1.6%, P<0.001) and women (1.3% vs 0.7%, P<0.001). In the survival analysis, hyperfiltration compared with normofiltration was proved to be an independent risk factor for all-cause mortality after adjustment for by age, diabetes, hypertension, body mass index, lipid profile, C-reactive protein, and serum albumin in men (hazard ratio 1.19, 95% CI 1.002-1.437, P=0.047). In contrast, hyperfiltration failed to predict mortality in women.

Conclusions: In this study, we disclose that glomerular hyperfiltration might be an independent risk factor for all-cause mortality, especially in men. The mechanism and clinical implication of glomerular hyperfiltration should be more clarified.
SA-PO252

Characteristics of Uninephric Chronic Kidney Disease (CKD) Patients

Andrew John Mallert,1,2,3 Anne Salisbury,1,2,3 Zaimin Wang,1,2 Helen G. Healy,1,2,3

George T. John,1,3 Wendy E. H. Oyo,1,3 'CKD, QLD; 1Centre for Chronic Disease, School of Medicine, Univ of Queensland, Brisbane, Queensland, Australia; 2Dept of Renal Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Queensland, Australia.

Background: CKD due to uninephria is infrequently reported. 0.9% of Australian and New Zealand patients starting renal replacement therapy (RRT) in 2011 had either “Loss of Single Kidney” (n=6) or “Congenital Renal Hypoplasia and Dysplasia” (n=20). Its frequency in the general CKD population is undefined.

Methods: To define characteristics of uninephric patients with CKD, CKD-QLD is a registry and research platform involving all consenting patients in public renal practices in Queensland (~10,800). Uninephric patients among the first 2359 enrolled were sought through Primary Renal Disease coding for nephrectomy, hypo/dysplastic, atrophic, and congenital kidneys. They were compared to all patients in the CKD-QLD registry.

Results: 136 uninephric patients were identified, or 5.8% of the total. Of these 76 (56%) had a surgical nephrectomy, 17 (12.5%) had a congenital malformation, 16 (11.7%) had an atrophic/dysplastic kidney, 13 (9.5%) had congenital single kidney, 10 (7.3%) had a functional nephrectomy, and 4 (3%) had a partial nephrectomy.

Uninephric patients in total and by subgroups were most commonly CKD Stage 3b(30%) and 4(26%). Their mean age was 64.2 years, compared to 65.5 years for CKD QLD. 47% of uninephric patients were female vs 45% of the CKD-QLD registry.

Among the 76 surgically nephrectomised patients, 6 were living kidney donors while 70 were for “other/non-living kidney donor” reasons. All living donors were female compared to 37% of the “other” group. CKD Stage 3a was most common in living donors (50%) and CKD Stage 3b most common in the “other” group (34%). Living donor mean age was 63yrs vs 67.5yrs in the “other” group.

Conclusions: There are small numbers of uninephric patients in this CKD group, though a proportion greater than represented in RRT data. They are youger that the broader CKD-QLD population and have greater prevalence in CKD stages 2 to 5. The identification of 6 living kidney donors is of concern.

Funding: Government Support - Non-U.S.

SA-PO253

Improvement in Renal Function Is Associated with Improved Outcomes after Ventricular Assist Device Implantation

Jay L. Koyner, Abhijit S. Naik. Sector of Nephrology, Univ of Chicago.

Background: Renal dysfunction is common in those with end stage heart failure including those requiring a ventricular assist device (VAD). Renal function improves following VADs in some patients although data on its impact on long-term mortality is limited.

Methods: We identified all patients who received a VAD from Jan. 2008 through Jan. 2012 at the University of Chicago and excluded subjects with ESRD and those who received pre-op renal replacement therapy (RRT). We defined Improved Renal Function (IRF) as a change in eGFR (MDRD) from baseline to day 7 of >10 ml/minute. The primary outcome was all cause mortality. The survival data was censored for cardiac transplantation and first RRT treatment. Kaplan Meier curves were then constructed and a Cox proportional hazards model was used to estimate the risk of mortality.

Results: 152 subjects were included in the cohort, 62 (41%) had baseline eGFR ≤45 ml/min/1.73m2 and 90(59%) had an eGFR > 45 ml/min. There was no difference in the number of patients who had postop AKI (RIFLE Risk) between the eGFR ≤45 and > 45 ml/min/1.73m2 groups (p=0.57). Patients with eGFR≤45 and no IRF (n=18) had an increased risk of all cause mortality [HR =2.87 (1.15,7.15) P=0.02] compared to those with an eGFR ≤45 ml/min and IRF (n=41). There was no mortality difference in patients with eGFR >45 ml/minute irrespective of their IRF status. Patients with eGFR ≤45 ml/min and IRF experienced outcomes similar to patients with eGFR > 45 ml/minute regardless of their IRF (p=0.85).

Conclusions: Patients with an eGFR ≤45 ml/min with IRF experienced outcomes on par with those who had a eGFR > 45 ml/min; these outcomes were significantly superior when compared to those with a eGFR ≤45 ml/min without IRF. The factors that impact IRF require further investigation which in turn may lead to improved VAD patient outcomes and may better identify patients who may benefit from a combined heart kidney transplant.

Funding: NIDDK Support

SA-PO254

Nephropathy in Illicit Drug Abusers – A Post-Mortem Analysis

Oliver Jung,1 Stefan Büttnner,1 Helmut Geiger,1 Kerstin U. Amann,2 Maike Julia Buechner,2 Nephrology, Goethe Univ Hospital, Frankfurt/Main, Germany; 1Pathology, Institute of Nephropathology, Friedrich-Alexander-Univ, Erlangen, Germany.

Background: Illicit drug abuse is an independent risk factor for chronic renal disease, but the pathogenic role of chronic exposure to illicit drugs and their contaminants under unsterile conditions remains unclear.

Methods: Retrospective investigation of all deceased that underwent forensic autopsy because of a suspected conjunction with illicit drug abuse between 01.01.2009 and 30.04.2011 in the Frankfurt/Main metropolitan area, Germany (3.8 million inhabitants). A total of 129 deceased were studied. Individuals were mostly Caucasian (99.2%), male (82.2%) and intravenous drug users (IVDU) (81.4%). Median age at time of death was 39 years and documented duration of drug abuse was 17 years, with the majority (87.2%) taking various drugs in parallel as assessed by toxicological analysis. Despite young age deceased had a high burden of co-morbidities, especially cardiovascular disease, liver cirrhosis and infections. Evaluation of kidneys demonstrated a broad spectrum of pathological alterations predominated by arteriosclerotic and ischemic damage, mostly mild interstitial inflammation, calcification of renal parenchyma and interstitial fibrosis/tubular atrophy, with hypertensive-ischemic nephropathy as the most common cause of nephropathy.

Interstitial inflammation (OR: 16.59, 95%CI: 3.91-70.39) and renal calcification (OR: 2.43, 95%CI: 1.03-5.75) were associated with prolonged as well as severe IVDU, whereas hypertensive and ischemic damage were associated with toxicological confirmed cocaine abuse (OR: 6.09, 95%CI: 1.27-28.44) in multivariate analysis. Neither specific glucocorticoid damage indicative for heroin- and hepatitis C related disease, e.g. FSGS or MPGN, nor signs of analytic nephropathy were found.

Conclusions: In the majority of illicit drug abusers chronic progressive renal failure is attributable to repeated insults to the kidney caused by multiple antigenic and pharmacological challenges. In addition, our data demonstrate the deleterious role of cocaine abuse in this setting by inducing hypertensive and ischemic damage, promoting progression of renal disease.

SA-PO255

How to Estimate Glomerular Filtration Rate in HIV Patients?

Corinne Isnard-Bagis,1 Laurence Pironier,2 Philippe Maksud,3 Rachida Inaoui,3 Stephanie Lallaurie,1 Nathalie I. Mbagu-lobe,1 Jerome Tourret,4 Anne Bissery,1 Alain Mallert,1 Gilbert Dery,1 Christine Kalilama,1 Sophie Teczenus du Montcel,1 1Nephrology, Groupe Hospitalier Pitie Salpetriere et Univ Pierre et Marie Curie, Paris, France; 2Biologie, Centre Hospitalier D’Avignon, Avignon, France; 3Nuclear Medicine, Groupe Hospitalier Pitie Salpetriere et Univ Pierre et Marie Curie, Paris, France; 4Rhumatology, Groupe Hospitalier Pitie Salpetriere et Univ Pierre et Marie Curie, Paris, France; 5Clinical Research Unit, Groupe Hospitalier Pitie Salpetriere et Univ Pierre et Marie Curie, Paris, France; 6Infectious Diseases, Groupe Hospitalier Pitie Salpetriere et Univ Pierre et Marie Curie, Paris, France.

Background: Chronic kidney disease is a frequent complication in the HIV population. The optimal way to estimate glomerular filtration rate (GFR) in HIV patients is not known.

Methods: 44 HIV patients were included in a transversal monocentric comparative study evaluating the accuracy of the different diagnostic tests available compared to the gold standard measurement of GFR. Adult, male, caucasian patients exhibiting an estimated (either Cockcroft or MDRD) GFR between 60 and 30 ml/min/1.73 m2 were included. Plasma creatinine dosages (Jaffé and enzymatic), urea, albumin, proteinuria, Cystatin C were obtained. GFR was estimated using Cockcroft, MDRD, CKD Epi, CKD Epikidney, and measured using isotopic Chrome51 EDTA clearance.

Results: Mean age was 62±10 with 82%-50 years, mean time from HIV diagnosis was 19±7 years. Mean BMI 23±4, with 9%-30. Prevalence of diabetes was 26%, HTA 47%. Viral load was <40 for 91% of patients and mean CD4 count was 438±195 cells/mm3. When compared GFR was 63.39±13.45 ml/min without IRF. The factors that impact GFR were assessed by MDRD and best accuracy by MDRD formulae. CKDEpi, CKDEpiKidney performed worse than the MDRD formula.

Conclusions: In HIV patients in stable immunovirologic conditions with CKD stage 3 and high prevalence of metabolic associated conditions, MDRD formula forms best although all formulae under estimate GFR. Cystatin C formulae do not perform any better.

Funding: Private Foundation Support
SA-PO256

Hyperuricemia Predicts Progression of Chronic Kidney Disease in Patients with Reduced Kidney Mass

Background: Hyperuricemia has been associated with an increase in the incidence of chronic kidney disease (CKD) in general population and with kidney disease progression in CKD patients. The aim of this study was to evaluate the role of hyperuricemia in kidney disease progression in patients with reduced kidney mass.

Methods: Three hundred thirty seven patients (182M, 155F), median age 59.8±1.7 years, being followed on an outpatient basis, were included in the study. The etiology of the reduced kidney mass was: nephrectomy in 188, kidney agenesis in 27 and kidney atrophy in 122. The median follow-up was 60 (0.16-38.97) months. The primary composite end-point was: doubling baseline serum creatinine, end stage renal disease or death.

Results: The mean reduction of GFR was 2.32 ml/min/1.73 m². Sixty-five (5.2%) 24 patients had a reduction of GFR higher than 2.32 ml/min/year/1.73m². The composite end point was reached in 34 (16.4%) patients (44 deaths, 15 patients developing serum creatinina) and 48 patients suffered from a cardiovascular event. The independent factors associated with the composite event adjusted to blood pressure were: age (HR 1.121 (1.051-1.193), p<0.001), hyperuricemia, defined as uric acid ≥7 mg/dl (HR 3.31 (1.24-8.58), p<0.017) and albuminuria (HR 3.56 (1.40-9.05), p=0.007). These factors also predicted CKD progression : age (HR 1.055 (1.027-1.083), p<0.001), hyperuricemia (HR 2.95 (1.64-5.28), p<0.001), and albuminuria (HR 2.44 (1.32-4.51), p<0.004). Age (HR 1.031 (1.006-1.056), p=0.014) and previous vascular disease (HR 5.14 (2.66-9.94), p<0.001) were independent predictors of cardiovascular events. Diabetes, dyslipidemia and renin angiotensin system blockers were not associated with CKD progression.

Conclusions: In patients with reduced renal mass due to loss of one kidney, progression of CKD is not frequent. Hyperuricemia is a risk factor for progression of renal disease and may be established as a new therapeutic target together with blood pressure and albuminuria.

SA-PO257

Plasmatic Renin Activity in Patients with Chronic Kidney Disease
Lidia Arruango,1 Marta Riera,2 Julio Pascal,2 Clara Barrios,2 Angela Berruto,2 Jose M. Valdivielso,2 Elvira Fernandez,2 María Jose Soler.1 Nephrology, IMIM-Hospital del Mar, Barcelona, Spain; 2Nephrology, Hospital Arnau de Vilanova, Lleida, Spain.

Background: The renin-angiotensin system is activated in Chronic Kidney Disease (CKD), with an increase of Plasmatic Renin Activity (PRA). Our aim is to study PRA in disease progression in patients with reduced kidney mass.

Methods: A total population of 148 patients from the NEFRONA study in different stages of CKD and without a history of CV disease was analyzed. Patients were distributed into three groups: CKD stages 1-2 (CKD1-2, n=51), non-dialysis CKD stages 3-5 (CKD3-5, n=50) and dialysis (CKDSD, n=48). Variables analyzed were: gender, diabetes, dyslipidemia, hypertension, age, antihypertensive treatments (ACEi and ARAI2) and treatment with vitamin D analogues (calcitriol, paricalciol, calcitrolol and hydroerol). PRA was analyzed using a fluorimetric assay.

Results: Distribution of the population: mean age of 56.97±12.24, 60.1% men, 49.3% diabetics, 62.8% dyslipidemias, 69.6% hypertensive, 21.6% with ACEi treatment and 35.1% with ARAI2 treatment.

There were significant differences in PRA levels between groups, with an increased PRA in CKD3-5 (199.1±12.1 RFU/l) as compared to CKD1SD (151.4±40.12) and CKD2-1 (116.6±11.1) (p<0.05).

In CKD3-5 patients, diabetic patients showed higher levels of PRA as compared to non-diabetic (229.9±20.9 vs 168.2±8.8; p<0.05). In this group, treatment with paricalciol showed a decrease in PRA compared to those patients without treatment (137.2±11.9 vs 205.9±12.9; p=0.05). In CKD2-1 patients, treated with ARAI2 had higher levels of PRA compared to those not treated (153.8±12.5 vs 102.4±4.5; p<0.05).

Conclusions: In CKD patients without a history of CV disease, CKD3-5 showed an increase in PRA. Patients on dialysis have lower levels of PRA as compared to CKD non-dialysis. In the CKD3-5 group, diabetic patients have an increased PRA, while the treatment with vitamin D (paricalciol) analogues is associated with lower levels of PRA.

SA-PO258

Impact of the Great East Japan Earthquake on Chronic Kidney Disease over 10 Years
Fredrik Jonsson,1 Frank S. Czerwiec, 2 Daniel I. Levy,3 Arlene B. Chapman,4 Berenice Y. Gitomer,5 Vicente E. Torres,6 Esli H. Dennis,7 Klaus Romero,7 D. Miskulin,8 Ronald D. Perrone.1,8 Pharsight, St. Louis, MO; 2Osuka, Rockville, MD; 3Pizer, Collegeville, PA; 4Emory Univ, Atlanta, GA; 5Univ of Colorado, Colorado, CO; 6Mayo Clinic, Rochester, MN; 7Critical Path Institute, Tucson, AZ; 8Tufts Medical Center, Boston, MA.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. The growth of cysts increases total kidney volume (TKV) and lead to renal failure. Radiological imaging can be used to measure TKV and monitor disease progression. The goal of this project was to qualify TKV as a prognostic biomarker for 30 and 57% decline of estimated glomerular filtration rate (eGFR) in ADPKD patients.

Methods: TKV data collected by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) and longitudinal research registries were used (University of Colorado, Emory University, and Mayo Clinic). TKV was measured by ultrasonography, computer assisted tomography scan or magnetic resonance imaging. Longitudinal TKV and the probability of 30 or 57% eGFR decline was assessed using a joint model.

Results: Patients with 30 or 57% eGFR decline had higher baseline TKV (1.5 and 1.9 L, respectively) than patients without (1.0 L). Baseline age and predicted TKV at the time of 30 or 57% eGFR decline were statistically significant. Probabilities of not meeting the 30 or 57% eGFR decline are shown below.

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Baseline TKV</th>
<th>57% eGFR</th>
<th>30% eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 L</td>
<td>92.6%</td>
<td>88.0%</td>
<td>83.9%</td>
</tr>
<tr>
<td>1 L</td>
<td>87.2%</td>
<td>82.6%</td>
<td>79.3%</td>
</tr>
<tr>
<td>2 L</td>
<td>80.5%</td>
<td>76.8%</td>
<td>73.1%</td>
</tr>
<tr>
<td>3 L</td>
<td>76.5%</td>
<td>72.8%</td>
<td>70.2%</td>
</tr>
</tbody>
</table>

Conclusions: Baseline TKV can be applied as a biomarker along with baseline age to predict eGFR decline. Patients with larger TKV have a greater risk of 30 or 57% eGFR decline. This information can be used to improve drug development programs and to plan for trial enrollment.

Funding: Private Foundation Support

SA-PO260

Total Kidney Volume Is a Prognostic Biomarker for the Progression to End-Stage Renal Disease in Patients with Autosomal Dominant Polycystic Kidney Disease over 10 Years
J.F. Marier,1 Mohammad-samer Moukasassi,1 Fredrik Jonsson,1 Frank S. Czerwiec,2 Daniel I. Levy,1 Arlene B. Chapman,4 Berenice Y. Gitomer,5 Vicente E. Torres,6 Esli H. Dennis,7 Klaus Romero,7 D. Miskulin,8 Ronald D. Perrone.1,8 Pharsight, St. Louis, MO; 2Osuka, Rockville, MD; 3Pizer, Collegeville, PA; 4Emory Univ, Atlanta, GA; 5Univ of Colorado, Colorado, CO; 6Mayo Clinic, Rochester, MN; 7Critical Path Institute, Tucson, AZ; 8Tufts Medical Center, Boston, MA.

Background: Total kidney volume is the severely devastated coastal zone, Ishinomaki. The applicable population is 220,000. The died or missed victims were 5,800, people as well as 30,000 buildings totally collapsed in Ishinomaki medical zone.

Methods: Using data from Miyagi Govtory study, we identified 156 patients who registered July and August/2008 in Ishinomaki Redcross Hospital.They were followed GFR, urinary findings, blood biochemistry findings, treatment and outcome annually. The Great East Japan Earthquake occurred after 3 years from registration. We described the outcome of 1 year after disaster compared with previous 3 years.

Results: One hundred and seventeen patients were valid in 2010. Annual check confirmed that 5 started dialysis and 3 died by disease. Four losted after January 2011, 4 died by the tsunami. After 1 year from disaster, 1 losted from June 2011, 7 moved, and 2 died by infectious disease in April 2011 and by heart failure in December 2011. Death and cardiovascular events didn’t increase compared with 2010. While 29.9% of patients showed eGFR decline over 5% between 2008 and 2010 of 77 patients observed through study period to 2012, 58.4% of them decreased eGFR over 5% between 2010 and 2012.

Conclusions: We concluded that the great tsunami disaster was possible to affect pre-RRT CKD patients. We should treat them carefully for more long term about the cardiovascular event and renal outcome.

Funding: Private Foundation Support
**SA-PO261**

**Relationship between Renal Complications and Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease from the Consortium for Radiologic Imaging of Polycystic Kidney Disease Cohort**

Federico F. Rahbari-Oskouei,1 Doug Landsittel,2 Vicente E. Torres,3 Kyongtae Ty Bae,2 Michal Mrug,2 Marie C. Hogan,2 Lisa M. Guay-Woodford,4 Jared J. Grantham,5 Michael F. Flessner,5 Arlene B. Chapman,2 William M. Bennett,6 Emory Univ,7 University of Pittsburgh,8 Mayo Clinic, MN,9 University of Alabama-Birmingham,10 NIDDK-NIH,11 Kansas Univ,12 Children’s Nat Med Ctr, DC,13 Legacy Good Samaritan Med Ctr, Portland, OR.

**Background:** Inclusion of renal complications of autosomal dominant polycystic kidney disease (ADPKD) as new endpoints for interventional clinical trials has been supported by the FDA. The relationship between these factors and height adjusted Total Kidney Volume (htTKV) is unknown.

**Methods:** We used the CRISP II cohort to establish the frequency of kidney pain (P), hypertension (HT), urinary tract infection (UTI), gross hematuria (H) and nephrolithiasis (N) and their relationship to the last observed htTKV. Differences in HTKVs by those with a baseline complication vs the No Complication group were calculated using the t-test; odds ratios (ORs) were calculated using logistic regression adjusting for age, BMI, gender, race, and baseline corrected high density lipid levels.

**Results:** 11 year follow up data from 202 participants were analyzed. Baseline (absolute or cumulative) percentage frequencies of P, HT, UTI, H and N were 60.8(84.7), 61 (71.4), 45.2(38.8), 32.8(48.1), and 13.3 (21.2) respectively. Mean (±SD) baseline htTKV were significantly higher (p < 0.05) in: 1- HT patients vs no-HT (736.0 ± 394.5 vs 404.6 ± 224.9 cc), 2- Patients with H vs without H (728.6 ± 409.3 vs 537.3 ± 297.2 cc), 3- patients with P vs without P (690.1 ± 405.3 vs 478.5 ± 274.3 cc). The differences in htTKV based on UTI and N were not significant. The adjusted ORs (ORs) for development of KP, HT, H, UTI, N based on a 100 cc difference in baseline htTKV were 1.17 (1.01, 1.36), 1.41 (1.19, 1.66), 1.17 (1.07, 1.28), 0.98 (0.89, 1.07) and 1.07 (0.98, 1.17).

**Conclusions:** In addition to established correlation with renal function, HTKVs is associated with specific renal complications of ADPKD. These findings reiterate the importance of htTKV as a marker of disease severity and support its use in the design of future studies.

**Funding:** NIDDK Support

**SA-PO262**

**Kidney Length Measured by Ultrasound (US) Predicts Development of Chronic Kidney Disease (CKD) Stage 3 in Autosomal Dominant Polycystic Kidney Disease (ADPKD): Findings from the Consortium for the Radiographic Imaging Studies of Polycystic Kidney Disease (CRISP) Cohort**

Federico F. Rahbari-Oskouei,1 Doug Landsittel,2 Vicente E. Torres,3 Kyongtae Ty Bae,2 Michal Mrug,2 Marie C. Hogan,2 Lisa M. Guay-Woodford,4 Jared J. Grantham,5 Michael F. Flessner,5 Arlene B. Chapman,2 William M. Bennett,6 Emory Univ,7 University of Pittsburgh,8 Mayo Clinic, MN,9 University of Alabama-Birmingham,10 NIDDK-NIH,11 Kansas Univ,12 Children’s Nat Med Ctr, DC,13 Legacy Good Samaritan Med Ctr, Portland, OR.

**Background:** ADPKD causes kidney cysts, enlargement and ultimately renal failure. Total kidney volume (TKV) measured by magnetic resonance imaging (MRI) is a measure of kidney cyst burden that strongly predicts future CKD Stage 3 within 8 years in ADPKD. Using simultaneous baseline US and MR imaging in the CRISP II cohort, we established the predictive power of US length for future CKD Stage 3 in ADPKD.

**Methods:** Correlations between baseline US length and MR TKV and length and the future development of CKD Stage 3 by isohalothane clearance determinations were examined in 241 ADPKD subjects, 15-45 years, and baseline estimated creatinine clearance ≥ 70 mL/min. Correlations were assessed using Pearson’s correlations. Area under the curve using receiver operator characteristics were performed based on US measured renal length at baseline in CRISP.

**Results:**

<table>
<thead>
<tr>
<th>Baseline Age</th>
<th>Baseline US Length (cm)</th>
<th>Baseline TKV (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>72.8 ± 40.93</td>
<td>578.6 ± 284.2</td>
</tr>
<tr>
<td>30-40</td>
<td>73.6 ± 40.93</td>
<td>580.4 ± 286.3</td>
</tr>
<tr>
<td>≥40</td>
<td>74.4 ± 40.93</td>
<td>582.2 ± 288.1</td>
</tr>
</tbody>
</table>

**Conclusions:** The above results were consistent with those derived with the US or CT-MRI datasets.

**Funding:** Private Foundation Support

**SA-PO263**

**Correlation of Total Kidney Volume and eGFR in Patients with ADPKD: Results from the TEMPO 3:4 Trial**

Ronald D. Perrone,1 Arlene B. Chapman,2 Frank S. Czerwiec,3 Olivier Devuyst,4 Ron T. Gangsevoort,5 Jared J. Grantham,6 Eiji Higashihara,7 Holly Krasa,8 John Ouyang,9 Vicente E. Torres,10 Boston, USA; 11 Atlanta, USA; 12 Otsuka USA; 13 Zurich, Switzerland; 14 Groningen, Netherlands; 15 Kansas City, USA; 16 Japan; 17 Mikea, Japan; 18 Rochester, USA.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) causes kidney cysts often associated with pain, hypertension, and kidney failure. Total kidney volume (TKV) is a measure of kidney cyst development and enlargement that has been correlated with renal function decline in smaller studies.

**Methods:** Correlations between baseline TKV and height-adjusted TKV slope and changes in eGFR were examined as post-hoc exploratory analyses. Correlations were assessed using Pearson’s correlations at different time points and by treatment group.

**Results:** Correlations between baseline TKV and eGFR slope on treatment was blunted in the tolvaptan compared to the placebo group.

**SA-PO264**

**Tolvaptan Administration to Patients with ADPKD Suppresses Urine MCP-1 Excretion: Results from the TEMPO 3:4 Trial**

Ronald D. Perrone,1 Arlene B. Chapman,2 Frank S. Czerwiec,3 Olivier Devuyst,4 Ron T. Gangsevoort,5 Eiji Higashihara,6 Holly Krasa,7 John Ouyang,8 Michael D. Perrone,9 Vicente E. Torres.10 Medicine, Kansas City, KS; 11 Medicine, Emory Univ, Atlanta, GA; 12 Development, Otsuka, Rockville, MD; 13 Medicine, Univ Zurich, Zurich, Switzerland; 14 Medicine, Univ Groningen, Groningen, Netherlands; 15 Urology, Kyorin Univ, Kyorin, Japan; 16 Medicine, Tufts Med Ctr, Boston, MA; 17 Medicine, Mayo, Rochester, MI.

**Background:** Monocyte chemotactic protein-1 is produced by cysts and excreted in the urine in ADPKD. MCP-1 derives from cysts that remain connected to downstream segments or from the cells of patent tubules. The effect of treatment that slows cyst development and enlargement on urine MCP-1 levels is unknown.

**Results:**

<table>
<thead>
<tr>
<th>All Patients (N=1445)</th>
<th>Tolvaptan (N=961)</th>
<th>Placebo (N=483)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline eGFR</td>
<td>0.175</td>
<td>0.451</td>
</tr>
<tr>
<td>Month 6 eGFR</td>
<td>0.181</td>
<td>0.431</td>
</tr>
<tr>
<td>eGFR slope on treatment</td>
<td>0.185</td>
<td>0.162</td>
</tr>
<tr>
<td>P&lt;0.005 for all comparisons</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** Results support the strong predictive value of baseline htTKV for predicting GFR decline, consistent with data reported from the CRISP II cohort. Since there is approximately 30% less eGFR decline in the tolvaptan group regardless of CKD stage, greater variability likely reflects a differential response among the treated population which is not entirely accounted for by baseline htTKV or baseline eGFR.

**Funding:** Pharmaceutical Company Support • Otsuka Pharmaceutical Development & Commercialization, Inc,
Methods: MCP-1 was prospectively measured (pre-treatment baseline, Month 12, 24, and 36) in 1445 patients treated with either tolvaptan or placebo for 36 months. Urine MCP-1 (ng/Mmol creatinine) was determined in 784 Tolvaptan and 429 Placebo subjects. Treatment group comparisons at each time point were determined using an observed case, intent to treat, MMRM analysis on log-transformed ratios.

Results: At baseline, the mean MCP-1 to creatinine ratio was balanced between treatment groups and associated positively with total kidney volume (R=0.221, P=0.0001) and negatively with eGFR (R=-0.124, P=0.0001) and Usorn (R=-0.148, P=0.0001). Urine MCP-1 creatinine ratio was less with tolvaptan than placebo beginning at Month 12, with significant reductions at Months 24 and 36 (mean difference -12%).

Conclusions: Tolvaptan administered over a period of 3 years reduced the excretion of the biomarker MCP-1 into the urine relative to placebo, consistent with potential amelioration of renal interstitial inflammation.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical Development & Commercialization, Inc; Rochester, Maryland

SA-PO265

The Effect of Tolvaptan onAlbuminuria in ADPKD. Results of the TEMPO 3:4 Trial Ron T. Gansevoort,1 Arlene B. Chapman,2 Frank S. Czerwiec,3 Olivier Devuyst,4 Jared J. Grantham,5 Eiji Higashihara,6 Holly Krasa,3 John Ouyang,3 Ronald D. Perrone,4 Vicente E. Torres.8

Background: The TEMPO 3:4 Trial, including 1445 ADPKD patients, suggested that use of tolvaptan (T) had no effect compared to placebo (P) on albuminuria. However, the use of categorical “albuminuria events” to express albuminuria may have resulted in a loss of sensitivity to detect changes. In the present study we therefore specifically investigated the effects of T on albuminuria.

Methods: Post-hoc analysis of prospective, blinded RCT. Microalbuminuria or higher (MA) was a priori defined as spot albumin/creatinine ratio (ACR) ≥2.8 in males and ≥2.0 mg/mmol in females.

Results: Baseline median ACR was 3.1 (T) and 3.4 (P) mg/mmol. 58.6% of ADPKD patients had MA. Subjects with MA had higher TKV and lower eGFR, but were as likely to be male, hypertensive and to use RAASi than subjects without MA. During follow-up T treated patients with MA had a similar rate of growth in TKV when compared to patients without MA (5.51 versus 5.47 %/yr), but more rapid eGFR loss (median -4.13 vs. -2.63 mL/min/1.73m²/yr). ACR rose in P treated patients (+0.23 mg/mmol), whereas it decreased in T treated patients (-0.40 mg/mmol). The difference in ACR in T versus P treated patients increased over time, reaching a maximum of 23% at month 36 (p<0.001), whereas no difference in blood pressure was observed. After T withdrawal the difference in ACR between the two treatment groups remained significant (16%, p=0.003). A beneficial effect of T on TKV growth and eGFR loss was observed in both MA subgroups, but stronger in patients with MA than without MA (effect on TKV growth: -53.7% vs. -43.7%; on eGFR slope: -29.5% vs. -20.2%, resp.).

Conclusions: In ADPKD patients MA is associated with eGFR loss. Tolvaptan decreased albuminuria compared to placebo, independent of blood pressure, and this effect remained after withdrawal of study drug. Treatment efficacy of tolvaptan was more readily detected in patients with MA.

Funding: Pharmaceutical Company Support - Otsuka Pharma, USA
SA-PO268
Achievement and Maintenance of Blood Pressure Targets in HALT-PKD
Vicente E. Torres, 1 Robert W. Schrier, 1 Arlene B. Chapman, 1 Ronald D. Perrone, 2 D. Miskulin, 3 Theodore I. Steinman, 4 Franz Winklhofer, 5 William E. Braun, 6 Marie C. Hogan, 7 Fredric F. Rahbari-Oskou, 7 Kaleb Z. Abebe, 4 Michael F. Flessner, 8 Mayo Clinic; 9 U CO; 1 Emory U; 2 Tufts U; 3 Beth Israel; 4 KUMC; 5 Cleveland Clinic; 6 Pittsburgh; 7 NIH/NIDDK HALT Study Group.

Background: HALT-PKD seeks to determine whether ACEI/ARB is superior to ACEI alone and low BP. BP<110/75 is superior to standard BP(120-130/70-80) in delaying cystic progression (eGFR<60mL/min/1.73m², Study A) and whether ACEI/ARB is superior to ACEI alone (BP target 110-130/70-80mmHg) in slowing eGFR decline (eGFR 25-60mL/min/1.73m², Study B).

Methods: Stepwise dosing of lisinopril(T) and telmisartan/placebo(T/P)(steps 1-4) followed by stepwise dosing of other agents (steps 5-10) was used to achieve BP targets. During 1/2006-12/2012, 519, 501, 490, 474, 433, 273, 154 A and 458, 447, 437, 411, 362, 191, and 80 B patients completed 4, 12, 24, 36, 48, and 72-month follow-up. BP control is assessed by home BP measurements.

Results: ACEI alone or ACEI/ARB achieves BP control and MAPs are within target in most subjects at 4-72 months of followup. Excellent separation in BP and doses of LIS and T/P between study A arms is achieved, without detectable differences in heart rate.

Conclusions: In relatively young ADPKD subjects with preserved GFR, reduction in LVEF was associated with increased urine aldosterone and hTfK and decreased BMI. Subclinical renal hyperfiltration due to reduced LVEF or enlarged kidney mass result in increased urinary aldosterone excretion, contributing to the pathogenesis of HTN in ADPKD.

Funding: NIH/NIDDK Support

SA-PO270
Analysis of Occlutech LAR Therapy after Four Years in Polycystic Liver and Kidney Disease
Marie C. Hogan, Eric J. Bergstralh, Maria V. Irazabal, James Glockner, Xujian Li, Victoria J. Torres, Mayo Clinic.

Background: We completed follow up of 25 patients with ADPKD or ADPLD who received occlutech occlLAR therapy for an average of 4 years. The occlutech occlLAR is a minimal access device that rapidly occludes targeted cysts. Potential benefits are diminished cyst growth and increased quality of life. The trial was a non-inferiority randomised parallel group study comparing occlLAR with the current option of high-dose medical treatment. It was terminated because of funding issues.

Results: Twenty-five of 42 patients (60%) on occlLAR (16 of the original 28 (O->O) group) or placebo (9 of original 14, (P->O) group) completed OLE. While off occlLAR, TLV increased at 3.4% per annum. After resuming occlLAR, TLV decreased again by 4.7% per annum. Despite regrowth off occlLAR, there was a progressive reduction in (mean ± SD) TTV (−11%; p<0.006; paired t test) on long-term occlLAR. Baseline TKV (777 ± 468ml) increased to 819 ± 508ml by yr2 & to 861 ± 525ml at OLE & was again suppressed to (879 ± 593 ml; 0.7±1.3% changes) at OLE. ΔGFR were similar in both groups.

Funding: Pharmaceutical Company Support - Novartis

SA-PO271
Autosomal Dominant Polycystic Kidney Disease Cyst-Cell Implants Develop Cysts and Vasculature That Is Inhibited by Antiangiogenic Treatment
Ilsa Bello-Reuss, Internal Medicine, Texas Tech Univ Health Sciences Center, Lubbock, TX.

Background: Previous studies described angiogenesis in Autosomal Dominant Polycystic Kidney Disease (ADPKD) kidneys, as well as increases in Vascular Endothelial Growth Factor (VEGF) and its receptors in ADPKD kidney sections and cyst cells in culture. We have reported that angiogenic growth factors expression correlate with disease severity in young patients with ADPKD and that interleukin-8 (IL-8) gene expression is also increased in ADPKD cells.

Methods: We studied the expression of IL-8 (at mRNA and protein level) and its receptors in ADPKD cyst cells and used ADPKD cyst cells -mixed with Matrigel- implanted in the immunoincompetent nude mouse and removed after 14 days, to study the development of cysts and angiogenesis in the implants and the inhibition of cyst growth by antiangiogenic drugs.

Conclusions: We report that, in cyst cells in culture, there is constitutive expression of IL-8 (at the mRNA and protein levels) and that IL-8 secretion is inhibited by an anti-IL-8 neutralizing antibody (anti-IL-8) but no by dexamethasone (DEXA), a nonspecific inhibitor. Cysts seeded in Matrigel and implanted in nude mice form cysts and the host provides the vascularization. Cysts grow to different sizes and on the mice exhibit cuboidal or flat shapes. In this model of angiogenesis, cyst cells express IL-8, VEGF and their receptors. Cyst volume and vascularization is significantly decreased in the implants removed from mice treated with anti-IL-8, compared with untreated controls.

Funding: Private Foundation Support, Clinical Revenue Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
SA-PO272
Analysis of Coronary Endothelial and Smooth Muscle Function Using 18O-Labeled Water PET in Early Stage Autosomal Dominant Polycystic Kidney Disease Naoko Matsuo,1 Yasunobu Ishikawa,2 Sekiya Shibazaki,1 Osamu Manabe,3 Keiichiro Yoshinaga,4 Saori Nishio,5 Tatsuya Atsumi,1 1Dept of Medicine II, Hokkaido Univ Graduate School of Medicine, Sapporo, Hokkaido, Japan, 2Dept of Molecular Imaging, Hokkaido Univ Graduate School of Medicine, Sapporo, Hokkaido, Japan.

Background: Cardiovascular problems are a major cause of morbidity and mortality in individuals with autosomal dominant polycystic kidney disease (ADPKD). Endothelial dysfunction has been used to predict future coronary artery disease before atherosclerotic changes. It has been reported that significant ED occurs in both normotensive and hypertensive patients with ADPKD. Polycystins are expressed in is endothelial and vascular smooth muscle cells. However, the association between ED and smooth muscle dysfunction has not been fully studied. Positron emission tomography (PET) can non-invasively myocardial blood flow (MBF). Using a cold pressor test (CPT) and adenosine triphosphate (ATP) infusion, PET can evaluate coronary endothelial function and coronary flow reserve (CFR). This study aimed to examine the coronary endothelium function in normotensive patients with ADPKD using 18O-labeled water PET.

Methods: Nine normotensive patients with ADPKD and 9 healthy controls were included in the study. Coronary endothelial function using was measured during CPT and vasodilator capacity, CFR was measured during ATP stress using 18O-labeled water PET.

Results: There was no significant difference between groups regarding age, body mass index, blood pressure, and lipid levels. The resting MBF was significantly higher in patients than in control (0.93±0.07 vs 0.73±0.13; P<0.001). MBF during CPT was no significantly different between the groups. MBF during ATP infusion that at rest, as an index of CFR, was significantly reduced in patients than in control (3.27±0.91 vs 5.06±1.28; P<0.001).

Conclusions: Normotensive patients with ADPKD with well-preserved renal function have reduced CFR indicating early atherosclerosis even in early stage of the disease. In contrast, there was no significant change in coronary endothelial function. Coronary endothelial changes might precede predominantly in vascular smooth muscle rather than endothelial dysfunction in ADPKD.

SA-PO273
Pravastatin and Angiogenesis in ADPKD Wei Wang, Melissa A. Cadnapaphornchai, Michel Chonchol, Robert W. Schrier, Berenice Y. Gitomer.
Univ of Colorado Anschutz Medical Campus.

Background: We have shown that serum levels of vascular endothelial growth factor (VEGF) correlate with total renal volume and renal function in young ADPKD patients suggesting that VEGF plays a key role in early cystogenesis. VEGF activity is regulated by its receptors including VEGF receptor -1 (Fl-1). A splice variant, soluble Fl-1 (sFlt-1) antagonizes VEGF signaling. Studies have diverse effects on angiogenesis and in human studies pravastatin has been shown to lower circulating VEGF levels. More recently pravastatin has been shown to slow the progression of renal structural disease in young patients with ADPKD. We hypothesized that statin may slow renal growth by mediating angiogenesis through reduction of VEGF levels in young ADPKD patients.

Methods: Subjects aged 8-22 years with ADPKD and normal renal function were randomized to either pravastatin (20mg or 40mg/day by age) or placebo. All subjects also received lisinopril. Serum and 24 hour urine were collected at each visit. VEGF and sFlt-1 levels were assayed by ELISA (RAD systems).

Results: After 18 months (m) of follow-up serum VEGF increased significantly compared to baseline in placebo (P) group (137.1±8.5pg/ml vs 109.2±7.0pg/ml, n=26, p<0.05) and was unchanged in the statin (S) group (157.1±11.5pg/ml vs 148.1±12.1pg/ml, n=25). Serum VEGF/sFlt-1, an index of VEGF bioavailability, increased significantly in group P at 18 m (1.5±1.2 vs 1.1±0.8, n=26, p=0.05) and 36m (1.2±0.6 vs 0.9±0.6, n=23, p=0.05) and was unchanged in group S at 18m (1±1.1 vs 1.71±1.4, n=24) and 36m (1±1.3 vs 1±1.2, n=23) relative to baseline. Urine VEGF levels increased significantly in group S at 36m (7.0±4.0ng/mmol Cr vs 5.4±3.2ng/mmol Cr, n=15, p=0.05) and were unchanged in group P (7.6±4.7 vs 6.2±3.4ng/mmol Cr).

Conclusions: Based on the outcome of the pravastatin clinical trial in young ADPKD patients, statin therapy significantly slows renal growth. Our present results suggest that this is related to stabilization of serum VEGF and serum VEGF/sFlt-1 ratio as well as increased urine VEGF. The current study indicates a potential anti-angiogenic effect of pravastatin by regulation of VEGF level.

Funding: NIDDK Support

SA-PO274
Thrombospondin and Autosomal Dominant Polycystic Kidney Disease Wei Wang, Michel Chonchol, Godela M. Brosnahan, Robert W. Schrier, Berenice Y. Gitomer.
Dept of Medicine, Univ of Colorado Anschutz Medical Campus.

Background: Thrombospondin(TSP) including TSP-1, TSP-2 are glycoproteins that inhibit endothelial cell migration, proliferation and survival as well as vascular endothelial growth factor (VEGF) activity. In contrast, VEGF and angiopoietins(Ang)1,2 are established angiogenic factors that correlate with renal structure and function in autosomal polycystic polycystic kidney disease (ADPKD). We hypothesized that dysregulated TSP expression results in an imbalance between pro- and anti-angiogenic factors in ADPKD that may favor angiogenesis early in disease.

Methods: Healthy adults were included and ADPKD patients stratified according to eGFR either ≥ 60 (I) or< 60 ml/min/1.73m2 (II). Serum levels of VEGF, Ang-1, Ang-2, TSP-1 and TSP-2 were assayed by ELISA.

Results: The key differences in pro and anti-angiogenic growth factor levels are summarized in table 1. Serum TSP-1 levels positively correlated with Ang-1 and Ang-2 levels in group I. Serum TSP-2 and Ang-2 levels were positively correlated in group II.

Conclusions: Serum levels of VEGF, Ang-1 and TSP-2 are elevated in ADPKD patients compared to the normal controls. The relationships between pro and anti-angiogenic factors differ in ADPKD patients based on renal function. The increased Ang-1/TSP-2 ratio in patients with earlier stages of ADPKD favors a pro-angiogenic environment in earlier disease. TSP’s are potent inhibitors of angiogenesis and tumor growth and as such may have potential therapeutic benefits in slowing cyst growth in ADPKD.

SA-PO275
Sacred Frizzled-Related Protein 4 Is a Marker of Autosomal Dominant Polycystic Kidney Disease Progression Stefan Zachéidrich,1 Klemens Budde,3 Christina Sommerer,1 Ulrich Kunzendorf,1 Bernhard Banas,1 Walter H. Hoerl,1 Nicholas Obermuller,1 Wolfgang Arns,1 Hermann Papadaki,1 Jens Gaedicke,1 Lothar Faerber,1 Peter Werner,1 Kai-Uwe Eckardt,1 Cerd Walz,1 1Renal Div, Univ Hospital Freiburg, Freiburg, Germany; 2Dept of Nephrology, Charité Universitätsmedizin Berlin - Campus Mitte; 3University Hospital Würzburg; 4Centre for Nephrology, Heidelberg; 5University Hospital Kiel; 6University Hospital Regensburg; 7Medical Univ of Vienna; 8University Hospital Frankfurt; 9Merheim Medical Center, Cologne; 10University Hospital, Münster; 11Karolinska Germany, Nuremberg; 12Univ of Erlangen and Community Hospital of Nuremberg.

Background: Sacred frizzled-related protein 4 (sFRP4) is expressed at elevated levels in the tissue of autosomal dominant polycystic kidney disease (ADPKD) kidneys, and detectable in blood, urine and cyst fluid of ADPKD patients. It is a molecule known to antagonize Wnt signaling, an intracellular pathway that controls cell migration, proliferation and cellular polarity. To monitor future therapeutic interventions, there is a need for reliable and inexpensive biomarkers of ADPKD disease progression.

Methods: We investigated sFRP4 levels from patient samples of the ‘Everolimus in patients with Autosomal Dominant Polycystic Kidney Disease’ trial to determine its capability as a progression marker. 3126 probes were analyzed and correlated to kidney function and total kidney volume of ADPKD patients followed over 24 months.

Results: sFRP4 levels were significantly increased after the two years follow-up of the study, correlating with an increase of serum creatine and deterioration of renal function. The increase was independent of the intervention and observed in everolimus- and placebo-treated patients. Total kidney volume (measured by MRI) did not correlate with sFRP4 levels.

Conclusions: Our results demonstrate that sFRP4 plasma levels increase in patients with ADPKD. Everolimus had no effect on sFRP4 levels. Thus, measurement of sFRP4 may be a reliable (and cheap) parameter of disease progression in ADPKD.

SA-PO276
Association of Plasma and Urinary GDF-15 Levels with Disease Severity in ADPKD Patients Ivan Formentini,1 Carolina Haeiger,6 Paolo Piraino,5 Maria Chiara Magnone,1 Anders Fernstrom,3 Peter F. Barany,4 Guillemette Duchateau-Nguyen,1 Matthias Meier,1 Maria Bobadilla,1 1Cardiovascular & Metabolism DTA, F Hoffmann - La Roche Ltd, Basel, Switzerland; 2Dept of Medical Sciences, Univ Hospital, Uppsala, Uppsala, Sweden; 3Dept of Medical and Health Sciences, Faculty of Health Sciences, Linköping Univ, Linköping, Sweden; 4Div of Renal Medicine, CLINTEC, Karolinska Institutet, Stockholm, Sweden; 5PP Statistical Consulting, Rende, Italy; 6Novartis Pharma AG, Basel, Switzerland.

Background: Growth differentiation factor 15 (GDF-15) is a distant TGF-β family member suggested to reflect inflammation and apoptosis processes under stressful conditions. Clinically, several investigations have demonstrated that circulating GDF-15 levels are increased and independently prognostic across a wide spectrum of cardiovascular diseases. The relationship between GDF-15 levels and renal functional loss severity has been described but not yet fully established, making of this marker a potential integrative predictor of kidney damage and CV risk in all CKD patients.

Methods: In the current study, we aim to investigate if urine and plasma GDF-15 levels are associated to renal functional parameters in a cross-sectional ADPKD patient (n=56) and controls (n=20) (THP045; ASN 2012). We also determined the potential impact of GDF-15 on ADPKD progression.

Results: Urine GDF-15 levels were not associated to disease stage (R=0.057, p=1.5e-2), baseline eGFR (R=0.082, p=4.3e-1) or UACR (R=0.056, p=7.2e-2) in cross-sectional cohort of ADPKD patients. Matching serum samples instead demonstrated
a strong relationship to CKD staging (R²=0.52, p<1.0e-6), eGFR_{init} at screening (R²=0.58, p<1.0e-6) while lacking correlation to log urine albumin levels (R²=0.0027, p=3.2e-3). In a Bayesian additive regression trees classification model plasma GDF-15 contributed to the prediction of ADPKD vs controls (ROC_{AUC}=0.867) much better then urinary levels (ROC_{AUC}=0.687). Plasma levels were also capable of discriminating control subjects vs. renal impaired patients (ROC_{AUC}=0.852).

**Conclusions:** In conclusion, the present results show that higher levels of plasma GDF-15 are associated to renal impairment state and CKD severity in ADPKD.

**Funding:** Pharmaceutical Company Support - F. Hoffmann - La Roche Ltd

---

**SA-PO277**

Is the Intrarenal Renin Angiotensin System the Culprit for Hypertension in Patients with Autosomal Dominant Polycystic Kidney Disease?  
Ismael Kocyiğit,1 Mahmut Ilker Yilmaz,2 Aydin Unal,1 Fahir Ozturk,3 Eray Eroglu,1 Cevat Yaziçi,4 Ozcan Orucelik,5 Murat H. Sipahioglu,1 Bulent Tokgoz,1 Oktay Oymak.1

**1** Dept of Nephrology, Erciyes Univ Medical School, Kayseri, Turkey; 2Dept of Internal Medicine, Erciyes Univ Medical School, Kayseri, Turkey; 3Dept of Biochemistry, Erciyes Univ Medical School, Kayseri, Turkey; 4Dept of Cardiology, Erciyes Univ Medical School, Kayseri.

**Background:** Early onset of hypertension and its consequences account for the great majority of death in patients with autosomal dominant polycystic kidney disease (ADPKD). Renin angiotensinogen system (RAS) components have been shown in ADPKD kidneys. Thus we examined the urinary angiotensinogen (UAGT) levels as a biomarker of intrarenal RAS status in ADPKD patients with/without hypertension and healthy subjects.

**Methods:** Eighty-four ADPKD patients (43 with hypertension and 41 without hypertension) and 40 healthy controls were studied cross-sectionally. Hypertension diagnosed with ambulatory blood pressure monitoring. Urinary and plasma concentration of angiotensinogen, spot urine microprotein and creatinine levels recorded for each participants.

**Results:** UAGT/UCre levels were higher in hypertensive ADPKD patients (23.7 ± 8.4) compared with normotensive ADPKD patients (16.6 ± 5.2) and healthy controls (6.9 ± 3.3) (p=0.001).

**Conclusions:** Intrarenal RAS activation which is monitoring by UAGT levels clinically may be a harbinger for the development of hypertension and kidney disease in ADPKD patients.

---

**SA-PO278**

Prevalence of and Survival on Renal Replacement Therapy for ADPKD in Europe  
Edwin M. Spithoven,1 Anneke Kramer,2 Christoph Wanner,2 Kitty J. Jager,2 Ron T. Gansevoort.1,2,3,4,5

1Dept Nephrology, UMC Groningen, The Netherlands; 2ERA-EDTA Registry, AMC Amsterdam, Netherlands; 3For the ERA-EDTA Registry; 4For the EuroCYST Consortium; 5For the WGIKD.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is the fourth most common diagnosis for starting renal replacement therapy (RRT). Still, there are few epidemiological data on the prevalence of and survival on RRT for ADPKD.

**Methods:** This study used data of the ERA-EDTA Registry on RRT prevalence and survival on RRT of 18 European countries with 385 million inhabitants. We studied four 5-year periods (1991-2010).

**Results:** Over the four periods the average incidence rate of RRT for ADPKD, adjusted for general population age and gender, increased slightly from 7.6 to 8.1 per million of the population (pmp). Differences in the incidence of RRT for ADPKD were noted among countries (range 5.3-9.9 pmp). The mean age at start of RRT increased from 56.6 to 58.1 years (Figure 1). No change over time was observed in the incidence of RRT for ADPKD up to the age of 50 years (Figure 1). However, in recent time periods the incidence of RRT for ADPKD above the age of 70 years increased. Among countries there was a clear positive association between take-on rate of RRT for non-ADPKD renal disease and for ADPKD (r=0.64, p<0.001).

**Conclusions:** During the last two decades the incidence of RRT for ADPKD, as well as the age at which RRT was started, has increased slightly. Our data suggest that this is likely due to an increased access of elderly ADPKD patients to RRT rather than providing evidence that effective renoprotective treatments have become available.

---

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

Underline represents presenting author/disclosure.

691A
SA-PO280

Maternal and Fetal Outcomes in Women with Autosomal Dominant Polycystic Kidney Disease Min Wu,1 Diping Wang,2 Peter C. Harris,3 Ladan Zand,4 Vesna D. Garovic,5 Cindy A. Kermott.6 1Dept of Cardiovascular Diseases, Guang’an Men’s Hospital, China Academy of Chinese Medical Sciences, Beijing, China; 2Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 3Div of Preventive Medicine, Mayo Clinic, Rochester, MN.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD), a common genetic cause of chronic renal failure in children and adults, is characterized by the accumulation of fluid-filled cysts in the kidney and other organs. As the diagnostic techniques advance, more and more female patients are diagnosed with ADPKD before or during their birth age. However, it is still not clear how ADPKD affects the maternal and fetal outcomes in these patients. The aim of this study is to determine whether ADPKD is associated with adverse fetal and infant outcomes, maternal complications and long-term post-pregnancy prognosis.

Methods: We identified a cohort of 146 patients seen for pregnancy and cystic kidney disease at the Mayo Clinic from 1975 to 2010. From this cohort, 54 patients met the ultrasound diagnostic criteria for ADPKD (ADPKD group) while the other 92 patients had been diagnosed as ‘Simple Cyst’ (the control group). We compared the fetal and maternal outcomes of pregnancy between these two groups as well as report on long-term maternal prognostic.

Results: Overall, the fetal complication rates were similar between the ADPKD group and the control group. The spontaneous abortion rate (15.1% vs. 14%, P=0.77) and premature rate (11.1% vs. 6.8%, P=0.44) were comparable in these two groups while the rates of fetal distress (3.4% vs. 0.7%, P=0.01) and birth defects (6% vs. 0%, P=0.001) were increased in ADPKD patients. Compared to the control group, pregnant ADPKD patients had higher risks for hypertension, edema, UTI, renal dysfunction and preeclampsia. Finally, follow-up studies after the last pregnancy clearly showed that rates of chronic hypertension and renal insuficiency were significantly increased in ADPKD patients.

Conclusions: ADPKD is associated with increased maternal complications during pregnancy but only has a slight potential of increased rates of fetal complications.

SA-PO281

Autosomal Dominant Polycystic Kidney Disease (ADPKD): A Risk Factor for New Onset Diabetes after Transplantation Anushka Mittal, Ashar Chami, Arlene B. Chapman. Emory Univ Hospital, Atlanta, GA.

Background: ADPKD is the fourth leading cause of ESRD and accounts for 8.3% of deceased donor and 11.7% of living donor yearly kidney transplants in the US. Our goal is to use an established cohort of PKD individuals evaluated for transplant to characterize their outcomes.

Methods: This is a retrospective cohort analysis of all ADPKD patients who presented for transplant evaluation at the Emory Transplant Center between 1/1/2002 and 1/1/2012, utilizing electronic medical records and the organ transplant tracking record (OTTR). Individuals were evaluated with regard to their graft and patient survival rates in those that did and did not have a nephrectomy.

Results: Of 286 ADPKD who presented for transplant evaluation, 169 (59.1%) were transplanted, 80 (28.0%) were evaluated but not yet transplanted, and 37 (12.9%) were ineligible for transplant. 5-year patient survival was 92.3% and 93.8% with and without a nephrectomy (p<0.001), respectively. 5-year patient survival for living and deceased donors was 98.0% and 92.9% (without a nephrectomy, p<0.001) and 100% and 89.7% (with a nephrectomy, p<0.001), respectively. 5-year graft survival was 82.9% and 88.9% with and without a nephrectomy (p<0.001), respectively. 5-year graft survival was 94.0% and 86.8% (without a nephrectomy, p=0.001) and 79.5% and 84.4% (with a nephrectomy, p=0.001) for living and deceased donor transplants, respectively. 5-year graft survival was 95.7% and 89.7% for African Americans and Caucasians, respectively, without a nephrectomy (p=0.001). 5-year graft survival was 75.0% and 84.1% for African Americans and Caucasians, respectively, with a nephrectomy (p=0.001). 5-year graft survival was 100.0% and 69.8% for pre- and post-transplant nephrectomies (p<0.001).

Conclusions: Nephrectomy is a significant risk factor for graft survival in this ADPKD cohort. Men are shown to have significantly higher graft survival than women with a nephrectomy, and patients with a nephrectomy after transplant are shown to have significantly higher graft survival than those with a nephrectomy before transplant.

SA-PO282

Nephrectomy and Renal Transplantation in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Anushka Mittal, Ashar Chami, Arlene B. Chapman. Emory Univ Hospital, Atlanta, GA.

Background: ADPKD is the fourth leading cause of ESRD and accounts for 8.3% of deceased donor and 11.7% of living donor yearly kidney transplants in the US. Our goal is to use an established cohort of PKD individuals evaluated for transplant to characterize their outcomes.

Methods: This is a retrospective cohort analysis of all ADPKD patients who presented for transplant evaluation at the Emory Transplant Center between 1/1/2002 and 1/1/2012, utilizing electronic medical records and the organ transplant tracking record (OTTR). Individuals were evaluated with regard to their graft and patient survival rates in those that did and did not have a nephrectomy.

Results: Of 286 ADPKD who presented for transplant evaluation, 169 (59.1%) were transplanted, 80 (28.0%) were evaluated but not yet transplanted, and 37 (12.9%) were ineligible for transplant. 5-year patient survival was 92.3% and 93.8% with and without a nephrectomy (p<0.001), respectively. 5-year patient survival for living and deceased donors was 98.0% and 92.9% (without a nephrectomy, p<0.001) and 100% and 89.7% (with a nephrectomy, p<0.001), respectively. 5-year graft survival was 82.9% and 88.9% with and without a nephrectomy (p<0.001), respectively. 5-year graft survival was 94.0% and 86.8% (without a nephrectomy, p=0.001) and 79.5% and 84.4% (with a nephrectomy, p=0.001) for living and deceased donor transplants, respectively. 5-year graft survival was 95.7% and 89.7% for African Americans and Caucasians, respectively, without a nephrectomy (p=0.001). 5-year graft survival was 75.0% and 84.1% for African Americans and Caucasians, respectively, with a nephrectomy (p=0.001). 5-year graft survival was 100.0% and 69.8% for pre- and post-transplant nephrectomies (p<0.001).

Conclusions: Nephrectomy is a significant risk factor for graft survival in this ADPKD cohort. Men are shown to have significantly higher graft survival than women with a nephrectomy, and patients with a nephrectomy after transplant are shown to have significantly higher graft survival than those with a nephrectomy before transplant.

SA-PO283

Patient-Reported Pain in Autosomal Dominant Polycystic Kidney Disease: Initial Concepts Based on Patient Focus Group Discussions Dorothee Oberdhan,1 Arlene B. Chapman,2 Sara N. Davison,2 Frank S. Czerwiec,1 Holly Krasa,1 Jason C. Cole.3 1Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD; 2Emory Univ, Atlanta, GA; 3Univ of Alberta, Edmonton, Canada; Covance Inc., San Diego, CA.

Background: Autosomal dominant polycystic kidney disease (ADPKD) involves significant kidney enlargement due to cyst development and expansion leading to kidney infections, bleeding, stones, chronic kidney disease and pain that is common, intermittent and debilitating, severely impacting a patient’s health-related quality of life. Surgical intervention and medications may be needed. Previous research demonstrated consistency in disease burden across regions and suggested ADPKD patients report pain varyingly.

Methods: In 18 focus groups, conducted in 5 cities in Europe (n=72) and 4 cities in the US (n=51), patients were asked about their pain symptoms and impact on daily life. New conceptual domains discussed were summarized based on themes mentioned by ≥2 participants in a group.

Results: Patients report chronic and episodic dull kidney pain, chronic fullness/discomfort and severe kidney pain plus general pain. Severe kidney pain is usually associated with cyst rupture or infection. Kidney pain is easily distinguished from other pain, especially with progressing disease. Pain severity is distinct for each of the types of pain reported.

Conclusions: Otsuka Pharmaceutical Development & Commercialization, Inc.

SA-PO284
Which Cyst to Drainage? — Mass Reduction Therapy for Autosomal Dominant Polycystic Kidney Disease Patients with Huge Liver Cysts
Takashi Iijima, Koki Mise, Rikako Hiramatsu, Kenneji Takachi. Dept of Nephrology, Toranomon Hospital.

Background: Percutaneous needle aspiration of cysts with subsequent sclerosis by injection of needle sclerosis (drainage therapy) has been reported to be effective for patients with autosomal dominant polycystic kidney disease (ADPKD). At present, it is widely accepted that aspiration of cysts with infection or hemorrhage is indicated. However, a detailed investigation of the factors that influence the success of cyst drainage has not yet been performed. Accordingly, we evaluated the factors with an influence on this therapy.

Methods: At our institution, cyst drainage therapy was performed in 16 ADPKD patients with a hepatic cyst volume of over 500 ml between January 2010 and April 2012. The hepatic cyst area was calculated with area assessment software after precisely outlining the cyst(s) on CT scans, and the volume was calculated by summing up each area of 1-cm thickness CT slices. The mean CT value of each cyst was also calculated, as was the ratio of the cyst volume at one year after treatment to that before treatment. Drained cyst fluid was submitted for analysis of its specific gravity. Then CT values and specific gravity were compared between group A (cysts showing over 80% volume reduction (mean of 92.4%) at one year after drainage and group B cysts with less than 80% volume reduction (mean of 31.1%). Statistical analysis was done by using the Mann-Whitney U test.

Results: Group A cysts had significantly lower CT values than group B cysts, with the values being 6.0U (4 to 10) and 19.6U (6 to 23) (p<0.004), respectively. Specific gravity was also significantly lower in group A than in group B, being 1.013 g/ml (1.007 to 1.017) versus 1.017 g/ml (1.009 to 1.031) (p=0.017). When the cut-off value to predict responsiveness of drainage therapy is set at 13 UH of CT value, the sensitivity was 70% and specificity was 100%.

Conclusions: Drainage therapy was effective for hepatic cysts with lower CT values and lower specific gravity, while the response was poor when hepatic cysts had higher CT values and higher specific gravity, which probably indicate “complicated” cyst with prior infection and/or hemorrhage.

SA-PO285
Transcatheter Arterial Embolization with Embosphere: Evaluation of Technical Safety and Outcome
Saori Nishio, 1 Yusuke Sakuhara, 2 Naoko Matsuoka, 1 Junya Yamamoto, 1 Tasuku Nakagaki, 1 Daigo Nakazawa, 1 Daisuke (PCLD). Guidelines for diagnosis and treatment are absent. The aim was to assess the polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (ADPL). Technical Safety and Outcome

Background: Polycystic liver disease (PLD) is the most common extrarenal manifestation associated with autosomal dominant polycystic kidney disease (ADPKD). PLD patients with a hepatic cyst volume of over 500 ml between January 2010 and April 2012.

Methods: Five PLD patients with severe symptom (1 male, 4 females) underwent TAE for hepatic artery branches using Embosphere. One patient had undergone TAE with metallic coils. We evaluated the technical safety and effectiveness of TAE using Embosphere for enlarged polycystic liver.

Results: TAE was considered technically successful when the target hepatic arteries were fully embolized, as demonstrated by hepatic arterial angiography performed at completion of the procedure. Technical success was achieved in all cases. No major complication related to TAE was found. Common adverse events were fever, epigastric pain, nausea, and vomiting. Two patients improved symptoms significantly one month after TAE. We found hepatic cyst volume reduction. No patient complained of worsening of the symptoms after the procedure.

Conclusions: We suggest that TAE using Embosphere is effective and safe in treating symptomatic polycystic liver in ADPKD patients, even who had treated by TAE using metallic coils.

SA-PO286
Characterization and Management of Patients with Renal or Hepatic Cyst Infection
Martin A. Lantinga, 1 Tom JG Gevers, 1 Wim JG Oyen, 2 Rudolph De Sevaux, 2 Joost HJ Drenth, 3 Hepatology, Radboud Univ Nijmegen Medical Centre, Nijmegen, The Netherlands; Nuclear Medicine, Radboud Univ Nijmegen Medical Centre, Nijmegen, The Netherlands; Nephrology, Radboud Univ Nijmegen Medical Centre, Nijmegen, The Netherlands.

Background: Cyst infection is the most critical complication in autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (PCLD). Guidelines for diagnosis and treatment are absent. The aim was to assess the clinical characteristics and therapeutic approach of patients with cyst infection.

Methods: Patients with cyst infection were ascertained and identified from clinical and radiological registers in a tertiary referral center from 2001-2013. Patients were included when there was a positive cyst aspirate, positive PDG-PET/CT and/or clinical findings suggestive for cyst infection. Clinical, radiological, biochemical and/or microbiological data were derived from medical records.

Results: We included 49 patients (86% ADPKD, 45% renal transplant, mean age 56 years (17-81)) with renal (57%), RCL or hepatic cyst infection. Some 20% had diabetes mellitus and 47% used immunosuppressive drugs. Urine cultures were positive in 13/24 (RCL) and 2/15 (HCl) of patients, whereas blood cultures were positive in 6/19 (RCL) and 11/16 (HCl) of patients. E. coli was the most frequent pathogen and was cultured from urine (53%) and blood (59%). Some 31% were refractory to treatment. Some 229 patients (453 episodes) who were hospitalized with a diagnosis of cyst infection. 80 patients were on dialysis. They were included in the analyses. Urine cultures were positive in 13/24 (RCL) and 2/15 (HCl) of patients, whereas blood cultures were positive in 6/19 (RCL) and 11/16 (HCl) of patients. E. coli was the most frequent pathogen and was cultured from urine (53%) and blood (59%). Some 31% were refractory to treatment. Some 229 patients (453 episodes) who were hospitalized with a diagnosis of cyst infection from 2004 to 2013 were enrolled. We investigated the causative bacteria detected by cyst fluid culture and their sensitivity to lipophilic antibiotics.

Results: A total of 93 patients (127 episodes of infection were enrolled from among 229 patients (453 episodes) who were hospitalized with a diagnosis of cyst infection from 2004 to 2013 were enrolled. We investigated the causative bacteria detected by cyst fluid culture and their sensitivity to lipophilic antibiotics. 80 patients were on dialysis. They were included in the analyses. Urine cultures were positive in 13/24 (RCL) and 2/15 (HCl) of patients, whereas blood cultures were positive in 6/19 (RCL) and 11/16 (HCl) of patients. E. coli was the most frequent pathogen and was cultured from urine (53%) and blood (59%). Some 31% were refractory to treatment. Some 229 patients (453 episodes) who were hospitalized with a diagnosis of cyst infection from 2004 to 2013 were enrolled. We investigated the causative bacteria detected by cyst fluid culture and their sensitivity to lipophilic antibiotics. 80 patients were on dialysis. They were included in the analyses. Urine cultures were positive in 13/24 (RCL) and 2/15 (HCl) of patients, whereas blood cultures were positive in 6/19 (RCL) and 11/16 (HCl) of patients. E. coli was the most frequent pathogen and was cultured from urine (53%) and blood (59%). Some 31% were refractory to treatment. Some 229 patients (453 episodes) who were hospitalized with a diagnosis of cyst infection from 2004 to 2013 were enrolled. We investigated the causative bacteria detected by cyst fluid culture and their sensitivity to lipophilic antibiotics. 80 patients were on dialysis. They were included in the analyses. Urine cultures were positive in 13/24 (RCL) and 2/15 (HCl) of patients, whereas blood cultures were positive in 6/19 (RCL) and 11/16 (HCl) of patients. E. coli was the most frequent pathogen and was cultured from urine (53%) and blood (59%). Some 31% were refractory to treatment. Some 229 patients (453 episodes) who were hospitalized with a diagnosis of cyst infection from 2004 to 2013 were enrolled. We investigated the causative bacteria detected by cyst fluid culture and their sensitivity to lipophilic antibiotics. 80 patients were on dialysis. They were included in the analyses. Urine cultures were positive in 13/24 (RCL) and 2/15 (HCl) of patients, whereas blood cultures were positive in 6/19 (RCL) and 11/16 (HCl) of patients. E. coli was the most frequent pathogen and was cultured from urine (53%) and blood (59%). Some 31% were refractory to treatment. Some 229 patients (453 episodes) who were hospitalized with a diagnosis of cyst infection from 2004 to 2013 were enrolled. We investigated the causative bacteria detected by cyst fluid culture and their sensitivity to lipophilic antibiotics. 80 patients were on dialysis. They were included in the analyses. Urine cultures were positive in 13/24 (RCL) and 2/15 (HCl) of patients, whereas blood cultures were positive in 6/19 (RCL) and 11/16 (HCl) of patients. E. coli was the most frequent pathogen and was cultured from urine (53%) and blood (59%). Some 31% were refractory to treatment. Some 229 patients (453 episodes) who were hospitalized with a diagnosis of cyst infection from 2004 to 2013 were enrolled. We investigated the causative bacteria detected by cyst fluid culture and their sensitivity to lipophilic antibiotics.
A Comprehensive Mutation Search within the PKD1/2 for Japanese Subjects with Autosomal Dominant Polycystic Kidney Disease

Katsuyuki Nishio,1,2 Kazuhiro Hanaoka,3 Koushi Kamiura,4 Kaori Hatanaka,5 Yoshihisa Ubara,6 Masahiko Ando,7 Kiku Nishita,8 Shigeo Horie,1,3 Urology, Teikyo Univ, Tokyo, Japan; 1Nephrology, Tokyo Woman's Medical U, Tokyo, Japan; 2The 2nd Dept of Internal Medicine, Hokkaido U, Sapporo, Japan; 3Nephrology, Itoji U, Tokyo, Japan; 4Urology, Chiba East Hospital, Chiba, Japan; 5Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; 6Nephrology, Osaka City U, Osaka, Japan; 7The 2nd Dept of Internal Medicine, Niigata Univ, Niigata, Japan; 8Urology, Chiba East Hospital, Chiba, Japan; 9Nephrology, Toranomon Hospital, Tokyo, Japan; 10Center for Advanced Medical and Clinical Research, Nagoya Univ, Nagoya, Japan; 11Urology, Koyorin U, Mitaka, Japan; 12Urology, Juntendo Univ, Tokyo, Japan.

Background: The PKD Sectional Committee of a Grant-in-Aid for Progressive Renal Diseases Research, from the Ministry of Health, Labour and Welfare of Japan established the first nationwide, web-based, and prospective registry system, the Japan PKD Registry (J-PKD), to record clinical, and laboratory data in Japan. Although the follow-up periods of this study were 5 years, we will report the compiling data at the time of enrollment in J-PKD registry.

Methods: Patient data including age, gender, family history, complication, medical history, and laboratory data were electronically recorded at each institution and registered via the Internet Data and Information Center for Medical Research system, which is part of the University Hospital Information Network.

Results: We included 271 ADPKD patients in this study (176 female and 95 male). Median age was 52 years. The mean estimated GFR was 49.3ml/min/1.73m². Several parameters including waist circumference (r²=0.06, p<0.001), systolic blood pressure (r²=0.05, p<0.001), total kidney volume (r²=0.25, p<0.001) were significantly inversely correlated with eGFR. There were significant correlations between eGFR and Hemoglobin level (r²=0.26, p<0.001), serum albumin (r²=0.08, p<0.001).

Conclusions: In this cohort study, we will clear the actual treatment course of PKD in Japan.
PDGF-R1 expression, which was lost in db/db mice. Numbers of leucocytes (T cells and macrophages, including CD11c+ macrophages) in Enalapril treated db/db mice were restored to comparable levels as in db/+ mice.

**Conclusions:** Enalapril treatment showed a temporary beneficial effect on albuminuria during the progression of diabetic nephropathy in db/db mice. However, despite lack of effect on albuminuria at 12 weeks of treatment, Enalapril increased numbers of distal tubular epithelial cells and other parenchymal cells and seemed to promote vascular inflammation, but also restored PDGF-R1 and macrophage numbers to non-diabetic levels. The trophic effect and restoration of M1 macrophage numbers suggests beneficial effects even in absence of reduction of albuminuria.

**Funding:** Pharmaceutical Company Support - Novo Nordisk A/S

SA-PO294

**Urinary Aminopeptidase A but Not ACE2 Is Upregulated by RAS Blockade in db/db Mice**

**Methods:** C57BL/6 mice were administered streptozotocin i.p. to induce diabetes mellitus. For inhibition of p38, the mice were subsequently treated with SB202190 i.p. Measurements from 4 consecutive urine collections 1-3 weeks apart were averaged for each experimental condition and expressed as enzyme activity/creatinine.

**Results:** In the urines from db/db mice under baseline condition, APA (188±18 vs. 107±8, RFU/ug creat/hr, p<0.001) and ACE2 activity (46±12 vs. 10±2 RFU/ug creat/hr, p<0.05) were both increased as compared to db/+ controls. When administered for several weeks, an ACE inhibitor, captoril (60 mg/kg/d) and a specific AT1 receptor blocker, telmisartan (2 mg/kg/d), increased significantly the levels of urinary APA activity in db/db mice as compared to baseline (650±114 and 378±72 vs. 188±18, p<0.001 and p<0.05 respectively) whereas they had no effect on urinary ACE2 activity (39±6 and 51±7 vs. 46±12, respectively). Both RAS blockers reduced albumin creatinine ratio significantly (p<0.05).

**Conclusions:** Urinary APA and ACE2 activities are increased in db/db mice. Whereas RAS blockade increases urinary APA activity, ACE2 activity in the urine is unaffected by either captoril or telmisartan. Altogether these findings suggest that urinary ACE2 and APA appear to be differentially regulated by RAS blockers and, moreover, raise the possibility that the therapeutic renal action of RAS blockers involves up-regulation of kidney aminopeptidase A and thus enhanced Ang II degradation.

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

SA-PO295

**In Vivo Quantification of Nephrin Endocytosis Mediated by MAPK p38 in Diabetic Animals**

**Methods:** C57BLKS/J db/db mice were obtained from Jackson Laboratories. Primary cultures of mesangial and proximal tubule cells (RPTC) were cultured under normal and hyperglycemic conditions (17 mM) and glycosphingolipids quantified. 

**Results:** In 9 and 18 week mice before and following treatment included: body weight; blood glucose; urinary protein excretion; pathological lesions in glomeruli and proximal tubules; changes in protein of the pro-inflammatory transcription factor nuclear factorκB (NF-κB), endothelial intracellular adhesion molecule-1 (ICAM-1), proliferotic transforming growth factor-β1 (TGF-β1), phospho-SMAD3- and alpha-smooth muscle actin (α-SMA); and IHC analysis of leaky slit membrane and collagen 1A2 (COL1A2) deposition.

**Conclusions:** Delayed administration of a single dose of suramin, a FDA-approved drug for generalized inflammation and fibrosis in an early model of type 1 diabetes-induced renal injury. These studies tested the hypothesis that delayed administration of a single dose of suramin decreases early and late stage diabetic nephropathy in a lep-receptor deficient C57BLKS/J db/db type 2 diabetic nephropathy (T2DN) mouse model.

**Funding:** NIDDK Support, Veterans Affairs Support

SA-PO296

**Vitamin D Improves Podocyte Hyperpermeability Induced by High Glucose and Advanced Glycosylation Endproducts**

**Methods:** C57BLKS/J db/db mice were obtained from Jackson Laboratories. Kidney cortices and mesangial cells and proximal tubules cells purified from kidney cortices. Primary cultures of mesangial and proximal tubule cells (RPTC) were cultured under normal and hyperglycemic conditions (17 mM) and glycosphingolipids quantified. 

**Results:** In the urines from db/db mice under baseline condition, APA (188±18 vs. 107±8, RFU/ug creat/hr, p<0.001) and ACE2 activity (46±12 vs. 10±2 RFU/ug creat/hr, p<0.05) were both increased as compared to db/+ controls. When administered for several weeks, an ACE inhibitor, captoril (60 mg/kg/d) and a specific AT1 receptor blocker, telmisartan (2 mg/kg/d), increased significantly the levels of urinary APA activity in db/db mice as compared to baseline (650±114 and 378±72 vs. 188±18, p<0.001 and p<0.05 respectively) whereas they had no effect on urinary ACE2 activity (39±6 and 51±7 vs. 46±12, respectively). Both RAS blockers reduced albumin creatinine ratio significantly (p<0.05).

**Conclusions:** Urinary APA and ACE2 activities are increased in db/db mice. Whereas RAS blockade increases urinary APA activity, ACE2 activity in the urine is unaffected by either captoril or telmisartan. Altogether these findings suggest that urinary ACE2 and APA appear to be differentially regulated by RAS blockers and, moreover, raise the possibility that the therapeutic renal action of RAS blockers involves up-regulation of kidney aminopeptidase A and thus enhanced Ang II degradation.

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

SA-PO297

**Therapeutic Potential of Suramin in Diabetic Nephropathy**

**Methods:** C57BLKS/J db/db mice were obtained from Jackson Laboratories. Primary cultures of mesangial and proximal tubule cells (RPTC) were cultured under normal and hyperglycemic conditions (17 mM) and glycosphingolipids quantified. 

**Results:** In the urines from db/db mice under baseline condition, APA (188±18 vs. 107±8, RFU/ug creat/hr, p<0.001) and ACE2 activity (46±12 vs. 10±2 RFU/ug creat/hr, p<0.05) were both increased as compared to db/+ controls. When administered for several weeks, an ACE inhibitor, captoril (60 mg/kg/d) and a specific AT1 receptor blocker, telmisartan (2 mg/kg/d), increased significantly the levels of urinary APA activity in db/db mice as compared to baseline (650±114 and 378±72 vs. 188±18, p<0.001 and p<0.05 respectively) whereas they had no effect on urinary ACE2 activity (39±6 and 51±7 vs. 46±12, respectively). Both RAS blockers reduced albumin creatinine ratio significantly (p<0.05).

**Conclusions:** Urinary APA and ACE2 activities are increased in db/db mice. Whereas RAS blockade increases urinary APA activity, ACE2 activity in the urine is unaffected by either captoril or telmisartan. Altogether these findings suggest that urinary ACE2 and APA appear to be differentially regulated by RAS blockers and, moreover, raise the possibility that the therapeutic renal action of RAS blockers involves up-regulation of kidney aminopeptidase A and thus enhanced Ang II degradation.

**Funding:** NIDDK Support, Veterans Affairs Support

SA-PO298

**The Role of Glycosphingolipids in Diabetic Nephropathy**

**Methods:** C57BLKS/J db/db mice were obtained from Jackson Laboratories. Kidney cortices and mesangial cells and proximal tubules cells purified from kidney cortices. Primary cultures of mesangial and proximal tubule cells (RPTC) were cultured under normal and hyperglycemic conditions (17 mM) and glycosphingolipids quantified. 

**Results:** In the urines from db/db mice under baseline condition, APA (188±18 vs. 107±8, RFU/ug creat/hr, p<0.001) and ACE2 activity (46±12 vs. 10±2 RFU/ug creat/hr, p<0.05) were both increased as compared to db/+ controls. When administered for several weeks, an ACE inhibitor, captoril (60 mg/kg/d) and a specific AT1 receptor blocker, telmisartan (2 mg/kg/d), increased significantly the levels of urinary APA activity in db/db mice as compared to baseline (650±114 and 378±72 vs. 188±18, p<0.001 and p<0.05 respectively) whereas they had no effect on urinary ACE2 activity (39±6 and 51±7 vs. 46±12, respectively). Both RAS blockers reduced albumin creatinine ratio significantly (p<0.05).

**Conclusions:** Urinary APA and ACE2 activities are increased in db/db mice. Whereas RAS blockade increases urinary APA activity, ACE2 activity in the urine is unaffected by either captoril or telmisartan. Altogether these findings suggest that urinary ACE2 and APA appear to be differentially regulated by RAS blockers and, moreover, raise the possibility that the therapeutic renal action of RAS blockers involves up-regulation of kidney aminopeptidase A and thus enhanced Ang II degradation.

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

SA-PO299

**In Vivo Quantification of Nephrin Endocytosis Mediated by MAPK p38 in Diabetic Animals**

**Methods:** C57BLKS/J db/db mice were obtained from Jackson Laboratories. Primary cultures of mesangial and proximal tubule cells (RPTC) were cultured under normal and hyperglycemic conditions (17 mM) and glycosphingolipids quantified. 

**Results:** In the urines from db/db mice under baseline condition, APA (188±18 vs. 107±8, RFU/ug creat/hr, p<0.001) and ACE2 activity (46±12 vs. 10±2 RFU/ug creat/hr, p<0.05) were both increased as compared to db/+ controls. When administered for several weeks, an ACE inhibitor, captoril (60 mg/kg/d) and a specific AT1 receptor blocker, telmisartan (2 mg/kg/d), increased significantly the levels of urinary APA activity in db/db mice as compared to baseline (650±114 and 378±72 vs. 188±18, p<0.001 and p<0.05 respectively) whereas they had no effect on urinary ACE2 activity (39±6 and 51±7 vs. 46±12, respectively). Both RAS blockers reduced albumin creatinine ratio significantly (p<0.05).

**Conclusions:** Urinary APA and ACE2 activities are increased in db/db mice. Whereas RAS blockade increases urinary APA activity, ACE2 activity in the urine is unaffected by either captoril or telmisartan. Altogether these findings suggest that urinary ACE2 and APA appear to be differentially regulated by RAS blockers and, moreover, raise the possibility that the therapeutic renal action of RAS blockers involves up-regulation of kidney aminopeptidase A and thus enhanced Ang II degradation.

**Funding:** NIDDK Support, Private Foundation Support
SA-PO299
Cathepsin S Promotes Endothelial Dysfunction, Proteinuria, Podocyte Loss, and Glomerulosclerosis in Type 2 Diabetes
Murthy Narayana Darisipudi,1 Onkar Kulkarni,1 Shrikant R. Mulay,1 Hartmann Guido,2 Hans J. Anders.3 1Nephrological Zentrum, Klinische Biochemie, Medizinische Klinik und Poliklinik IV der LMU, Munich, Germany; 2CV & Metabolism DTA, Hoffmann La Roche, Basel, Switzerland.

Background: Cathespin S is an elastolytic cysteine protease, known to drive atherogenesis and vascular wall degeneration in aging as well as in the accelerated atherogenesis of chronic kidney disease. To date a pathogenic role of cathepsin S in microvascular complications of type 2 diabetes is entirely speculative.

Methods: Male diabetic mice were fed either with food-drug mix contained cathepsin S inhibitor, ROS46111 and standard food from 16 weeks of age till 24 weeks. Kidneys were harvested for histopathological evaluation and splenocytes were used to estimate the Lip10 level. Blood and urine samples were obtained at monthly intervals.

Results: We found increased plasma cathepsin S activity and increased cathepsin S protein expression in kidney especially upon accelerating the onset of disease by early uninephrectomy. Immunostaining localized cathepsin S protein to tubular epithelial cells, endothelial cells and infiltrating leukocytes in advanced diabetic nephropathy, while in diabetic mice with less advanced disease the tubular signal was most obvious. However, tubular cathespin S mRNA expression was abolished by in situ hybridization. Treatment with ROS46111 significantly reduced albuminuria, podocyte loss, and glomerulosclerosis in association with lower macrophage infiltrates as well as pro-inflammatory cytokines, adhesion molecules mRNA expression and restored eNOS expression. In vitro studies with glomerular endothelial cells documented a toxic effect of cathepsin S in terms of viability, detachment, and permeability. In vivo microscopy studies revealed that cathepsin S inhibition improved oxidative stress-induced microvascular permeability.

Conclusions: Cathespin S is a circulating mediator of endothelial dysfunction driving albuminuria and progressive kidney disease in type 2 diabetes, a process that can be prevented by cathepsin S inhibition, e.g. with ROS46111.

SA-PO300
Complement C3a, C5a Regulate Endothelial-Myofibroblast Transition Via Wnt/β-Catenin Signaling Pathway in Diabetic Nephropathy
Li Huang,1 Ling Li,1 Jing Zang,1 Jie Zhang,2 Qinghua Yin,1 Lu Cheng,1 Yanrong Lu,2 Jingqiu Wnt,1 Liang Li,3 Min Wu,2 Yu Lijia Chen,1

Background: Endothelial-myoﬁbroblast transition (EndMT) is considered to be involved in the development and progression of renal ﬁbrosis in diabetic nephropathy (DN). We aimed to investigate whether the C3a and C5a as the novel profibrotic factors could induce EndMT via Wnt/β-catenin signaling pathway in DN.

Methods: Male SD rats were randomized into four groups: normal control, DN, DN+C5aRA (C5a receptor antagonist) and DN+C5aRA (C5a receptor antagonist), which were slaughtered after eight weeks. In vitro cultured human renal glomerular endothelial cells (HRGECs) were divided into ten groups: normal glucose, mannitol, TGF-β1, high glucose, HG+C3a, HG+C3a+C3aRA, HG+C3a+DKK1, HG+C5a, HG+C5a+C5aRA and HG+C5a+DKK1. DKK1 was used as Wnt/β-catenin pathway inhibitor. Double-labeled ﬂuorescent staining was performed to detect the expression of CD31 and α-SMA. The expression of anti-SMA, CD31, C3a, C5a, C3α, C5α, β-catenin, TGF-β1, and col-1 were detected by real-time PCR, western blot and immunohistochemistry.

Results: C3a, C5a, C3α and C5α were found up-regulated in glomeruli in DN group. Strong staining of α-SMA and β-catenin with decreasing staining of CD31 was observed in glomerular endothelial cells in DN group, which were retrieved by C3αRA or C5αRA treatment. And up-regulation of α-SMA, β-catenin, TGF-β1, col-1, and down-regulation of CD31 were also detected by real-time PCR, western blot and double-labeled fluorescent staining. HRGECs stimulated by high glucose, C3a and C5a, which were retrieved by C3αRA or C5αRA and DKK1.

Conclusions: Complement C3a and C5α-induced EndMT is a novel mechanism in DN. Blockage of Wnt/β-catenin signaling pathway may alleviate EndMT and fibrosis in DN.

SA-PO301
Renoprotective Effects of Luseogliflozin (TS-971), a Novel SGLT2 Inhibitor, in Diabetic db/db Mice
Yumi Takayama, Manami Kobayashi, Jun Honjo, Yukihito Fujita, Tsuyoshi Yanagimachi, Hiroyo Kitusuri, Yuichi Makino, Masakazu Haneda.1 Division of Metabolism and Biosystemic Science, Dept. of Medicine, Asahikawa Medical Univ, Asahikawa, Hokkaido, Japan.

Background: Sodium glucose cotransporter 2 (SGLT2) represents a novel target for normalizing glycemia. To address in vivo the efficacy and tolerability of a novel SGLT2 inhibitor Luseogliflozin(LUSEO), we investigated whether LUSEO can prevent renal insufficiency and glomerulosclerosis in diabetic mice, and determined potential mechanisms of renoprotective effects.

Methods: db/db mice were treated with 15 mg/kg LUSEO for 8 weeks. The regulation of SGLT2 expression was evaluated using human renal proximal tubular epithelial cells (HRPTC) by RT-qPCR.

Results: LUSEO significantly improved plasma glucose levels in db/db mice. Then, consistent with lower filtered glucose load, urinary glucose excretion in db/db treated with LUSEO was decreased. Moreover, LUSEO showed renoprotective effects, which significantly attenuated urinary protein excretion, glomerular mesangial matrix expansion, glomerular and interstitial fibrocellulose accumulation, and Armanni-Ebstein lesions in db/db mice. Of interest, LUSEO augmented pimonidazole staining of the S3 segment of the proximal tubules cells which expressed SGLT1, in the outer stripe of the kidney, in db/db mice, suggesting improved glucose absorption.

Conclusions: These data demonstrate that LUSEO can protect against the progression of diabetic nephropathy, which is probably sufficient to overcome the adverse effects of TGF-β1 or compensatory hyperplasia.

Funding: Pharmaceutical Company Support - Taisho Pharmaceutical Co., Ltd.

SA-PO302
Defective Autophagy Sensitizes Podocytes to Secondary Attack by Amplifying Inflammation Activation in Diabetic Nephropathy
Li Fang, WeiChun He, ChunWei Dai, Junwei Yang.2 1Affiliated Hospital of Nanjing Medical Univ.

Background: The mechanisms for the development of diabetic nephropathy (DN), the leading cause of end-stage renal disease (ESRD) in many industrialized countries, are not fully understood. Our previous data demonstrated that defective podocyte autophagy was associated with the progression of DN, here the underlying mechanism for defective podocyte autophagy leading to the progression of DN was investigated.

Methods: Both diabetic patients and animal experiment were included in this study. For the animal experiment, the C5-1 mice were divided into four groups: normal control, hyperuricemia group (250mg/kg/d uric acid intraperitoneal injection for 14 days), diabetic group (3 months after onset), diabetic plus hyperuricemia group (hyperuricemia for 4 months). In the diabetic patients, immunohistochemical staining for the kidney glomeruli was performed to detect inflammatory cytokines, adhesion molecules mRNA expression, and restored eNOS expression. In vitro studies with glomerular endothelial cells documented a toxic effect of uric acid on viability, detachment, and permeability. In vivo microscopy studies revealed that uric acid-induced urinary albumin excretion rates, glomerular mesangial matrix expansion, glomerular and interstitial fibrocellulose accumulation, and Armanni-Ebstein lesions in db/db mice. Of interest, LUSEO augmented pimonidazole staining of the S3 segment of the proximal tubules cells which expressed SGLT1, in the outer stripe of the kidney, in db/db mice, suggesting improved glucose absorption.

Conclusions: These findings suggest that defective autophagy sensitizes the podocytes to the secondary attack by amplifying inflammation activation in diabetic nephropathy.

Funding: Government Support - Non-U.S.

SA-PO303
Hypovolemia, Not Hyperoxaluria, Causes Nephropathy following Gastric Bypass in Obese Rats
Benjamin Canales,1 Margarette Hatch,2 Saed R. Khan.2 1Urology, Univ. of Florida, Gainesville, FL; 2Pathology, Immunology and Laboratory Medicine, Univ. of Florida, Gainesville, FL.

Background: In the morbibly obese, Roux-en-Y gastric bypass (RYGB) can decrease renal hyperfiltration, improve glycemic control, and lower blood pressure. Its overall effect on renal function remains debatable, as RYGB can be also associated with recurrent oxalate lithiasis and post-procedural hypovolemia. We hypothesized that a diet-induced obese (DIO) model of RYGB with appropriate controls could address this question, providing end of study renal histology while controlling dietary oxalate content.

Methods: Male DIO Sprague-Dawley rats, aged 23 weeks, were randomly assigned to RYGB, or Sham control group. Animals were placed on a lab normal calcium, high fat (40%) diet with 1.5% potassium oxalate (Ox) or without (No Ox). Weekly weights, food and water intake, complications, and clinical interventions were recorded.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Urine and serum were collected at baseline and every 5 weeks until euthanasia. At study endpoint, renal histology was assessed using a quantitative glomerular and tubular scoring system. All rats developed advanced phenotypic traits, and animals were grouped into normal (NH) or abnormal (AH) histology. Animals that died prior to reaching endpoint were excluded from final analysis.

**Results:** Survival to endpoint was 63% (47/74) in RYGB and 90% (36/40) in controls. Over 36% (17/47) of RYGB animals had AH compared to 6% (2/36) of controls. Factors associated with developing RYGB AH included: age ≥20 weeks, 4 or more fecal bile acid abnormalities, and serum bicarbonate <25 mmol/L. One-week-old male Sprague-Dawley rats were housed in groups of five. Rats were weighed daily, and food and water were provided ad libitum. The experimental group consisted of four groups: control, STZ-induced diabetic rats at 4 weeks, and STZ-induced diabetic rats that were administered 100 mg/kg streptozotocin (STZ) intraperitoneally twice weekly for 8 weeks before sacrifice. Blood glucose levels were significantly increased in the diabetic rats compared with controls (80.4±4.9 vs. 16.6±0.7 mg/mg protein, p<0.005), which were significantly reduced in rats treated with telmisartan (35.7±5.5 mg/mg protein, p=0.0005).

**Conclusions:** The diabetic kidney showed increased cytoplasmic glucose levels mediated by enhanced SGLT2 expression in the proximal tubules and increased gluconeogenesis enzymes, which were suppressed by ARB treatment.

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

**SA-PO305**

**TXNFR Causes Podocyte Cholesterol Accumulation and Apoptosis in Diabetic Kidney Disease**

Chouaieb El F Pedrero,1 Armando Mendez,2 Matthias Kretzler,2 Christopher E. Pedigo,1 Armando Mendez,4 Matthias Kretzler,2 Robert G. Nelson,3 George William Burke,4,5 Alessia Fornoni,1,4 Sandra M. Merscher-Gomez.1

**Background:** Diabetic nephropathy (DN) is a serious complication of diabetes leading to loss of renal function. Proximal tubular epithelial cells (PTCs) contribute to the hypertrophic response of the kidney. Early stages of DN are also associated with alterations in renal sodium handling as well as hypertension; processes linked by involvement of the arachidonic acid (AA) metabolites 20-hydroxyicosatetraenoic acid (20-HETE) and epoxyeicosatetraenoic acids (EETs). This study aims to determine the specific AA-metabolizing CYP450 isoforms present in proximal tubules that are altered by high glucose (HG) or hyperglycemia and to investigate the effects of their alterations on DN.

**Methods:** We show that exposure of rats proximal tubular epithelial cells to high glucose (HG) resulted in increased extracellular matrix accumulation and hypertrophy. HG treatment increased ROS production and was associated with alteration in CYP4A and 2C11 expression and alteration in 20-HETE and EETs formation. HG-induced tubular injury was blocked by 20HETE inhibition. In contrast, inhibition of EETs promoted the effects of HG on cultured proximal tubular cells. We also show that alteration in CYP 4A/2C expression and 20-HETE/EETs formation regulates the activation of the stearoyl-CoA desaturase pathway, having a major role in the development of DN. In parallel experiments we show that inhibition of the Cyp4A-mediated 20-HETE production or induction of EETs formation in animal model of diabetes prevent tubular cell injury and proteinuria. Our in vivo observations were correlated by increased urine levels of 20-HETE in diabetic rats and these levels were reduced by modulation of 20-HETE with its inhibitor HET0016.

**Conclusions:** Our results indicate that hyperglycemia in diabetes has a significant effect on the expression of AA-metabolizing CYPs, manifested by increased AA metabolism, and might thus alter kidney function through alteration of type and amount of AA metabolites. These observations provide a strong rationale to study cytochrome P450 as a promising target for therapeutic drug development in DN.

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

**SA-PO306**

**Role of Bone Morphogenetic Protein-7 (BMP7) in Diabetic Tubulopathy**

Ruix Lai,1 Wai Han Yiu,2 Hao-Jia Wu,2 Miao Lin,3 Dickinson WL Wong,4 Loretta Y.Y. Chan,1 Joseph C.K. Leung,1 Kar Neng Lai,5 Sydney C.W. Tang.1 Medicine, Queen Mary Hospital, Hong Kong, China.

**Background:** The potential renoprotective role of BMP7 in diabetic nephropathy remains unknown. These observations provide a strong rationale to study cytochrome P450 as a promising target for therapeutic drug development in DN.

**Methods:** Nine-week-old db/db mice and their db/+ littermates underwent uninephrectomy (Unx) or sham operation, and received rh-BMP7 (300μg/kg body weight) or vehicle intraperitoneally every other day for 8 weeks before sacrifice. Primary human proximal tubular epithelial cells (PTECs) were grown and exposed to glycated human serum albumin (AGE-HSA) with or without rh-BMP7.
Results: Compared with vehicle control, Unx dh/db mice treated with rh-BMP7 for 8 weeks had significantly lower urinary albumin-to-creatinine ratio (4,566±2,767 μg/mg vs. 7,300±2,839 μg/mg, p<0.05), serum BUN (33.3±3.46 mg/dl vs. 37.5±2.95 mg/dl, p<0.05), and renal cortical gene expression of IL-6, ICAM-1, CCL-2 and CCL-5. PAS staining of kidney tissue showed significantly less severe tubular damage and interstitial inflammatory cell infiltration in the BMP7-treated group. In cultured human PTECs, exposure to AGE-HEMA in high osmolarity of sICAM-1, CCL-2, IL-8 and IL-6, involving activation of p44/p42 and p38 MAPK signaling. BMP7 dose-dependently attenuated AGE-induced upregulation of sICAM-1, CCL-2, IL-8 and IL-6 at both mRNA and protein levels. Moreover, BMP7 suppressed AGE-induced p38 and p44/p42 MAPK phosphorylation and reactive oxygen species production in PTECs.

Conclusions: Our results demonstrated for the first time that BMP7 ameliorates tubular pro-inflammatory responses in diabetic kidney disease by suppressing oxidative stress and multiple signaling pathways including p38 and p44/42 MAPK. Its potential application as a therapeutic molecule in diabetic nephropathy warrants further investigation.

This study is supported by a General Research Fund of the Research Grants Council (Grant number: HKU 7770/09M) of Hong Kong.

SA-PO309

Activated Local Renin-Angiotensin System within Glomerular Endothelial Cells Is Associated with Morphological and Functional Changes under Diabetic Conditions

Shin-Wook Kang,1,2 Ji Sun Paeng,1 Hye-Young Kang,1 Hyung Jung Oh,2 Seung Hyeok Han.2 1Brain Korea 21, Yonsei Univ, Seoul, Korea; 2Internal Medicine, College of Medicine, Yonsei Univ, Seoul, Korea.

Background: The role of renin-angiotensin system (RAS) within glomerular endothelial cells (GECS) in the pathogenesis of diabetic nephropathy (DN) has not been fully elucidated. We aimed to investigate the effects of AGE and changes in RAS components in high glucose (HG)-stimulated GECS and the role of local RAS in morphological and functional changes of GECS under diabetic conditions.

Methods: In vitro, GECS were exposed to 5.6 mM glucose (NG) or 30 mM glucose (HG) for 24 hours. In vivo, 32 Sprague-Dawley rats were injected with dinitro (n=16, C) or streptozotocin intraperitoneally (n=16, DM), and 8 animals in each group were treated with 10 mg/kg losartan for 6 weeks. The activation of local RAS was examined by Real-time PCR, Western blot analysis, and ELISA. Morphological changes were evaluated by scanning electron microscopy (SEM). FITC-tagged albumin permeability was determined by a transwell assay.

Results: Angiotensinogen mRNA and protein expression were significantly increased in HG-stimulated GECS compared to NG cells (p<0.01). AI and AII concentrations were also significantly higher in HG-conditioned medium (p<0.01). However, there were no differences in the mRNA and protein expression of ACE and AI type 1 and type 2 receptors. On SEM examination, the number and diameter of fenestrae were significantly increased in HG-stimulated GECS and these changes were significantly abrogated by losartan (p<0.05). A tranwell assay revealed that FITC uptakes in filtered media through HG-stimulated GECS were 4.3-fold higher compared to NG cells, and the increased uptakes were significantly ameliorated by losartan (p<0.05). In addition, diameter of GEC fenestrae and urinary albumin excretion were significantly greater in DM rats than those in C rats (p<0.05), which were significantly attenuated by losartan (p<0.05).

Conclusions: Local RAS within GECS was activated under HG conditions, and it seemed to be associated with alterations in GEC fenestration, resulting in the development of albuminuria in DN.

Funding: Government Support - Non-U.S.

SA-PO310

Oral Treatment with PBI-4050, a Novel First-in-Class Anti-Fibrotic Compound, Improves Kidney Function and Reduces Hepatic Steatosis in the Diabetic db/db Mouse Model


Background: Diabetic nephropathy (DN) is often associated with myocardial and oxidative stress. MIOX, a tubular enzyme, modulates redox imbalance and apoptosis in tubular cells in diabetes, but the mechanisms remain unclear.

Methods: We investigated the role of MIOX in perturbation of mitochondrial dynamics and autophagy under high glucose (HG) ambience contributing to mitochondrial-mediated ROS generation and apoptosis in vitro and in vivo.

Results: Following HG treatment of HK-2/LCC-PK1 cells, an increased expression of MIOX and mitochondrial fusion proteins, Drp1 & Fis1, and mitochondrial fragmentation was observed. Expression of fusion protein, Mfn2, and autophagy related proteins (LC3B, Atg5 and Beclin1) was decreased. MIOX-transfected tubular cells had an increased Drp1 expression and mitochondrial fusion under HG & LG ambience, whereas LC3B, Atg5 and Beclin1 expression was decreased. At times, in diabetes alets, plaque etc. These changes were accompanied with Bax activation, mitochondrial cytochrome C release, ROS overproduction and apoptosis. MIOX siRNA & D-glucarate, an inhibitor of MPIOX partially reversed these perturbations. An increased MIOX expression and mitochondrial fragmentation was also seen in proximal tubules during early stages of STZ-induced DN in mice, together with upregulation of Drp1, Bax and cytochrome C expression, but reduced expression of Mfn2 and autophagy related proteins. Dietary supplementation of D-glucarate to diabetic mice decreased MIOX expression and improved renal functions, as reflected by the reduction of serum creatinine, urinary albumin-to-creatinine ratio and tubular damage score. D-glucarate treated mice had partial attenuation of mitochondrial fragmentation and restoration of autophagy, accompanied with decreased oxidative stress and apoptosis in tubules. Conceivably, MIOX regulates mitochondrial dynamics, autophagy and apoptosis under HG ambience via modulation of Drp1 & Mfn2 activation.

Conclusions: Data suggest that MIOX modulates mitochondrial dynamics and autophagy in tubular cells in diabetic milieu, which may be a novel mechanism for ensuing redox imbalance and tubular cell injury and death.

Funding: NIDDK Support

SA-PO312

High Glucose Increases Formation and Pro-Oxidative Activity of Endothelial Microparticles

Dylan Burgess, Kevin D. Burns. Kidney Research Centre, Ottawa Hospital Research Institute, Univ of Ottawa, Ottawa, Canada.

Background: Microparticles (MPs) are submicron membrane fragments released from the cell under conditions of stress or damage. Changes in the expression of MPs in response to high glucose in epithelial endothelial MP levels are increased and predict risk of future cardiovascular events. Moreover, emerging evidence suggests that MPs may themselves exert deleterious biological effects. However, the stimuli responsible for increased MPs in diabetes, and the impact of diabetic conditions on the biological activity of endothelial MPs are not clear.

Methods: Human dermal microvascular endothelial cells (ECs) were cultured in media containing 5.6 mM glucose, 25 mM D-glucose, or 25 mM L-glucose (osmotic control). MP levels were assessed by Annexin V labeling and flow cytometry as well as nanoparticle tracking analysis in response to high glucose. MPs generated under high glucose increased MP formation from human vascular smooth muscle or proximal tubule epithelial cells, although it had no effect on human mesangial cell MP formation. Interestingly, exposure to 25 mM glucose increased the mean size of endothelial MPs (5.6 mM: 203±7 nm vs. 25 mM: 260±14 nm, P<0.05 n=6). Moreover, MPs generated under high glucose conditions were more potent inducers of endothelial cell ROS production than MPs generated under normal glucose conditions.

Results: Exposure of ECs to high glucose conditions was associated with a significant increase in MP formation over 24 hrs as assessed by flow cytometry (~2.5-fold vs. osmotic control, P<0.05, n=4) and NTAs (~2.5 fold vs. osmotic control, P<0.01, n=6). Similarly, high glucose increased MP formation from human vascular smooth muscle or proximal tubule epithelial cells, although it had no effect on human mesangial cell MP formation. Interestingly, exposure to 25 mM glucose increased the mean size of endothelial MPs (5.6 mM: 203±7 nm vs. 25 mM: 260±14 nm, P<0.05 n=6). Moreover, MPs generated under high glucose conditions were more potent inducers of endothelial cell ROS production than MPs generated under normal glucose (25 mM MPs: ~6-fold vs untreated control, 5.56 mM MPs: ~2.5 fold vs. control, P<0.05 n=4).

Conclusions: Our results suggest that elevated glucose is a potent inducer of endothelial MP formation while also increasing the pro-oxidative effects of endothelial MPs. Such effects may contribute to progressive endothelial injury in diabetes.

Funding: Government Support - Non-U.S.
SA-PO313

The Paradoxical Effect of Lycopene on Diabetic Nephropathy in Type 2 Diabetic Mice Young Sun Kang,1 Mi Jin Lee,1 Jin Joo Cha,1 Young Youl Hyun,2 Ji Eun Lee,1 Hyeonwook Kim,2 Jung Eun Kim,3 Miwha Lee,*4 Hye Kyong Song,1 Jee-young Han,1,5 Dae R. Cha.1,6

1Nephrology, Korea Univ Ansan Hospital, Ansan, Kyunggido, Republic of Korea; 2Nephrology, Sungkyunkwan Univ Kangbuk Samsung Hospital, Seoul, Republic of Korea; 3Nephrology, Woyang Univ Sambong Hospital, Gunpo, Republic of Korea; 4Pathology, Inha Univ Hospital, Incheon, Republic of Korea.

Background: Lycopene, a dietary carotenoid found in fruits, has been under investigation as its antioxidant benefit in cancer, cardiovascular disease, and the metabolic syndrome. There is rare data of lycopene in kidney disease. The aim of this study is to investigate the effect of lycopene on diabetic nephropathy in type 2 diabetic animal models.

Methods: 8-week-old male diabetic db/db mice were treated with vehicle or lycopene of 1mg/kg body weight for 4 weeks. The biochemical parameters were measured and RT-PCR, western blot analysis, and IHC were performed.

Results: After lycopene treatment, there was a noticeable decrease in body weight, food and water intake, urine amount, and blood sugar level. But, lycopene had no significant effect on plasma Cr level, BUN level, BP, and HR. Interestingly, Lycopene improved ITI(insulin tolerance test), plasma lipid profile such as total cholesterol, triglyceride and LDL cholesterol in diabetic mouse group. However, lycopene aggravated renal injury in diabetic animal model. This result was the opposite of the known anti-inflammatory effect. Lycopene increased proteinuria, the expression of renal inflammatory markers of PAI-1, TGFB1, and TNF-a, and 8-isoprostane as the oxidative stress marker. It increased the gene expression of lipid-regulating enzyme of FAS, and activated the insulin signaling pathway. Lycopene increased the expressions of Akt, MAPK, IR, P85, and IRS.

Conclusions: Lycopene presented the paradoxical effect of the aggravation of proteinuria via the insulin signaling and nephrin pathway, although it is believed to activate AMPK in liver leading to improve the metabolic syndrome. Our results suggest the anti-diabetic or anti- lipid agents are able to have a harmful effect on the kidney.

SA-PO314

Collagen-Secreting Angiogenic Macrophages in Diabetic Nephropathy Chandigarh, India; 2Translational and Regenerative Medicine, PGIMER, Chandigarh, India; 3Natural and Human Science Center, Universidade Federal do ABC, Santo André, Sao Paulo, Brazil.

Background: Oxidative stress and mitochondrial dysfunction are the key contributors to diabetic nephropathy (DN). The presence of these cells in vivo may intervene in carnosin metabolism, since this can be manipulated without affecting diabetic state.

Methods: A total of 649 subjects (196 T2DM subjects without nephropathy (DM), 212 type 2 diabetic nephropathy stage II-IV (DN), 167 with diabetic nephropathy stage II-IV (DN) (40%); 168 healthy control (HC)) were genotyped for UMOD variant rs4293393T>C by restriction fragment length polymorphism (RFLP). Serum uromodulin levels were quantified using human uromodulin enzyme linked immunosorbent assay (ELISA).

Results: A significant difference was found in genotype and allele frequency of this polymorphism (rs4293393 T>C) among DM, DN II-IV, DN-V, C KD and HC; UMOD TC/T C and CAT/C AT genotypes were significantly more frequent in DN II-IV, DN-V compared to DM and HC (p<0.01). Significant higher serum uromodulin levels 12/10 in patients with T2DM compared to healthy controls. UMOD expression was higher in DN compared to DM.

Conclusions: We found evidence for local carnosin metabolism in the glomerulus (podocytes) as well as in the tubuli. lycopene model shows simultaneous regulation of both genes, which indicated common response elements in their promoters. The fact that their expression level is independent from diabetes provides the therapeutic opportunity to intervene in carnosin metabolism, since this can be manipulated without affecting diabetic state. Future research will be focused on quantification and modulation of carnosine levels in DN kidneys.

SA-PO315

Association of Uromodulin Genetic Variant and Serum Levels with Renal Function in Diabetic Kidney Disease Krishnan L Gupta,1 Vinod Sharma,2 Ashok Kumar Yadav,3 Vinay Sakhuja,1 Vivekanand Jha.1 1Nephrology, PGIMER, Chandigarh, India; 2Translational and Regenerative Medicine, PGIMER, Chandigarh, India.

Background: Uromodulin a UMOD gene encoded 95kDa, glycoprotein exclusively synthesized in kidney cells and released into urine. Mutation in UMOD lead to Uromodulin enzyme linked immunosorbent assay (ELISA).

Methods: A total of 649 subjects (196 T2DM subjects without nephropathy (DM), 167 with diabetic nephropathy stage II-IV (DN), 168 healthy control (HC)) were genotyped for UMOD variant rs4293393T>C by restriction fragment length polymorphism (RFLP). Serum uromodulin levels were quantified using human uromodulin enzyme linked immunosorbent assay (ELISA).

Results: A significant difference was found in genotype and allele frequency of this polymorphism (rs4293393 T>C) among DM, DN II-IV, DN-V, C KD and HC; UMOD TC/T C and CAT/C AT genotypes were significantly more frequent in DN II-IV, DN-V compared to DM and HC (p<0.01). Significant higher serum uromodulin levels 12/10 in patients with T2DM compared to healthy controls. UMOD expression was higher in DN compared to DM.
renal metabolic effects may mediate the progression to late stage DN. Few mouse models showed decline in renal function. Accelerating the development of ANG II blockade (4 weeks). Glomerular filtration rate (GFR) and renal metabolic efficiency (QO2/TNa, where TNa = total sodium reabsorbed) were measured at week 4 after induction of DM.

**Results:** Compared with the normal, in 4wk untreated diabetic kidney GFR and RBF tended to increase (p<0.05) decreased indicated by an elevation of QO2/TNa. The altered normal QO2 and QO2/TNa were corrected by ANG II inhibition but not by apocynin, a NADPH oxidase inhibitor.

**Conclusions:** The normal kidney is on the border of hypoxia. A huge increase in QO2 occurs in diabetic kidney, which may intensify renal tubular hypoxia. The substantial elevation of QO2/TNa suggests that diabetic kidneys have a much higher demand for O2 to support Na transport and nontransport events. Chronic ANG II inhibition reduces the demand for O2 without altering GFR.

**Funding:** NIDDK Support

### SA-PO319

**High Fat Feeding Accelerates Decline of Renal Function in db/db Mice**

**Background:** Recent studies have demonstrated that angiotensin II blockade has beneficial effects on chronic kidney disease, especially for diabetic nephropathy, but the mechanism is unknown. The present study tests our hypothesis that ANG II blockade corrects increased oxygen consumption (QO2) in diabetic kidneys, which may be part of the mechanism underlying the therapeutic effects of ANG II blockade.

**Methods:** Rats were made diabetic by a single intraperitoneal injection of streptozotocin (65mg/kg). 4 groups of rats were used: 1) Normal; 2) Diabetic rats (DM) untreated; 3) DM + apocynin (40 mg/kg/day) were administrated in the drinking water (65mg/kg,); 4) DM + apocynin, Captopril (C, 20mg/kg/day), losartan (L, 20 mg/kg/day) and apocynin (40 mg/kg/day) were administered in the drinking water for 4 weeks. Glomerular filtration rate (GFR) and renal blood flow (RBF), QO2 and renal metabolic efficiency (TNa, where TNa = total sodium reabsorbed) were measured at week 4 after induction of DM.

**Results:** Compared with the normal, in 4wk untreated diabetic kidney GFR and RBF tended to increase but did not reach statistical significance. QO2, was double increased and renal metabolic efficiency was decreased indicated by an elevation of QO2/TNa. The altered normal QO2 and QO2/TNa were corrected by ANG II inhibition but not by apocynin, a NADPH oxidase inhibitor.

**Conclusions:** The normal kidney is on the border of hypoxia. A huge increase in QO2 occurs in diabetic kidney, which may intensify renal tubular hypoxia. The substantial elevation of QO2/TNa suggests that diabetic kidneys have a much higher demand for O2 to support Na transport and nontransport events. Chronic ANG II inhibition reduces the demand for O2 without altering GFR.

**Funding:** NIDDK Support

### SA-PO320

**Activation of P2X2, Receptors and the Oxidative Stress in the Diabetic Nephropathy**

**Background:** Previous studies in our Laboratory showed the role of oxidative stress and the favorable effects of exercise training, on the progression of diabetic nephropathy in rats. P2X2, receptors (P2X2,R), in pathological conditions, are significantly up-regulated, increasing the levels of oxidative stress. The aim of this study was to evaluate the P2X2,R and the oxidative stress in the kidneys of diabetic rats submitted to aerobic training.

**Methods:** Diabetic mellitus (DM) was induced in adult Wistar rats, with streptozotocin (65mg/kg,); control animals (C) received its vehicle. The animals were submitted to aerobic training on treadmill at a work rate of 16m/min for 60 min/day, 5 days a week/8weeks (DM-EX and CTL+EX); DM-SE and CTL-SE were kept resting on the treadmill at the same schedule (n=12 for each group). Half of the animals all groups were treated with N-acetylcysteine (NAC); the other, water as vehicle. One way ANOVA; significance at p<0.05.

**Results:** DM-SE vs CTL-SE increased the urinary excretion and renal tissue thiobarbituric acid reactive substances; there was also a reduced urinary excretion and renal tissue nitric oxide (NO). NAC and exercises reduced TBARS and increased NO in urine and kidney. Confoclal microscopy analysis of P2X2,R in the kidneys showed with 100µm BZATP (preferential agonist to receptor) there was an increase in DM-SE vs CTL-SE (1.0±0.23 vs 0.1±0.06), which was reduced in DM-SE+NAC received NAC (0.27±0.06), aerobic training (0.31±0.08) or both (0.17±0.04), all p<0.05.

**Conclusions:** Our data show that the NAC administration, routine exercise or both either decrease the activation of P2X2,R in the kidneys of diabetic rats. The attenuation of oxidative stress through this mechanism, which also resulted in the increase of NO bioavailability, suggests that the control of these receptors’ up-regulation could be useful to delay the progression of diabetic nephropathy.

**Funding:** Pharmaceutical Company Support - Novo Nordisk A/S
uninephrectomized at age 10 weeks and fed a HFD (60% fat energy ratio) or normal fat diet (NFD) (10% fat energy ratio) for 12 weeks. Mice overexpressing Lc3-GFP, an autophagosome marker, were also studied under the same protocol.

**Results:** Mice fed a HFD showed increases in body weights and blood glucose levels, compared with NFD-fed mice, with no differences in these parameters between HFD-fed megalin KO mice and control mice. In HFD-fed control mice, cytosolic vascular forma
tion was induced in HFD-fed control mice, which was ameliorated in HFD-fed megalin KO mice. Glomerular hypertrophy with mesangial expansion, evident in HFD-fed control mice, was also ameliorated in HFD-fed megalin KO mice. Advanced glycation product-modified BSA, an endocytic ligand of megalin, induced giant autophagosome formation in in cultured cells.

**Conclusions:** In conclusion, megalin-mediated autophagosome dysfuntion in PTECs is primarily associated with the development of tubulo-glomerular alteration in HFD-induced kidney disease.


---

**SA-PO323**

**Linagliptin Ameliorates Free Fatty Acid-Bound Albumin-Induced Tubulointerstitial Injury**

**Background:** Severe proteinuria-induced tubulointerstitial injury indicates poor renal prognosis in patients with diabetic nephropathy. Establishment of new therapeutic strategy against proteinuria-induced tubulointerstitial injury in diabetic nephropathy is required. Dipeptidyl peptidase (DPP) inhibitors, a new class of oral anti-diabetic agents for type 2 diabetes, have recently been suggested exerting pleiotropic effects beyond glucose lowering.

**Methods:** We thus examined renoprotective effect of linagliptin, a DPP4 inhibitor, on free fatty acids (FFA)-bound albumin-induced tubulointerstitial injury in mice. Mice were fed either standard diet (SD) or SD with linagliptin, and intraperitoneally injected with FFA-bound albumin or PBS for 11 days. In addition, renoprotective effect of linagliptin was examined in cultured mouse proximal tubular (mProx) cells stimulated with FFA-

**Results:** We first confirmed that neither FFA-bound albumin injection nor linagliptin treatment altered systemic characteristics including body weight, fasting blood glucose and food intake. In SD group, FFA-bound albumin caused tubular cell apoptosis, interstitial inflammation characterized by macrophage infiltration and increased mRNA expression of inflammatory cytokines, such as MCP-1, IL-6 and TNF-α, and interstitial fibrosis with increased expression of fibronectin and PAI-1. These alterations were all prevented by the treatment with linagliptin. Furthermore, in cultured mProx cells, linagliptin inhibited FFA-

**Conclusions:** These results indicate that DPP4 inhibitors exert anti-inflammatory and anti-fibrotic effect as an additional pleiotropic effect, and may serve as a therapeutic strategy to protect proximal tubular cells against proteinuria in patients with diabetic nephropathy.

**Funding:** Pharmaceutical Company Support - DaVita Clinical Research.
SA-P0327
Reveratrol Ameliorated High-Glucose Induced Oxidative Stress through Nrf2 Activation Min Zhang, Chuanning Hao. Nephrology Div, Huashan Hospital, Shanghai, China.

Background: Hyperglycemia-mediated oxidative stress plays a crucial role in the progression of DN. Nrf2 controls the ARE-dependent gene regulation in response to oxidative stress. Reveratrol is a polyphenolic phytoalexin that exhibits benefits including antioxidant and anti-inflammatory. Reveratrol is also shown to confer renoprotection in animal models of type 2 diabetes. However, the mechanisms by which resveratrol exerts its antioxidative protective effects are not completely understood. The current study is aimed at examining the mechanism of resveratrol on defense against high glucose-induced oxidative damage in glomerular endothelial cells.

Methods: Endothelial cells were serum starved for 24h, and then exposed to media containing low glucose plus mannitol (2.5mM+22.5mM, LG+M), normal glucose plus mannitol (5mM+20mM, NG+M) or high glucose (25mM, HG) with resveratrol(1.5,10,25uM) for 24 hours. Then the cells were treated with Nrf2 activator sulforaphane (Sigma, USA) or transfected with Nrf2-siRNA. Cells were harvested for either protein or RNA assay. The expression levels of Nrf2, HO-1 and SIRT1 were measured by Western blot and qPCR. For ROS measurement, cells were incubated for 30 min with H2DCFDA (Sigma,USA), and the fluorescence intensity was measured by flow cytometry. The expression levels of SIRT1 and Nrf2 were down-regulated at high glucose concentration (P<0.05). Sulforaphane, an agonist of Nrf2, significantly increased the expression of HO-1 and decreased the production of ROS. Resveratrol, in a dose-dependent manner, significantly increased expression level of Nrf2. Accordingly, resveratrol significantly upregulated the expression of the Nrf2 target gene: HO-1. Resveratrol treatment also significantly attenuated high glucose-induced oxidative stress. The aforementioned effects were significantly attenuated by the small interfering RNA downregulation of Nrf2. The results of co-immunoprecipitation showed a relationship between Nrf2 and SIRT1.

Conclusions: Our results indicated that resveratrol ameliorated high-glucose induced oxidative stress through Nrf2 activation.

SA-P0328

Background: Metabolic syndrome is known to be an important risk factor involved in the development of diabetic nephropathy. An oral adsorbent AST-120 has been used clinically as a drug for treatment of chronic kidney disease (CKD) patients to slow the progression of CKD. However, there is little evidence when AST-120 should be prescribed for subjects with early stage overt diabetic nephropathy. In this study, we aimed to assess the effect of AST-120 in the early stage of nephropathy using SHR/Ndmc-cp, a rat model of metabolic syndrome/ type 2 diabetes.

Methods: Male SHR/Ndmc-cp (SHR/Nd) rats, aged 7 weeks, were administered 0% or 8% AST-120 for 12 weeks in their diets. WKY rats were used as a normal. At every 4 weeks, serum and 24-hour urine samples were collected for biomedical studies. We analyzed metabolic parameters in serum and SMACs harvested from SHR/Nd rats with or without AST-120 treatment for 16 weeks by capillary electrophoresis mass spectrometry with time-of-flight (CE-TOFMS) and applied CE-TOFMS data to principal component analysis (PCA). We also examined the gene expression of oxidative stress markers by real-time PCR and the glomerular podocyte marker nephrin expression by qPCR. For ROS measurement, cells were incubated for 30 min with H2DCFDA (Sigma, USA), and the fluorescence intensity was measured by flow cytometry

Results: AST-120-administered SHR/Nd rats showed significantly lower level of urinary albumin excretion, urinary protein excretion and urinary 8-OHdG excretion as compared with SHR/Nd rats. PCA score plot showed clear separation among three groups (Normal, SHR/Nd and AST-120-administered SHR/Nd). We could detect 40 metabolites, such as o-hydroxybenzoic acid, hippuric acid and indole-3-acetic acid, which accumulated in the serum of SHR/Nd rats, and of which serum levels were reduced by administration of AST-120. The gene expression of oxidative stress markers in renal tissues was lower in AST-120-administered SHR/Nd rats than in SHR/Nd rats. And also the ratio of podocyte injured maker, desmin, positive glomerulitis was lower in AST-120-administered SHR/Nd rats than in SHR/Nd rats.

Conclusions: It indicated that the administration of AST-120 at an early stage has a protective effect on the progression of diabetic nephropathy.

SA-P0329
Inflammation Stress Induces Lipid Redistribution in db/db Mice via the Disruption of LDL Receptor Pathway Kun Ling Ma, 1 Yang Zhang, 1 Jing Liu, 1 Wu Yu, 1 Bi-Cheng Liu. 1 Institute of Nephrology, Southeast Univ School of Medicine, Nanjing, China; 1 Institute of Nephrology, Southeast Univ School of Medicine, Nanjing, China.

Background: Dyslipidemia and inflammation play crucial roles in the progression of diabetic nephropathy (DN). Our previous studies in vivo and in vitro demonstrated that inflammation induced lipid accumulation in liver, aorta, and kidney in apolipoprotein E knockout mice through the disruption of low-density lipoprotein receptor (LDLR) feedback regulation. This study aimed to investigate the effects of inflammation on lipid redistribution in DN.

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

702A
Methods: Twenty db/db mice were injected with cassein to induce an inflamed DN model. Serum levels of inflammatory cytokines and lipid profile were respectively measured by enzyme-linked immunosorbent assay and biochemical analysis. Effects of inflammation stress on lipid accumulation in liver, aorta, and kidney were evaluated by hematoxylin–eosin staining, Oil Red O staining, filipin staining, and intracellular cholesterol quantitative assay. The protein expression of low density lipoprotein receptor (LDLR), sterol regulatory element binding protein-2 (SREBP-2) and SREBP cleavage activating protein (SCAP) in tissues was checked by immunohistochemical staining, immunofluorescent staining, or Western blotting.

Results: Significantly elevated serum levels of tumour necrotic factor-a and serum amyloid A were detected. In in vitro study, cell treated with high glucose concentration showed upregulated expression of the Nrf2 target gene: HO-1. Resveratrol treatment also significantly attenuated high glucose-induced oxidative stress. The aforementioned effects were significantly attenuated by the small interfering RNA downregulation of Nrf2. The results of co-immunoprecipitation showed a relationship between Nrf2 and SIRT1.

Conclusions: Inflammatory stress may induce lipid redistribution of db/db mice from circulation to target organs. The potential mechanism is through the disruption of LDLR feedback regulation.

SA-P0330
Role of HDAC in the Development of Type 2 Diabetes Related Nephropathy Hang Yuan, Nian Liu, Ye Jia, Yingchun Cui, Ping Luo, Liming Mao. Div of Nephrology, Second Hospital of Jilin Univ, Chang Chun, Ji Lin, China.

Background: Histone deacetylase (HDAC) emerged as a new molecular target in the control of obesity and type 2 diabetes. Inhibition of HDACs has been demonstrated as players in ameliorated renal fibrosis, and the internal mechanism is associated with profibrogenic genes regulation such as collagen and PAI-1. But the role of HDACs in the process of diabetic complications development is still unclear. In this study, we evaluated potential role of HDAC in type 2 diabetes related nephropathy.

Methods: Blood karvacyte and serum were separately collected from 20 health adults, new diagnosed type 2 diabetes (18 cases) as well as type 2 diabetic renal dysfunction patients (23 cases). We detected HDAC gene expression by QRT-PCR. In vivo relevance was tested using renal cortex from high fat diet with streptozotocin injection induced type 2 diabetic rat, as well as diabetic rat fed with valproic acid, which was known as HDAC inhibitor.

Results: In compare with health adults, HDAC 1, 2, 3, 4, 10, 11 mRNA expression were increased in new diagnosed diabetes patients, while HDAC 2, 5, 9, 11 and SIRT 1 mRNA expression were significantly enhanced but HDAC 10. SIRT 4 expression decreased in diabetic renal dysfunction patients compared with new diagnosed diabetes patients. Interestingly, in vivo results showed that diabetic rats have more HDAC 1, 2, 3, 4, 10, 11 mRNA expression in the renal cortex in compare with none diabetic control group; valproic acid administration inhibited HDAC 1, 2, 3, 4, 11 expression; at same time increased proteinase as well as profibrogenic genes such as collagen 1a1, CTGF and α-smooth muscle actin (α-SMA) in diabetic kidney were attenuated by valproic acid.

Conclusions: These results demonstrate that overexpressed HDACs such as HDAC 1, 2, 3, 4, 10, 11 may involve in the pathogenesis of type 2 diabetes and related nephropathy; select inhibition of HDACs by valproic acid attenuated renal fibrogenic genes expression and diabetes related proteinuria, therefore suggest HDACs might be a new target in the control of diabetic nephropathy.

Funding: Government Support - Non-U.S.

SA-P0331
Non-Esterified Fatty Acid Levels Modulate Adiponectin and Insulin Sensitivity in a Rat Model of Type 2 Diabetes Mellitus through a Nitric Oxide Dependent Mechanism Sharma S, Prabhakar. Internal Medicine, Texas Tech Univ Health Sciences Center.

Background: Mechanisms leading to insulin resistance in type 2 diabetes mellitus (T2DM) remain incompletely understood. Adiponectin levels and signaling mechanisms are down regulated in obesity induced T2DM. Recent work from our laboratory showed that angiotensin blockade enhanced insulin sensitivity besides the renoprotection in diabetic rats (J Invest Med 2013). We hypothesized that adiponectin activity and insulin signaling is regulated by non-esterified fatty acid (NEFA) levels in obesity induced T2DM.

Methods: To test our hypothesis we used obese ZSF rat, a murine model of T2DM previously characterized in our laboratory (JASN 2007). Lean ZSF rats were used as controls as obesity develop DM. Obese rats were fed high calorie diet while control rats were given standard rat chow. Another group of obese ZSF rats received losartan (1mg/ml). All rats were obtained at 7th week and euthanized at 26 weeks and adipose tissue harvested. Plasma samples were collected at the start and end of the study to measure adiponectin (by ELISA), NEFA levels(by colorimetric assay) and Nitric Oxide metabolites or Nox (by chemiluminescence). Adipose tissue was homogenized and the protein was examined for the expression of adiponectin receptor 1, insulin receptor substrate 1 and glucose transporter GLUT 4 using immunoblotting.

Conclusions: These results demonstrate that overexpressed HDACs such as HDAC 1, 2, 3, 4, 5, 9, 11 may involve in the pathogenesis of type 2 diabetes and related nephropathy; select inhibition of HDACs by valproic acid attenuated renal fibrogenic genes expression and diabetes related proteinuria, therefore suggest HDACs might be a new target in the control of diabetic nephropathy.

Funding: Government Support - Non-U.S.
Results: Our results showed that the plasma levels of adiponectin and NOx were decreased and NEFA levels increased in obese ZSF rats compared to lean ZSF rats. Furthermore, the expression of AdipoR1 and IRS1 and GLUT4 were decreased in fat cells of obese rats compared to lean counterparts. Losartan treatment increased NOx and adiponectin levels and insulin sensitivity.

Conclusions: We conclude that NEFA may be involved in modulation of adiponectin activity and insulin signaling through mechanisms that involve NO generation in murine TZDM.

Funding: Private Foundation Support

SA-PO332 Glycemic Memory in Diabetes Nephropathy, Potential Role of SHP-1

Farah Lizotte, Nicolas Drapeau, Andréanne Guay, Chris R. Kennedy, Marie-Odile Guimond, Pedro Miguel Geraldes, Medecine, Div. of Endocrinology, Univ of Sherbrooke, Quebec, Canada; Kidney Research Center, Canada.

Background: Renal podocytes apoptosis induced by hyperglycemia and insulin resistance is an early event leading to diabetic nephropathy (DN). Intensive blood glucose control reduced the development of DN. However, if not started early in the disease, it is not sufficient to prevent DN progression, introducing the concept of “glycemic memory”. Recent studies demonstrated that SHP-1, a protein tyrosine phosphatase, is elevated in renal cortex of type 1 diabetic mice (Akita) causing insulin unresponsiveness and DN. We hypothesize that SHP-1 expression remains elevated in spite systemic glucose blood glucose normalization after 4 months of diabetes that triggers insulin inhibition, podocytes apoptosis and glycemic memory in DN.

Methods: The in vivo contribution of SHP-1 in glycemic memory was evaluated using Akita mice treated with insulin implants after 4 months of diabetes. Also, mouse and human podocytes were cultured in normal (5.6mM; NG), high glucose concentrations (25mM; HG) or HG prior returning glucose levels to NG for an addition 24-48h (HG+NG).

Results: Renal function was assessed by measuring urinary albuminuria secretion and glomerular filtration rate. Both parameters were significantly increased in diabetic mice and remained elevated after normalization of blood glucose levels, compared to non-diabetic mice. Renal dysfunction was associated with a 98% increase of SHP-1 expression in renal cortex and insulin action inhibition that were not normalized following insulin implants to decrease glucose levels. In vitro, we observed that Akt and ERK phosphorylation induced by insulin was abolished in HG and maintained lower following glucose normalization (HG+NG). The increase of SHP-1 protein and mRNA expression in HG conditions remained elevated in spite return glucose concentration from HG to NG.

Conclusions: In conclusion, hyperglycemia causes persistent and irreversible high expression of SHP-1 leading to podocyte unresponsiveness to insulin leading to glycemic memory in DN.

SA-PO333 TGF-β1-Mediated Signalling Is Increased by TZDs through Increased IHH-1 Expression

Fionnuala B. Hickey, James B. Corcoran, Finian Martin, Madeline Murphy, Catherine Godson, Trinity Health Kidney Centre, Trinity College Dublin, Dublin 2, Ireland; 1UCD Diabetes Complications Research Centre, Univ College Dublin, Dublin 4, Ireland.

Background: Induced in high glucose-1 (IHH-1) is a highly conserved transcript upregulated in experimental models of renal fibrosis and in human diabetic nephropathy (DN). We have reported that IHH-1 enhances responses to TGF-β1 [Murphy et al. JASN 2008]. IHH-1 is a mitochondrial protein and increases mitochondrial mass through stabilisation of PPARα coactivator 1-α (PGC-1α) [Hickey et al. JASN 2011]. Thiazolidinediones (TZDs) are PPARγ agonists that act as insulin sensitising agents and are effective therapeutic agents in diabetes. Here we have explored the effect of TZDs on TGF-β1-mediated signalling and fibrosis.

Methods: mRNA was measured by qRT-PCR. Mitochondrial biogenesis was assessed by comparison of mitochondrial to nuclear DNA and by analysis of a TFAM promoter was inhibited using tetracyclin-inducible shRNAi. Mediated signalling was analysed via western blotting. Expression of endogenous IHG-1 was reduced in HG and maintained lower following glucose normalization of EMT. To study the mechanism of increased IHG-1 in diabetic nephropathy, we investigated the role of carbonyl stress in diabetic mice treated with paricalcitol, 19-nor-1,25-dihydroxyvitamin D2, an activated vitamin D analog. Deletion of the Vitamin D receptor worsens diabetic nephropathy, we investigated the role of carbonyl stress in diabetic mice treated with paricalcitol, 19-nor-1,25-dihydroxyvitamin D2, an activated vitamin D analog.

Results: IHH-1 expression was increased by TZDs in human renal epithelial cells in vitro. Increased IHH-1 expression was associated with increased levels of PGC-1α and increased mitochondrial mass. TGF-β1-mediated increases in IHG-1 may drive the hypoxia-enhanced TGF-β1-mediated signalling downstream of EMT. TGF-β1-mediated increases in IHG-1 may drive the hypoxia-enhanced TGF-β1-mediated signalling downstream of EMT. In conclusion, hyperglycemia causes persistent and irreversible high expression of SHP-1 leading to podocyte unresponsiveness to insulin leading to glycemic memory in DN.

Funding: Government Support - Non-U.S.

SA-PO334 Astragaloside IV Attenuates Glycated Albumin-Induced Proximal Tubular Epithelial-to-Mesenchymal Transition via Inhibiting ERK1/2 and JNK Phosphorylation

Yong Gu, Jianyong Niu, Weiwei Qi, Div of Nephrology, The Fifth People's Hospital of Shanghai, Fudan Univ, Shanghai, China; Div of Nephrology, Huashan Hospital, Fudan Univ, Shanghai, China.

Background: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) in developed countries. Tubulointerstitial accumulation of extracellular matrix leads to tubulointerstitial fibrosis which closely correlates with the development of ESRD. The epithelial-to-mesenchymal transition (EMT) is the main source of ECM in kidney. In our previous study we showed that glycated albumin (GA) could cause EMT in tubular cells and Astragaloside IV (AS-IV), the main active ingredients of Astragalus membranaceus, alleviated such damage by inhibiting oxidative stress. In order to further study the mechanism of AS-IV on tubular cells in DKD, we observed the changes of redox balance and MAPK pathway by adding AS-IV under GA stimulation.

Methods: The NRK-52E cells' intercellular reactive oxygen species (ROS) level was detected by H2DCFDA. NADPH oxidase activity was assayed by adducing exogenous NADPH oxidase. The activities of superoxide dismutase (SOD), glutathione peroxides (GSH-Px) and catalase (CAT) were tested by assay kit. Western blot was used to examine the protein expression of α-SMA, E-cadherin, phosphorylation of ERK1/2, JNK and p38 MAPKs.

Results: AS-IV significantly attenuated GA-generated reduction of ROS, lowered the increased level of NADPH oxidase activity. GA reduced the contents of SOD, GSH-Px and CAT in NRK-52E cells but there was no obvious change by adding AS-IV. Moreover, GA-induced NRK-52E cells showed increased expression of α-SMA and decreased expression of E-cadherin which could be attenuated by AS-IV. GA stimulated the phosphorylation of ERK1/2, p38 and JNK and AS-IV reversed the changes in ERK1/2 and JNK but not p38 phosphorylation.

Conclusions: Our data demonstrate that GA could induce tubular cells EMT through oxidative stress. Supplementation of AS-IV attenuates GA-induced EMT. AS-IV weakens the oxidative stress by inhibited NADPH oxidase activity but not increasing the contents of antioxidants. ERK1/2 and JNK intracellular signaling pathways, not p38 pathway, mediate the effect of AS-IV on EMT.

Funding: Government Support - Non-U.S.

SA-PO335 PKC-α Mediates Albuminuria by Heparanase-Dependent Loss of Endothelial Cell Glycocalyx in Diabetic Mice

Joan-Keun Park, Torsten Kirsch, Nelli Shushakova, Anna Bertram, Putri Andina Agustian, Jan Menne, Hermann G. Haller. Clinic of Hypertension and Nephrology, Hannover Medical School, Hannover, Germany.

Background: We have recently demonstrated that hyperglycemia induces albuminuria in hyperglycemic mice via the activation of PKC isof orm alpha. Since the polysaccharide-rich endothelial glycocalyx and surface layer (ESL) acts as a filtration barrier, and heparanase is the predominant enzyme that degrades heparan sulfate (HS), the main polysaccharide of the ESL we tested the hypothesis that PKC-alpha in hyperglycemia leads to loss of ESL on glomerular endothelium via the activation of heparanase.

Methods: PKC-α/-/- and wild-type (WT) mice received STZ or buffer. After 2 or 8 weeks of hyperglycemia, the animals were analyzed. Albumin in urine was measured by ELISA. Immunohistochemistry for PKC-α was performed on cryostat/paraffin sections. EM analysis of ESL was carried out after perfusion with Alcian blue. Gene and protein expression was analyzed by real-time qPCR and western blot analysis.

Results: PKC-α was predominantly expressed in the glomeruli. Under diabetic conditions, an increased expression of PKC-α in glomeruli was observed. The increase in albumin excretion was prevented in hyperglycemic PKC-α/-/- mice. Only a weak expression of heparanase was observed in nondiabetic control animals of both groups. Under diabetic conditions, a significant increase of heparanase was observed in the WT but not in PKC-α/-/- mice. Loss of HS in the glomeruli was significantly reduced in PKC-α/-/- mice. We also observed that ESL-associated molecules such as thrombomodulin were regulated by PKC-α.

Conclusions: Hyperglycemia-mediated loss of endothelial glycocalyx is mediated by the PKC isoform alpha. PKC-alpha regulates heparanase expression under diabetic conditions. Inhibition of PKC-alpha in diabetic nephropathy may restore damaged glycocalyx and thereby influence inflammation and proteinuria.

Funding: Government Support - Non-U.S.

SA-PO336 Low Dose of Vitamin D Analog, Paricalcitol, May Promote Carbohydrate Stress and Kidney Disease in Diabetic Mice

Xinyi Zheng, Wuxing Dong, Vivek Bhalla. Medicine / Nephrology, Stanford Univ School of Medicine, Stanford, CA.

Background: Diabetic nephropathy (DN) represents the primary cause of morbidity and mortality for patients with diabetes mellitus. Because Vitamin D analog therapy has been shown to attenuate diabetic nephropathy in combination with losartan, and genetic deletion of the Vitamin D receptor worsens diabetic nephropathy, we investigated the role of carbonyl stress in diabetic mice treated with paricalcitol, 19-nor-1,25-dihydroxyvitamin D2, an activated vitamin D analog.

Methods: Diabetic DBA/2 mice were induced by STZ injection (40mg/kg body weight for consecutive days, then administered paricalcitol (0.4-8µg/kg body weight) or vehicle intraperitoneally three times weekly for 24 weeks. Diabetes was validated by glucose tolerance tests at the end of the study. Urine albumin to creatinine ratio, glomerular volume

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

Underline represents presenting author/disclosure.

Poster/Saturday

Diabetes Mellitus and Obesity: Basic - Experimental - II

703A
and podocyte number, and quantification of the carbonyl stress marker, 4-hydroxynonenal (4-HNE) were tested. Additionally, MES-13 mesangial cells were treated with 4-HNE and paricalcitol vs. vehicle prior to qPCR.

Results: Fewer diabetic mice survived until the study end-point with a trend toward decreased survival in the paricalcitol-treated vs. vehicle-treated diabetic mice. Surprisingly, paricalcitol-treated mice had significantly higher albuminuria (207.7 ± 35.3 vs. 31.0 ± 14.7 mg albumin / mg creatinine, p<0.05). Glomerular volume was not significantly different between these two groups, but there were significantly fewer podocytes per glomerulus in the paricalcitol-treated mice. Glomerular 4-HNE was lower in paricalcitol-treated mice (0.47 ± 0.01 vs. 0.31 ± 0.05 positive cells/mm2, p<0.05). Low-dose paricalcitol (0.5 mg/kg/day) significantly increased 4-HNE-induced fibronectin1 expression while higher doses (5 mg/kg or 50 mg/kg) were not significantly different or lower vs. vehicle alone. Paricalcitol did not modulate 4-HNE-induced TGF-β1 expression vs. vehicle.

Conclusions: Taken together, in contrast to shorter duration of therapy, low dose, longer-term paricalcitol treatment may worsen diabetic nephropathy and survival, possibly by modulating the response to 4-HNE through increased fibronectin production, podocytopenia, and consequently increased albuminuria. Funding: Pharmaceutical Company Support - Abbott-Renal Care

SA-PO337

Effects of Cannabinoid Receptor Type 2 (CB2) Agonist in a Mouse Model of Type 2 DN

Carlamaria Zoja,1 Daniela Rottoli,1 Daniela Corna,1 Monica Locatelli,2 Mauro Abbate,3 Agnes Benardeau,3 Karin Conde-kanpe,3 Giuseppe Remuzzi,1,3 Ariela Benigni.1

1IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; 2Unit of Nephropathy and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; 3F. Hoffmann-La Roche AG, Basel, Switzerland.

Background: Experimental evidence suggested that CB2 activation had a protective role in early STZ-induced diabetes in mice. Here we investigated the effects of the CB2 agonist R06806207 given at a phase of overt disease in BTBR ob/ob mice, a recently characterized model of type 2 DN.

Methods: BTBR ob/ob mice received from 10 to 21 wk of age, CB2 agonist (10mg/kg i.p. or lisinopril (30 mg/kg in drinking water) as standard therapy for comparison (n=7-9 mice/group). BTBR wild-type mice (n=6) served as controls.

Results: Both CB2 agonist and lisinopril reduced albuminuria. The antiproteinuric effect was associated with amelioration of defective nephrin expression of diabetic mice. CB2 agonist limited renal lesions to a similar extent as ACEi. Intersitial inflammation was lowered by 36% and 60% after CB2 agonist and lisinopril, respectively. Both compounds reduced osteopontin and TGFβ1 urinary excretion. Treatments did not affect hyperglycemia and dyslipidemia of diabetic mice.

Conclusions: CB2 agonist halted progressive renal damage when given to BTBR ob/ob mice during overt nephropathy. These findings may have therapeutic implications for human DN. Funding: Pharmaceutical Company Support - F. Hoffmann-La Roche AG, Basel, Switzerland

SA-PO338

L-carnitine Protects against Cyclosporine-Induced Pancreatic and Renal Injury in Rats

Can Li,1 Chul Woo Yang.2

1Nephrology, Yonsei Univ Hospital, Yonji, Jilin, China; 2Nephrology, The Catholic Univ of Korea, Seoul, Korea.

Background: L-carnitine has a protective effect against various types of injuries. This study was designed to evaluate the beneficial effects of L-carnitine on pancreatic and renal injuries caused by cyclosporine A (CsA).

Methods: Rats maintained on a low sodium diet were given vehicle (olive oil, 1 mL/kg/day), CsA (15 mg/kg/day), CsA (50 or 200 mg/kg/day), and a combination of CsA and L-carnitine for 4 weeks. The impact of L-carnitine on pancreatic injury was assessed by blood glucose level, plasma insulin concentration, and HbA1c. In addition, the protective effect of L-carnitine against CsA-induced renal injury was evaluated in terms of renal function, histopathology (inflammatory cell influx and tubulointerstitial fibrosis), oxidative stress (8-hydroxy-2′-deoxyguanosine, 8-OHdG), the transforming growth factor-β1 (TGF-β1), apoptosis (caspase-3), and autophagy (LC3-II).

Results: L-carnitine treatment caused diabetes, renal dysfunction, tubulointerstitial inflammation (ED-1-positive cells), and fibrosis, which were accompanied by an increase in 8-OHdG production and upregulation of TGF-β1, caspase-3, and LC3-II. Concomitant administration of L-carnitine increased plasma insulin concentration and decreased the levels of plasma glucose and HbA1c. In the kidney, L-carnitine induced a dose-dependent improvement of renal function, inflammation, and fibrosis in parallel with suppression of the expression of TGF-β1 and 8-OHdG. Furthermore, the administration of L-carnitine at a high dose inhibited the expression of caspase-3 and LC3-II.

Conclusions: These findings suggest that L-carnitine has a protective effect against CsA-induced pancreatic and renal injuries.

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

Underline represents presenting author/disclosure.

SA-PO339

Effects of Plant Steroid α-Spinasterol on Regulating Cell Proliferation and TGF-β1 Signaling Pathways through Thrombospondin-1 in Mesangial Cells

Kevin Yang,1 Mi Liu,1 Tianxin Yang.1,2

1Div of Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; 2CLEA Japan, Inc., Tokyo, Japan.

Background: TGF-β is the central cytokine responsible for the development of diabetic nephropathy, and usually secreted as a latent procytokine complex that has to be activated before it can bind to its receptors. It is reported that thrombospondin-1 (TSP-1) is the major activator of latent TGF-β in diabetic nephropathy in vivo. So this study is to examine the effect of α-spinasterol on TSP-1 production and downstream of TGF-β through TSP-1 induced by high glucose in mesangial cells.

Methods: α-spinasterol was isolated from roots of Phytolacca americana. Mouse mesangial cells were incubated for 24 hour with normal (5.6 mM) or high (30 mM) glucose containing medium in the presence or absence of α-spinasterol (1 ng/mL). Mesangial proliferation was determined by cell number. Real time qRT-PCR was performed to observe the TSP-1, TGFRI, TBRII, and fibronectin mRNA expression. Protein expressions of TSP-1, Smad2/3, and fibronectin were determined by western blot.

Results: α-spinasterol inhibited the high glucose-stimulated proliferation of mouse mesangial cells, but did not affect to the growth of mouse mesangial cells cultured under normal glucose. TSP-1 mRNA expression and protein expression was increased in cultured mesangial cells under high glucose concentration. α-spinasterol attenuated TSP-1 mRNA expression and protein expression in cultured mouse mesangial cells under the high glucose, but not under the normal glucose concentration. TGFRI mRNA expressions was increased in high glucose-stimulated mesangial cell, but decreased by α-spinasterol. Smad2 and p38 activities were increased in high glucose-stimulated mesangial cell, decreased by α-spinasterol. Fibronectin mRNA and protein expression were decreased by α-spinasterol.

Conclusions: We demonstrated that α-spinasterol attenuated TSP-1 protein expression in high glucose cells under the high glucose, and resulted in inhibiting cell proliferation and TGF-β1 signaling pathways, Smad2/3 and p38 signaling. These results suggest that α-spinasterol may be considered as a promising future treatment option for diabetic nephropathy.

SA-PO340

Anti-Oxidative Effects of β-Blocker Carvedilol on Diabetic Nephropathy

Yuriko Yonekura,1 Hideki Fujii,1 Shunsuke Goto,2 Kentaro Nakai,1 Keiji Kono,1 Riko Kitazawa,1 Masami Shinohara,3 Shinichi Nishi.1

1Div of Nephrology and Kidney Center, Kobe Univ Graduate School of Medicine, Kobe, Japan; 2Div of Molecular Pathological Medicine, Dept of Internal Medicine, Kobe Univ Graduate School of Medicine, Kobe, Japan; 3CLEA Japan, Inc., Tokyo, Japan.

Background: Oxidative stress has a major role in the pathogenesis of diabetic nephropathy. β-blocker carvedilol has been shown to have a protective effect from oxidative stress in this study. We investigated the effect of carvedilol on the progression of diabetic nephropathy using non-obese type 2 diabetes mellitus model rats.

Methods: In the present study, we used Spontaneously Diabetic Tori (SDT) rats, which is a model of non-obese type 2 diabetes. Sprague-Dawley (SDT) rats were used as control (SD, n = 5). At 20 week, SDT rats were divided into three groups: vehicle-treated SDT rats (DM, N=6), insulin-treated SDT rats (INS, N=6), and carvedilol-treated SDT rats (CAR, N=6). At 30 week, blood and urine analysis, histomorphometrical analysis, analysis of mRNA expression of NADPH oxidase and blood pressure measurement were performed among these four groups.

Results: At baseline, characteristics of these rats were comparable. At 30 week, comparable blood pressure, urinary excretion of albumin and 8-hydroxydeoxyguanosine (8-OHdG) were lower in the CAR group than in the DM group. In addition, relative kidney weight was lower in the CAR group compared to the DM group. The mRNA expressions of NADPH in the whole kidney were significantly decreased in the CAR group compared to the DM group. Further immunohistological analysis revealed that the number of 8-OHdG positive cell in glomeruli and tubules was reduced by administration of carvedilol.

Conclusions: Our findings suggested that carvedilol prevent the progression of glomerular and tubular injury possibly through the reduction of oxidative stress in non-obese type 2 DM.
Background: Diabetes is the leading cause of renal failure in the United States. The renin-angiotensin system (RAS) protects against glomerular injury but does not prevent the ultimate decline in renal function. Disease progression is strongly linked to the degree of tubulointerstitial injury, therefore, we examined the effects of RAS blockade on renal tubular injury in a rat model of diabetes.

Methods: Rats were made diabetic using streptozotocin (STZ) (I.V. 65mg/kg) and were supplemented with insulin allowing for modest hyperglycemia (n=10). One group (n = 5) received an angiotensin receptor blocker (ARB), candesartan (3 mg/kg/day) for 4 weeks. Blood glucose levels were monitored twice weekly and blood pressures were obtained using the tail cuff method. After 4 weeks, rats were placed in metabolic cages to measure dietary intake and to collect 24 hour urine for protein and creatinine, and were then sacrificed. Tubular injury was assessed by measuring the urinary biomarkers, kidney injury molecule-1 (KIM-1), neutrophil cytosol-associated lipocalin (NGAL), and N-acetyl-b-D-glucosaminidase (NAG) using ELISA.

Results: As expected, all rats exhibited polydipsia, polyphagia, and hyperglycemia. ARB treatment resulted in lower blood pressure (P<0.05) and a trend towards lower urinary protein excretion (P=0.08). Our previous studies demonstrated after 4 weeks of diabetes, there was an increase in urinary KIM-1, NGAL, and NAG in diabetic rats compared to controls without a concomitant rise in proteinuria. In this study, ARB treatment had no effect on urinary KIM-1, NGAL, or NAG.

Conclusions: Short-term treatment with ARB does not prevent early tubular damage in STZ diabetes. These findings justify additional studies of longer duration and also highlight the need for alternate therapies targeting the tubulointerstitium.

SA-PO344
The Effects of COMP-Angiopoietin-1 on Lipolysis, Vascular Endothelial Cells and Macrophages in Streptozotocin-Induced Diabetic Mice
Won Kim, Aein Lee, Dal Kim, Kyung Pyo Kang, Yujin Jung. Internal Medicine, Chonbuk National Univ Medical School, Jeonju, Republic of Korea.

Background: Streptozotocin(STZ)-induced diabetes mellitus increased inflammatory immunity and STZ-induced hyperglycemia leads to diabetic microvascular complications like diabetic nephropathy. Angiopoietin-1 (Ang1) is a potent angiogenic factor. We hypothesized that a variant of Ang1, COMP-Ang1 preserves diabetic nephropathy. However, there is controversy in mechanism of COMP-Ang1 in kidney protection. Especially metabolic effects of COMP-Ang1 in STZ-induced diabetic complications remain to be clarified. Therefore, in this study, we examined effects of COMP-Ang1 on fat droplet size, vascular endothelial cell (EC), and macrophage infiltrations in epididymal adipose tissue and metabolic parameters in STZ-induced diabetic mice.

Methods: To investigate the effects of COMP-Ang1, we administered COMP-Ang1 or LacZ adenovirus intravenously twice after STZ injection and harvested epididymal adipose tissue and blood 4 weeks after STZ injection.

Results: COMP-Ang1 ameliorated STZ-induced decrease of fat droplet size (lipolysis) and preserved PECAM-1-positive vascular EC in EAT. We also found that COMP-Ang1 decreased F4/80-positive macrophage infiltration. COMP-Ang1 diminished CD68 (M1 macrophage) and FIZZ1 expression in EAT. COMP-Ang1 reduced STZ-induced hyperglycemia (fasting glucose). Serum levels of triglyceride and free fatty acid after COMP-Ang1 treatment were decreased than that after STZ injection. Phosphorylation of Akt in adipose tissue was significantly increased after administration of COMP-Ang1. We also injected COMP-Ang1 at same time with STZ to evaluate the preventive effect.

Con-co treatment COMP-Ang1 preserved PECAM-1-positive EC and reduced macrophage infiltrations in EAT. In addition, COMP-Ang1 decreased random blood glucose level in STZ-induced diabetic mice.

Conclusions: All of these results demonstrate that COMP-Ang1 treatment can decrease STZ-induced inflammatory molecule and hyperglycemia, and conserve vascular EC and lipid droplet size. Our data suggest that COMP-Ang1 may ameliorate STZ-induced diabetic nephropathy through metabolic regulation.

Funding: Government Support - Non-U.S.
expression significantly decreased in DB mice, and correlated (r=0.6, P<0.01). ACE gene expression decreased in KO groups. Collagen V was higher in DB and KO groups. 

---

**SA-PO347**

**Endoplasmic Reticulum Was Stressed in Rat Kidney on Hyperinsulinemia Induced by High Palmitate Feeding**

**Jianling Tao, Yingjia Liu, Yuhing Wen, Hang Li, Xuewang Li.** Div of Nephrology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China.

**Background:** Insulin resistance is the basic pathophysiological feature of metabolic syndrome, carrying higher risk to the renal diseases onset and progression. Endoplasmic reticulum stress (ERS) is believed to play a triggering role in many diseases development. We tried to explore if ERS occurs in kidney challenged by hyperinsulinemia induced by high palmitate feeding.

**Methods:** Four-week-old Wistar male rats (n=36) were either fed by a regular diet (Control group) or a high palmitate diet (r=18). At three, six and nine weeks, six mice in each group were sacrificed. Body weight, serum insulin, creatinine, BUN, lipid profile, and glucose were assayed. Renal histology were reviewed by PASM. WT-1 stain was applied after palmitate feeding and continue to be higher at the nine weeks’ point.

**Results:** Serum insulin level was significantly increased after six weeks’ feeding by palmitate. Even without statistical significance, serum glucose and body weight tended to rise at the same time point. Lipid profile, and renal functions remain similar between two groups at any observation time point. Renal histology including WT-1 positive podocyte number and kidney syntapodin amount did not change much during nine weeks’ palmitate feeding. While GRP 78 protein expression started to significantly increase at six weeks after palmitate feeding and continue to be higher at the nine weeks’ point.

**Conclusions:** ERS is initiated by hyperinsulinemia in kidney before measurable biochemical or histological abnormalities occur. (Supported by National Natural Science Foundation of China 81170665).

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

---

**SA-PO348**

**New Vertebrate Model for Human Obesity-Related Glomerulopathy**

**Tomoko Obara.** Cell Biology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.

**Background:** Obesity, an ongoing significant public health problem, is a part of a complex disease characterized as metabolic syndrome. Despite the growing public health imperative, substantial hurdles exist in developing new animal models to study the mechanisms of obesity-related kidney diseases and identify newers modes of therapy to slow progressive chronic kidney disease (CKD) and halt end-stage renal disease (ESRD). We have recently generated a versatile vertebrate model that allows rapid and efficient generation of humanized adipose tissue and generated obesity-related kidney diseases. This model is the genetically tractable vertebrate model that is in response to a high fat diet (HFD) develops ORG, which mimics the human counterpart.

**Methods:** In the present study, to explore the possibility that the adult medaka fed with HF diet (HFD-medaka) can be used as an animal model for human ORG, we analyzed, serum glucose, glomerular histopathology and alterations in protein expression in the kidney of HFD-medaka.

**Results:** In 4 weeks, the HFD-medaka exhibited hyperglycemia, developed enlarged glomerular (glomerulomegaly) and mesangial proliferation. In addition, by proteomic analysis with mass spectrometry, 18 human CKD-related proteins were found up-regulated while two proteins [Nephrilysin (Nep) and Mitochondrial enoyl CoA hydratase]were down-regulated in kidneys from HFD-medaka compared to medaka fed a control diet. Recent studies involving humans and mice also suggest that NEP has a role in obesity. NEP knockout mice as well as mice treated with a NEP inhibitor (cardosint) developed obesity due to dysregulation of hyperglycemia and lipid metabolism. The role of NEP in ORG has not been studied. Therefore, we knocked down the Nep gene in a control diet and found that they developed glomerulomegaly, suggesting that mutations in nep or Nep protein deficiency could result in ORG.

**Conclusions:** This is the first study to systematically investigate using HFD-medaka as a metabolic syndrome model that will help us to explore the mechanism underlying human ORG, to identify protein markers and candidate genes for ORG. Successful completion of this study will lead us for new therapeutic strategies for patients in combing ORG and halting progression of CKD into ESRD.

**SA-PO350**

**Can Urine Glucose Be Used to Adjust Diabetes Therapy?**

**Anil K. Mandal, Linda M. Hibbert, Harry J. Khoo.** Diabetes & Endocrinology, University of Florida, Gainesville, Florida, FL; 2Dept of Veterinary Biomedical Sciences, Univ of Saskatchewan, Saskatoon, Canada; 3Statistical Consulting Center, Wright State Univ, Dayton, OH.

**Background:** Assay of urine glucose is simple and cheaper than finger-stick glucose testing. Validity of urine glucose assay to adjust diabetes therapy has not been widely studied. In the kidney, glucose is filtered and reabsorbed by the proximal tubules until blood glucose exceeds 180 mg/dL, then appears in urine, 180 mg/dL is tubular maximum. This number may be less with reduced kidney function. Our aim was to gauge if urine glucose levels relate to blood glucose in fasting or postprandial periods, determining if urine glucose testing could replace blood glucose testing to adjust therapy. Average monthly cost in the USA of urine glucose testing, $17.00, is much less than finger-stick glucose testing, $78.00.

**Methods:** 66 diabetic patients were treated with insulin Glargine twice daily, and regular insulin with meals. Urine samples were tested for glucose (Ug) in the fasting state (FUG) and at 2 hour postprandial (2hPPUG), along with blood samples [fasting blood glucose (FBG), 2hPP blood glucose (2hPPG) and fasting hemoglobin (Hgb) g/dL]. Serum creatinine (Ser, mg/dL) and estimated glomerular filtration (eGFR, ml/min) were obtained at both time periods (FScr, 2hPPScr and 2hPPeGFR, respectively). Urine glucose was measured using Roche chemstrip IOUG as normal (negative), trace (50 mg/dL), 1+ (100 mg/dL), 2+ (250 mg/dL), 3+ (500 mg/dL), 4+ (1000 mg/dL). Correlation between parameters was determined using Spearman’s non-parametric correlation. P<0.05 was deemed significant.

**Results:** Correlation was high between FUG and FBG (r=0.9999, r=0.4867) but not between FUG and Ser or FeGFR (r=0.8810 and 0.2005; r=-0.0193 and 0.1635 respectively). Likewise correlation was high between 2hPPUG and 2hPPG (r=0.9991, r=0.5228) but not between 2hPPUG and 2hPP Ser or 2hPPeGFR (r=0.5062 and 0.5084; r=-0.0911 and 0.0886, respectively). No correlation was seen between Hgb and FUG (p=0.1388).

**Conclusions:** These data suggest that urine glucose predicts changes in FBG and 2hPPG but these changes are independent of renal function.
SA-PO351
A Gene Variant in the CERS2 Gene Is Associated with Worsening Albuminuria in Diabetic Patients of ON TARGET and TRANSCEND
Dov Shiffman,1 Guillaume Pare,2 Judy Z. Louie,1 Charles M. Rowland,3 James J. Devlin,1 Matthew McQueen.2 1Celeria, Alameda, CA; 2Population Health Research Institute, Hamilton Health Sciences and McMaster Univ, Hamilton, Canada.

Background: Microalbuminuria is a risk factor for chronic kidney disease (CKD) among diabetics. However, the rate of albuminuria worsening varies among patients. Genomewide association studies identified genetic variants associated with estimated glomerular filtration rate (eGFR). We asked whether these genetic variants were also associated worsening albuminuria among diabetic patients of the ON TARGET and TRANSCEND studies—two randomized controlled trials of ramipril, telmisartan, both, or placebo in patients with vascular disease or high-risk diabetes.

Methods: We investigated 16 genetic variants that were reported to be associated with eGFR at a genome-wide level (P<5×10−8). We evaluated the association of these variants with annual rate of change in urine albumin: creatinine ratio (uACR).

Results: We found that only one of the 16 variants (rs267734) was associated with differential rate of uACR progression (P=0.0013, P=0.05 after Bonferroni correction for testing 16 variants). The annual rate of increase in uACR was 11.3% (95% CI 7.5% to 15.3%) for carriers of two risk alleles, 5.0% (95% CI 3.2% to 6.7%) for heterozygotes, and 1.6% (95% CI 1.8% to 5.2%) for non-risk homoygotes, after adjustment for age, sex, hypertension, treatment group, self-reported ethnicity, and the principal components of genetic variability. Consistent with previous reports, this variant was also associated with baseline eGFR in those with European ancestry (P=0.002), although not in other ethnic groups. This variant (rs267734) is in almost perfect linkage disequilibrium (r2=0.96) with rs267738, a single nucleotide polymorphism encoding an alanine to glutamic acid change at position 115 of the ceramide synthase 2 protein encoded by the CERS2 gene. This enzyme catalyzes the synthesis of dihydro-ceramide from sphinganine and is expressed in the kidney. However, it is not known how CERS2 function might influence albuminuria.

Conclusions: We found that rs267734 in CERS2 is associated with uACR progression rate among diabetics in ON TARGET and TRANSCEND.

Funding: Pharmaceutical Company Support - Celeria, Government Support - Non-U.S.

SA-PO352
The Association of Glucose Variability with Diabetic Complication in Korean Diabetic Patients
Mi Jin Lee,1 Jin Joo Cha,1 Young Youl Hyun,2 Dae R. Cha,1 Jung Eun Kim,1 Mihwa Lee,1 Hye KYoung Song,1 Young Sun Kang.1 1Nephrology, Korea Univ Ansan Hospital, Ansan, Kyunggido, Republic of Korea; 2Nephrology, Sungkyunkwan Univ Kangbuk Samsung Hospital, Seoul, Republic of Korea.

Background: Tight glycemic control lowers the risk of diabetic complications, but it is uncertain that glycemic variability influences diabetic complications.

Methods: We examined the associations of plasma glucose variability with diabetic complications in a prospective cohort of 161 Korean diabetic patients from 2002 to 2013. Intra-personal mean and standard deviation (SD) of fasting plasma glucose calculated. Also we calculated percent coefficient of variation (%CV=100X SD/mean).

Results: Over the duration of 11 years follow up, diabetic retinopathy and neuropathy, nephropathy developed 14%, 9%, 9.9% of patients compared to start of study. Patients who had retinopathy until the end of study, had higher percentage of coefficient of variation(23.25±10.31 vs 18.46±9.40, p[thinsp]=0.005) than patients without retinopathy. Patients who had neuropathy, nephropathy until the end of study, had higher percentage of coefficient of variation(27.94±12.09 vs 20.34±9.34, p =0.014) than non-progression.

Conclusions: Taken together, long-term glycemic variability was association with diabetic complication.

SA-PO353
Seong Woo Lee, Sejoong Kim, Kwon Woo Joo, Chun Soo Lim, Yon Su Kim, Dong Ki Kim.1 Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea.

Background: There has been a paucity of literature on the interaction between 25-hydroxyvitamin D(25OHD) status and insulin resistance (IR) according to the severity of obesity in Asian populations.

Methods: Data from the Korea National Health and Nutrition Examination Survey in 2008-2010 were analyzed. The study subjects comprised 12,895 normo-glycemic participants aged ≥20 years. IR was estimated by Homeostatic model assessment (HOMA). Obesity and its severity were assessed by body mass index (BMI) and its quartile. The association between HOMA-IR and 25OHD was assessed by segmented linear regression. In addition, the breakpoint between HOMA-IR and 25OHD was assessed by segmented linear regression.

Results: In scatter plot of HOMA-IR against 25OHD with segmented linear regression line, we found the break point within the range of 10-20 mg/ml of 25OHD. In multiple linear regression analysis, the beta value of 25OHD on HOMA-IR was -0.016 (p<0.001). In subgroup analysis according to the severity of obesity, the beta values of 25OHD on IR were -0.003 (p=0.68), -0.007 (p=0.39), -0.028 (p=0.002) and -0.033 (p<0.001) in Q1-4 of BMI, respectively.

Conclusions: The relationship between 25OHD and IR was inverse, but there might be threshold value in the range of 10-20 mg/ml of 25OHD in decreasing IR. Since the effect of 25OHD on IR increased as BMI increased, the benefit from 25OHD supplementation in reducing IR might be maximized by stratified approach according to the severity of obesity. Future studies need to be followed.

SA-PO354
Independent Predictors of Development of Albuminuria and GFR Decline in Japanese Type 2 Diabetic Patients
Michino Takagi, Tetsuya Babazono, Izumi Nyumura, Yasuko Uchida. Diabetes Center, Tokyo Women’s Medical Univ School of Medicine, Tokyo, Japan.

Background: Diabetic kidney disease has been diagnosed by albuminuria and decreased eGFR, however, whether these renal manifestations share common risk factors in type 2 diabetic patients remain to be elucidated. The aim of this study was to determine independent predictors of albuminuria and eGFR decline in Japanese type 2 diabetic patients.

Methods: This was a single-center observational cohort study involving 1,803 Japanese type 2 diabetic patients with normal albuminuria and an eGFR ≥ 60 ml/min/1.73 m2. There were 740 women and 1,062 men, and the mean age was 58 ± 12 years. Two independent endpoints were specified: development of albuminuria (≥ 30 mg/g creatinine, albuminuria cohort, N=1,777) and eGFR decline (< 60 ml/min/1.73 m2, GFR cohort, N=1,655). Cox proportional hazard model was used to identify significant predictors of each endpoint.

Results: During the median follow up period of 6.9 (IQR: 3.5-8.1) years for albuminuria cohort and 8.0 (IQR: 3.8-8.5) years for GFR cohort, 181 and 316 patients reached each endpoint, respectively: the 5-year cumulative incidence of reaching the endpoint was 8.3% for albuminuria cohort and 10.4% for eGFR cohort. In the multivariate Cox model, increased albuminuria, higher HbA1c levels, and the presence of diabetic retinopathy at baseline were commonly associated with both endpoints. Additional independent risk factors for albuminuria were male gender and elevated uric acid levels; those for eGFR decline were higher age, lower eGFR, and lower HDL cholesterol levels.

Conclusions: Identification of some distinct predictive factors for albuminuria and GFR decline suggests that different mechanisms are implicated in the development of these two renal manifestations in diabetic patients.

SA-PO355
Urinary Sodium Excretion in Relation to All-Cause Mortality and GFR Decline in Diabetic Nephropathy
Gudbjorg Andressdottir,1 Tine Hansen,1 Peter Rossing,1,2 1Steno Diabetes Center, Gentofte, Denmark; 2Aarhus Univ, Aarhus, Denmark; Copenhagen Univ, Copenhagen, Denmark.

Background: The association of urinary sodium excretion with all-cause mortality and decline in GFR in patients with type 1 diabetes and nephropathy, but without heart failure needs clarification.

Methods: In a retrospective observational setting we included all 281 patients with three or more 24 hr urinary samples during 2000-2010. Mean urinary sodium excretion was calculated from all (median 24) samples. Vital status was determined with a mean follow-up of 8.8 years. GFR (Cr-EDTA) was measured annually. The excretion was analyzed as a continuous variable in regression analysis and as quintiles in mortality analysis due to nonlinearity (cutoff-points: 7.0, 8.6, 10.1 and 12.2 g/24h).

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

707A
SA-PO356

Diabetes Mellitus Is Not Associated with Increased 5-Year Mortality in Adult Patients with Vascular Access for End Stage Renal Disease

Paola De Rango, Basso Parente, Luca Farchioni, Beatrice Fiorucci, Lydia Romano, Giuseppe Giordano. 
Vascular and Endovascular Surgery; Hospital S.M. Misericordia; Univ of Perugia, Perugia, Italy.

Background: Patients with end stage renal disease (ESRD) are exposed to limited life expectancy. As to whether diabetes mellitus may further decrease survival in these patients is not universally demonstrated. This study aimed to investigate the impact of diabetes on survival of patients with vascular access performed at a single vascular surgery center.

Methods: Data from consecutive patients with ESRD admitted for vascular access surgery from 2006 to 2013 were reviewed. Data were collected prospectively. Five-year outcomes of diabetic and non-diabetic patients were compared. Primary end-point was 5-year survival assessed by Kaplan Meier analysis with log rank test.

Results: A consecutive series of 458 patients (293 males; mean age 69.9±14.3) received 686 vascular access procedures during the study period. One hundred nineteen were affected by Type II diabetes mellitus at the time of admission. Diabetic patients showed lower survivorship probability due to the increased prevalence of hypertension (90.7% vs 77.6%; P<0.002), coronary disease (58.3% vs 42.8%; P<0.06), hyperlipidemia (27.2% vs. 17.6%; P=0.04) and were more common on statins therapy (51.0% vs 29.5%; P<0.001) when compared to non-diabetic patients. Kaplan Meier survival rates at 3 and 5 years were 71.8% and 61.3% for patients with diabetes mellitus and 70.9% and 58.5% for non-diabetics (P=0.86). Cox regression analysis failed to show any significant association between diabetes mellitus and mortality. Primary parity rates of vascular accesses at 3 years were 44.8% in diabetic and 41.5% in non-diabetics (P=0.895).

Conclusions: Diabetes mellitus is not associated with worse major outcomes in patients with ESRD requiring vascular access.

SA-PO357

The Circulating microRNA Expression Profile of Diabetic Nephropathy Patients

Qiuling Fan, Dept of Nephrology, The First Hospital, China Medical Univ, Shenyang, China.

Background: To explore the pathogenesis and the biomarkers for early detection of diabetic nephropathy (DN), the circulating microRNA expression profile of DN patients was analyzed by AB Taqman human miRNA array.

Methods: We obtained serum samples from 5 diabetic nephropathy patients proven by renal biopsy as nodular diabetic glomerulosclerosis, 5 diabetic patients without microalbuminuria (DM) and 5 healthy controls (N). Serum miRNAs were analyzed with the TaqMan Low Density Array and then confirmed with a quantitative reverse-transcription PCR assay with 30 individual samples.

Results: The urinary microRNA/creatinine ratio and serum creatinine in diabetic nephropathy patients were higher than that of diabetic patients and healthy controls (P<0.05). 20 miRNAs were upregulated and 22 miRNAs were downregulated in serum of diabetic patients compared with that of healthy controls. 42 miRNAs were upregulated and 19 miRNAs were downregulated in serum of diabetic nephropathy patients compared with that of diabetic patients. Among them, along with the progression of diabetes and diabetic nephropathy, miR-1179 was gradually increased (2.03 times in DM/N and 2.14 times in diabetic patients). Among them, along with the progression of diabetes and diabetic nephropathy, miR-1179 was gradually increased (2.03 times in DM/N and 2.14 times in diabetic patients).

Conclusions: The circulating microRNA profile of DN patients for Analyzing Progression of Diabetic Kidney Disease and Vascular Complications in Type 2 Diabetic Patients

Ming Li,1 Huajing Chen,2 Xun Liu,1 Wenbo Zhao,1 Tan-Qi Lou,1 1Dept of Nephrology, The Third Affiliated Hospital of SUN Yat-sen Univ, Guangzhou, Guangdong, China; 2Dept of Paediatrics, The First Affiliated Hospital of SUN Yat-sen Univ; Guangzhou, Guangdong, China.

Background: To investigate the clinical features of patients with type2 diabetic kidney disease and analyze the risk factors for the progression of Diabetic Kidney Disease, also to evaluate the risk for diabetic vascular complication.

Methods: 1645 Chinese adult patients with type 2 diabetic from June 2008 to September 2012 were included in this study. They were grouped according to Composite ranking for relative risks by GFR and albuminuria(KDIGO 2009). The clinical features and risk factors of DKD were compared and analyzed.

Results: 1) Rate of T2DM patients with CKD was 37.2%; According to Composite ranking for analyzing progression of diabetic kidney disease and vascular complications in type 2 diabetic patients 189 patients (11.5%); According to Composite ranking for analyzing progression of diabetic kidney disease and vascular complications in type 2 diabetic patients 189 patients (11.5%). 2) Multivariate regression analysis indicated that diabetic nephropathy (OR) (OR:1.770,95% CI 1.001-2.072), systolic pressure(OR:1.012, 95%CI 1.001-1.023), CysC(OR:5.369, 95%CI 2.306-12.499) were the independent risk factors for the progression of low risk group to moderate risk group. The risk factor for the progression of moderate risk group to high risk group were DR(OR:3.18, 95%CI 1.399-7.039), systolic pressure(OR:1.033, 95%CI 1.013-1.053), CysC(OR:9.723, 95%CI 3.110-30.394). Serum creatinine(OR:1.105, 95%CI 1.069-1.142) was the risk factor for high risk group to very high risk group. 3) Among the GFR(OR:2.142,95%CI 1.53-3.02) and CysC(OR:1.892,95%CI 3.138-11.82) were the independent risk factor for increasing the risk of CKD.

Conclusions: The Correlation between Renal Tissue Disorder and Mast Cell Chymase on Patients with Diabetic Nephropathy

Sayuri Shirai,1 Daisuke Ichikawa,1 Kayori Tsuruoka,1 Yugo Shibagaki,1 Takashi Yasuda,2 Kenjiro Kimura,3 Nephrology and Hypertension, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan; Cardiovascular Disease, Fukuoka Univ Chikushi Hospital, Chikushino, Fukuoka, Japan.

Background: Human chymase is known to produce angiotensin II (AII) but the pathophysiological role of chymase is not fully understood. We investigated relationships between chymase and renal pathological abnormality on patients with diabetic nephropathy.

Methods: We enrolled 34 type 2 diabetic patients with diabetic nephropathy who underwent renal biopsy from 2002 to 2012. Immunohistochromical staining for chymase (C+) and tryptase (T+) was performed on renal sections from patients. The number of C positive (C+) and T positive (T+) mast cell per unit area were counted. Correlation between those positive cells and patients’ clinical and pathological indices was analyzed.

Results: Both C+ mast cells and T+ mast cells were found in the interstitium, but not in the glomeruli, of renal cortex. Both cell numbers had positive correlation with tubulointerstitial injury, progression of diabetic nephropathy and advanced CKD stage, respectively. The ratio of C+ to T+ cell number had same correlation with above clinical parameters. The positive correlation between global sclerosis and interstitial injury were found on low intensity C+ group (<2/mm²), but was not found on high intensity C+ group (>2/mm²).

Conclusions: This study suggests that mast cells, especially C+ mast cells, are involved in development of diabetic nephropathy. Through release of bioactive substances like tryptase and chymase into the tubulointerstitial area, mast cells could promote renal inflammation and fibrosis, and thus contribute to diabetic nephropathy.

SA-PO360

Hyperglycemia Is Associated with Tubular Injury in Subjects with Type 2 Diabetes Mellitus

Ernesto Sabath,1 Ma. Ludwina Robles-osorio,2 Renal Dept, SESEQ,1 Metabolism and Endocrinology, Universidad Autónoma de Querétaro.

Background: Microalbuminuria indicates the presence of early glomerular disease in patients with diabetes and it has yet to be determined whether testing for markers of tubular injury can also identify persons who are at risk of progressive renal disease. The association of hyperglycemia with markers of tubular injury is currently unknown and the aim of the current study was to determine if hyperglycemia is associated with tubular injury.

Methods: Subjects aged >20 years old were included, and those with uncontrolled hyperglycemia (HbA1c >7%) were excluded. The patients and controls had a median age of 59 (20-78) years and 107 of 142 patients and controls had a median HbA1c 7.3% (5.6-10.9) and 7.3% (5.3-9.6). Urine albumin and a1M excretion were measured in 142 patients and controls with a median 0.7 ± 1.2 mg/g creatinine (0.03 ± 0.9 mg/g creatinine) and 10.3 ± 5.3 mg/g creatinine (2.0 ± 0.7 mg/g creatinine) respectively.

Results: a1M excretion a multiple linear regression analysis was used.

Conclusions: A total of 190 subjects with T2DM were included, the mean age was 52.6 ± 12.5 years, median time from diagnosis was 7.6 ± 7.2 years and mean BMI was 29.9 ± 5.4.

In 168 subjects we have determination for a1M, 76 (45.2%) had aM higher than 10 µg/gCr; these subjects were older (56 ± 11 vs 48 ± 11, p = 0.002), and glucose serum concentration was significantly higher (227 ± 75 vs 166 ± 60 mg/dl, p < 0.001), but no differences in AU was found; in multiple regression analysis the most important factor associated with a1M was serum glucose (p<0.001) and there was a significant correlation between fasting glucose levels with A1M excretion (r=0.11, p<0.1). Subjects <50 yrs and abnormal a1M had a decrease in GFR (66.2 ± 16 vs 77.3 ± 18 mg/min, p = 0.04) compared with those with normal values of a1M.

Conclusions: Hyperglycemia is associated with higher urinary excretion of a1M, reflecting a clinical significant effect of glucose concentration on tubulo-interstitial injury; a1M excretion is associated with decrease in renal function in a subgroup of patients with T2DM.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author/disclosure.

708A
SA-PO361

Background: Glucagon-like peptide(GLP)-1 receptor has been expressed at renal proximal tubule, and acts on natriuresis through Na+ (H+) exchanger isoform 3 (NHE3). On the other hand, not only GLP-1 but also brain natriuretic peptide (BNP) is contained in the substrate of dipeptidyl peptidase-4 (DPP). The aim of study is to clarify the mechanisms of natriuresis of DPP-4 inhibitors, clinically.

Methods: We gave DPP-4 inhibitor (either of sitagliptin 50-100 mg, vildagliptin 50-100 mg, alogliptin 12-25 mg) for Japanese patients with Type 2 diabetes less than 2.0 mg/dl of serum creatinine level. The patients were collected first month, 1 week and 1 month before DPP-4 inhibitors administration, and the patients were collected third month after DPP-4 administration. The average value of twice urine Na and K excretion was evaluated. Furthermore, the changes of urine Na and K excretion were also examined.

Results: The 46 patients and 60 outpatients were enrolled, and the diuretics was used together at 3%, and 65% each, respectively. By administration of DPP-4 inhibitors, urinary Na excretion significantly increased from 148±11 to 185±24 mEq/gCr (p< 0.01) in the patients with diuretics combination, and increased from 34±3 to 39±4 mEq/gCr (p< 0.05) in the patients who combined diuretics other than K sparing diuretics. On the other hand, BNP observed the upward tendency in 94±25 to 112±28 pg/ml in the outpatients by dosage of DPP-4 inhibitors.

Conclusions: It was considered that DPP-4 inhibitors regulate Na re-absorption in upper renal tubule since urinary Na K and excretion in diuretics combined use, and BNP might participate in natriuresis.

SA-PO362
25(OH)D3 Is an Effective Indicator of Mineral Metabolism for Patients with Diabetic Nephropathy Li Wang. Renal Dept, Shichuan Provincial People’s Hospital.

Background: Serum P, Ca and PTH concentration are traditional indicators to reveal the mineral metabolism. However they are usually affected by other factors, and hence not sensitive. Vitamin D is also associated with mineral metabolism. We assess the impact of 25(OH)D3 on early screening of mineral metabolism for patients with type 2 diabetic nephropathy.

Methods: Cross-sectional study of 162 type 2 diabetic patients with diabetic nephropathy, where no statistical significance exists for age, gender, duration and season. They are sorted by different concentration of 25(OH)D3 according to KDOQI Clinical Practice Guidelines for Bone Metabolism. The distributions of three concentration groups are compared, for serum P, Ca and PTH respectively.

Results: This statistical analysis shows that, along with 25(OH)D3 concentration decreases, for insufficient and deficient groups, the proportions of high-P, low-Ca and high-PTH are significantly, which are (3.6%-10.7%-85.7%, p< 0.05) (9%-12%-88%, p=0.256) respectively. The clinical data for PTH groups is limited (only 60 patients), which would be the reason for its non statistical significant difference. Meanwhile, a large proportion patients belonging to normal serum P, Ca and PTH groups have the phenomenon of 25(OH)D3 anomaly (deficiency or insufficient), which count to 82.9%, 83%, 100% respectively.

Conclusions: 25(OH)D3 is an effective indicator of mineral metabolism for patients suffering type 2 diabetes with diabetic nephropathy, and it is more sensitive comparing to serum P, Ca and PTH respectively. We suggest to detect 25(OH)D3 in mineral metabolism for early screening of the type 2 diabetic nephropathy.

SA-PO363
Role of Magnesium, Fibroblast Growth Factor-23 and Phosphorus in Cardiovascular Outcomes in Type 2 Diabetic Patients with Nephropathy Ana Paula Silva, André Fragoso, Pedro Neves. Nephrology, Hospital de Faro E.P.E, Faro, Portugal.

Background: To evaluate the role of magnesium (Mg), fibroblast growth factor-23 (FGF-23) and Phosphorus (Pi) levels in co-morbidity (hospitalization) and cardiovascular mortality. To evaluate the association between Mg and cardiovascular risk factors in type 2 diabetic patients with mild to moderate CKD.

Methods: An observational, prospective study involving 150 patients divided into groups according to baseline apelin levels: 1) <98 pg/mL, 2) 98-328 pg/mL and 3) >328 pg/mL. Baseline characteristics were analyzed and compared. Multivariate Cox regression was used to find out predictors of hospitalization and disease progression. Simple linear regression and Pearson correlation were used to investigate correlations between apelin and renal disease, and between apelin and cardiovascular risk factors.

Results: There were 1515 patients (48.5% Male and 51.2% Chinese). Mean duration of DM was 10.9±8.6 years. GFR decline was associated with increasing age and albuminuria as opposed to HDL-cholesterol (p<0.01). Vascular function was affected when GFR<60mL/min as evidenced by impaired endothelium dependent vasodilatation(Ach) and increase PWV.

Conclusions: Apelin levels might have a significant clinical use as a marker/predictor of cardiovascular mortality and hospitalization or even as a therapeutic agent for CKD patients with cardiovascular disease.

SA-PO364
What Is the Role of Apelin Regarding Cardiovascular Risk and Progression of Renal Disease in Type 2 Diabetic Patients with Diabetic Nephropathy? Ana Paula Silva, André Fragoso, Nelson Almeida Tavares, Pedro Neves.

Background: To evaluate the association of different apelin levels with cardiovascular mortality, hospitalizations, renal function and cardiovascular risk factors in type 2 diabetic patients with mild to moderate CKD.

Methods: A cross-sectional study of 162 type 2 diabetic patients with diabetic nephropathy, where no statistical significance exists for age, gender, duration and season. They are sorted by different concentration of 25(OH)D3 according to KDOQI Clinical Practice Guidelines for Bone Metabolism. The distributions of three concentration groups are compared, for serum P, Ca and PTH respectively.

Results: This statistical analysis shows that, along with 25(OH)D3 concentration decreases, for insufficient and deficient groups, the proportions of high-P, low-Ca and high-PTH are significantly, which are (3.6%-10.7%-85.7%, p< 0.05) (3%-12%-88%, p=0.256) respectively. The clinical data for PTH groups is limited (only 60 patients), which would be the reason for its non statistical significant difference. Meanwhile, a large proportion patients belonging to normal serum P, Ca and PTH groups have the phenomenon of 25(OH)D3 anomaly (deficiency or insufficient), which count to 82.9%, 83%, 100% respectively.

Conclusions: 25(OH)D3 is an effective indicator of mineral metabolism for patients suffering type 2 diabetes with diabetic nephropathy, and it is more sensitive comparing to serum P, Ca and PTH respectively. We suggest to detect 25(OH)D3 in mineral metabolism for early screening of the type 2 diabetic nephropathy.
High Fibroblast Growth Factor-23 Levels Are Associated with Early Diastolic Dysfunction in Type 1 Diabetic Patients with No or Early Diabetic Nephropathy

Background: Recent studies showed that higher fibroblast growth factor-23 (FGF-23) and lower soluble klotho levels are associated with cardiovascular disease. The aim of the study is to investigate the possible links between klotho and FGF-23 levels and cardiovascular risk factors in type 1 DM patients.

Methods: We included 87 type 1 diabetic patients with eGFR > 60 ml/min (DM) (50 females, mean age 34.2 ± 9.1 years) and 78 healthy controls (43 females, 34.5 ± 9.8 years) in the study. Demographic characteristics, albuminuria, lipid profiles, Ca, P, PTH and vitamin D levels were recorded. Echocardiographic examination was performed and eGFR was calculated. The presence of diabetic retinopathy and neuropathy were also noted. Serum klotho and FGF-23 levels were determined by ELISA method.

Results: FGF-23 levels were not different in diabetics (76.2 ± 15.7 pg/ml) compared with controls (75.3 ± 15.7 pg/ml). FGF-23 levels were only correlated with IVRT (isovolumetric relaxation time) (r = 0.231, p = 0.023) and E’med (early diastolic velocity at medial/septal annulus) (r = 0.293, p = 0.041) in DM. There were no relationships between FGF-23 and albuminuria, eGFR, diabetic retinopathy and vitamin D levels and other parameters. Soluble klotho levels in DM (532.58 ± 228.66 pg/ml) were also similar with controls (552.19 ± 425.22 pg/ml). Soluble klotho levels were found not to be related with demographic, laboratory and echocardiographic parameters.

Conclusions: Elevated FGF-23 levels are associated with higher IVRT and E’med which indicate early diastolic cardiac dysfunction in type 1 DM patients with eGFR > 60 ml/min. Soluble klotho levels are not changed in type 1 DM with early or no diabetic nephropathy in contrast with type 2 DM. High rate of hypertension, advanced age and other cardiovascular risk factors in type 2 DM might be responsible for this discrepancy between type 1 and 2 DM.

Impacts of Dyslipidemia on Diabetic Nephropathy, Cardiovascular Mortality, and All-Cause Mortality in Patients with Diabetes: A Systematic Review and Meta-Analysis

Background: Some meta-analysis reported the effects of statins for renal and cardiovascular outcome, and all-cause mortality. However, treatment of statins has two main effects. One is improvement of dyslipidemia and another one is other pleiotropic effects. When we treat patients with diabetes, we should understand precise impacts of dyslipidemia, because lifestyle changes are first-line treatment. In this study, we explored impacts of dyslipidemia on cardiovascular mortality, all-cause mortality, and renal failure in diabetes mellitus and examined inconsistency between studies.

Methods: Relevant studies were searched from MEDLINE and CINAHL by using key words of medical subject headings that included words related to “dyslipidemia”, “diabetes mellitus,” “renal failure,” “cardiovascular diseases,” and “mortality”. Studies examining the risk of the events related to dyslipidemia (cardiovascular mortality, all-cause mortality, renal failure) associated with high LDL cholesterol (LDL-C) were included. The extracted estimates were combined using a random-effects model. To investigate the cause of heterogeneity, we performed a meta-regression analysis.

Results: The literature search yielded 6624 articles, of which 390 papers were reviewed in full. Seventeen studies, which fulfilled criteria, were included in the analysis. The presence of dyslipidemia (LDL-C ≥ 1 mmol/l) was 1.08-fold increase in risk of presence of albuminuria. The presence of dyslipidemia was also a risk factor for cardiovascular mortality (relative risk 1.37), and all-cause mortality (relative risk 1.21). In the meta-regression analysis, long-term follow-up period was associated with higher relative risks of the outcome of cardiovascular mortality and all-cause mortality.

Conclusions: High LDL-C is risk factor for cardiovascular mortality, all-cause mortality, and renal failure in diabetic patients. Long-term follow-up may have stronger impact of high levels of LDL-C on outcomes of diabetic patients.

Impaired Physical Fitness in Obese Diabetic Patients with Chronic Kidney Disease

Background: Patients with diabetes, obesity, and chronic kidney disease (CKD) are generally physically inactive which may be an important contributor to their high mortality rate.

Methods: We examined baseline data from a VA funded randomized controlled trial (NC10103X6900) to assess physical fitness in this population. Inclusion criteria were type 2 diabetes, obesity (body mass index ≥ 30 kg/m²), chronic kidney disease (stage 2-4) and persistent proteinuria (≥ 200 mg/day for at least 3 months). Data from the baseline symptom-limited treadmill test were analyzed. We calculated a perceived exertion-workload index (PEWI) for each subject, defined as the ratio of perceived exertion ( Borg scale) to the energy cost of peak physical activity (METs).

Results: Baseline data (mean ± SD) on 30 subjects were evaluated. Mean values (± SD) were as follows: age 66 ± 8.1 yrs, body mass index 36.5 ± 4.9 kg/m², percent body fat 41.3 ± 6.6%, hemoglobin 12.5 ± 1.7 g/dL, glycated hemoglobin 8.1 ± 1.8%, serum creatinine 2.1 ± 1.0 mg/dL, creatinine clearance 46.5 ± 35.7 mL/min, urinary albumin excretion rate 1013 ± 1073 mg/24h. Average treadmill time was 6.8 ± 3.8 minutes and peak oxygen consumption (VO2 peak) was 13.1 ± 3.6 mL/kg/min (peak METS 3.7 ± 1.0; range 2.0-5.8). Peak METS was positively correlated with baseline average weekly pedometer step count (r = 0.62, p < 0.01). The peak perceived exertion-workload index (PEWI) was 1.4 ± 0.86, with higher values indicating greater perceived exertion relative to workload. There was a negative correlation between peak PEWI and both treadmill time (r = −0.60, p < 0.001) and average weekly pedometer step count (r = −0.63, p < 0.01). There was no correlation between peak PEWI and hemoglobin, glycated hemoglobin, serum creatinine, creatinine clearance, body mass index, or percent body fat.

Conclusions: These data indicate that obese diabetic subjects with CKD have markedly impaired baseline physical fitness, which may in part be due to increased perceived exertion at a given workload with resultant decreased ability to exercise.
and after alogliptin treatment. In contrast, alogliptin treatment significantly decreased plasma glucagon levels from 116.1 ± 38.7 pg/mL to 89.6 ± 17.3 pg/mL (p < 0.017). Moreover, there were significant correlations among HbA1c, GLP-1, and glucagon levels.

Conclusions: Alogliptin improves steroid diabetes by decrease of glucagon levels through an increase in plasma GLP-1 levels. Thus, alogliptin may be effective for the treatment of steroid diabetes in CKD caused by immunological abnormalities.

Funding: Private Foundation Support

SA-P0371
Insulin-Sitagliptin Combination Therapy Stabilizes Blood Glucose Level in Japanese Patients with Diabetic Nephropathy
Masayo Toyota, Masafumi Fukagawa. Internal Medicine, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.

Background: The use of oral hypoglycemic agents in patients with diabetic nephropathy who are sensitive enough to insulin therapy (IIT) is often prescribed. Similar to Western countries, the concomitant use of dipeptidyl peptidase-4 inhibitors and insulin has also been recently approved in Japan, and it is expected that the combination treatment could lead to stable euglycemia. In Western countries, adjusted doses of sitagliptin can be administered to patients with severe renal dysfunction or end-stage renal disease (ESRD); but this is contraindicated in Japan. Therefore, a retrospective study was conducted to evaluate the safety and efficacy of the combination of sitagliptin and IIT in Japanese type 2 diabetic patients with low estimated glomerular filtration rates (eGFR).

Methods: We selected 116 patients who were already receiving IIT combined with sitagliptin. From these patients, we selected 40 patients with eGFR of <60 mL/min/1.73 m².

Conclusions: At 12 month follow-up, there was a significant decrease in BMI and fat mass. Bariatric surgery increased kidney function (Table). Fasting insulin, hs-CRP and leptin levels decreased, while HMW-adiponectin increased following surgery (Table).

The improvement in kidney function correlated with the reduction in lepitin (rho=-0.86, p=0.001) and insulin resistance (rho=-0.73, p=0.01). Decreased leptin was significantly correlated with lower fat mass (rho=-0.63, p=0.04) and insulin resistance (rho=-0.75, p=0.01).

Conclusions: In CKD, bariatric surgery improves kidney function, insulin resistance, and adipokines in obese subjects with CKD.

Funding: Other NIH Support - NCRR

SA-P0375
Glycemic Indices and Dialysis Modality in Diabetic (DM) and Non-Diabetic (NDM) Patients
Neal Mittrnan,1 Lin Ma,2 Mark E. Williams,3 Julia I. Brennan,4 Robert D. Toto,1 Christoph Sanner,1 John Gerich,3 Afshin Salsali,4 Thomas Hach,4 Gabriel Kim,4 Stefan Hantel,4 Hans-Juergen Woerle,4 Uli Christian Broedl.4 1Univ of Texas Southwestern Medical Center, Dallas; 2Univ of Wurzburg, Germany; 3Univ of Rochester School of Medicine, Rochester, NY; 4Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; 5Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

Background: The SGLT2 inhibitor EMPA is in development for the treatment of T2DM. SGLT2 inhibitors lead to osmotic diuresis, which could lead to volume depletion. Methods: Using pooled data from Phase I, II and III trials, adverse events (AEs) consistent with volume depletion were evaluated through a search of investigator-reported AEs (8 prospectively defined terms: BP decreased, BP ambulatory decreased, fluid loss, peripheral edema, peripheral oedema, orthostatic hypotension, hypovolemia, and syncope) in patients with T2DM treated with placebo (PBO; n=3522), EMPA 10 mg (n=3630) or EMPA 25 mg (n=4062) in subgroups of age <50, 50-65, 65-75, >75 years, eGFR <90, 90-60, 60-30, <30 mL/min/1.73 m² and diuretic use. Mean (SD) baseline age was 59.6 (10.0) yrs and eGFR 80.1 (22.1) mL/min/1.73 m².

Results: The percentage of patients with volume depletion events was similar with PBO (40/3522 [1.1%]), EMPA 10 mg (52/3630 [1.4%]) and EMPA 25 mg (67/4062 [1.7%]). The percentage of patients with events increased from 0.9%, 0.4% and 0.7% with PBO, EMPA 10 mg and EMPA 25 mg, respectively, in the youngest group to 2.1%, 2.3% and 4.4%, respectively, in the oldest group. The percentage of patients with events increased from 0.8%, 0.6% and 0.7% with PBO, EMPA 10 mg and EMPA 25 mg, respectively, in the highest eGFR group to 9.6%, 14.3% and 7.1%, respectively, in the lowest eGFR group.

Conclusions: EMPA was not associated with an increased frequency of volume depletion events versus PBO, except with EMPA 25 mg in patients >75 yrs of age.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim

SA-P0372
Effect of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Cardiovascular Events in Patients with Diabetes Mellitus: A Meta-Analysis
Jianhua Chen. Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.

Background: Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) may have different effects on cardiovascular (CV) events in diabetic patients. We conducted a meta-analysis to separately evaluate the effects of ACEIs and ARBs on major CV events in diabetic patients.

Methods: MEDLINE, Embase, Cochrane Library, and article reference lists were searched for RCTs that compared ACEIs and ARBs with controls. Twenty-one RCTs compared ACEIs with controls (32,141 patients) and twelve compared ARBs with controls (23,617 patients). When compared with controls, ACEIs significantly reduced the risk of major CV events by 14% (95% CI: 7-21%), including cardiovascular death, non-fatal MI and non-fatal stroke, while ARBs did not significantly affect the risk of major CV events (p=0.62). ACEIs were better than ARBs for stroke prevention (p=0.01), but similar effects on MI and non-fatal MI (p=0.83).

Conclusions: ACEIs rather than ARBs are the first choice of treatment may result in considerable benefit in MI and heart failure risk. More data are needed to clarify the role of ARB in survival benefits for diabetic patients.

Funding: Other NIH Support - NCRR
Effectiveness of the Diabetic StepAhead Program in Improving Patient Care among Diabetic ESRD Patients

Background: Diabetes mellitus (DM) is a leading cause of mortality and morbidity in end-stage renal disease (ESRD). StepAhead is an integrated DM care management program aimed at enhancing patient outcomes via physician-driven DM-management, regular eye exams and foot-checks, and patient education on DM self-management. While the program is undergoing a year-long study to assess the reduction in lower limb amputations and mortality rates among this population, this interim analysis assessed its effectiveness after 6 months of implementation.

Methods: StepAhead was initiated in January 2012 and included 447 identified diabetic ESRD patients from 11 participating clinics. Information on clinical management of DM as well as DM-education was obtained from the electronic medical record at baseline and at 6 months of implementation.

Results: At 6-month follow-up, enrolled patients were 64 years old, 54.5% male, and 48.9% black. Cumulative outcome metrics (N = 356) show that 336 (94.4%) were provided physician management; 319 (89.6%) had an eye exam within the past year; 330 (93.5%) had received blood glucose education; and 330 (92.7%) had a glomerulot as the end of six months. Of the 211 patients who were not physician managed for DM at baseline, 151 (72%) completed 6 months in the program, 136 (86.8%) became physician managed, and 36 (23.9%) were referred to a physician for DM-management at 6 months. Among the 218 patients who did not have an eye-exam within a year of enrollment at baseline, 120 (76.4%) received an eye-exam and 33 (21.0%) were referred for one at 6 months. Of the total 163 (73.0%) patients without a glucometer at baseline, 136 (84.0%) received one. Finally, 322 (89.2%) of the patients undertook at least one foot-check within 6 months of enrollment.

Conclusions: The data suggest that the StepAhead Program successfully enhances physician-driven DM-management and self-monitoring. The preventive measures included in the program potentially allow for early detection of complications and delay progression, i.e. A1c reflecting 2-3 months of exposure while SF and GA reflects only 2-3 weeks. Since GA is the predominant SF, stronger correlation between them is expected. In future follow-up data may be influenced by differential protein losses and diastolic glycose exposure times.

SA-PO376

Effect of the Improvement in Prognosis in Simultaneous Pancreas-Kidney Transplantation and Kidney Transplantation Alone for Type 1 Diabetic Patients with End-Stage Renal Disease

Background: Kidney transplantation has been demonstrated to prolong survival in diabetic patients with ESRD; however, it is unclear whether simultaneous pancreas-kidney transplantation (SPK) yields additive benefit in type 1 diabetes (T1D) patients with ESRD compared with kidney transplantation alone (KTA). We therefore conducted this study to compare prognosis in patients with T1D undergoing chronic dialysis, KTA, and SPK. The results of transplantations were also compared between the two transplant groups.

Methods: 128 T1D patients with EASD (84 women and 44 men) were studied, comprising of 54, 45 and 27 patients undergoing dialysis, KTA and SPK respectively. We compared survival among the three renal replacement therapy (RRT) groups after the start of dialysis. Patient and graft survival rates were also compared between the two transplant groups.

Results: Age of dialysis initiation, diabetes onset and duration of diabetes were significantly higher in SPK and KTA than chronic dialysis group. There were no significant differences among the three RRT groups in terms sex and dialysis treatment recipient’s age was not different between SPK and KTA. In KTA 96% were from living donors. Ten-year patient survival rates after the start of dialysis was 63% for the dialysis group, 94% for the KTA group, and 92% for the SPK group, respectively (P<0.001). In multivariate analysis, SPK and KTA were associated with a lower mortality risk than dialysis patients, respectively (hazard ratio 0.10 and 0.28, P=0.003 and 0.029). Patient survival at 10 years was 90% for the KTA group, 91% for the SPK group, respectively (P=0.25). Graft survival at 10 years was 74% for the KTA group, 59% for the SPK group (P=0.52).

Conclusions: Prognosis for patients receiving SPK or KTA may be superior to that for patients undergoing dialysis. Patient and kidney graft survival were similar for SPK and KTA, because favorable results would be achieved with KTA.
SA-PO380

Does Iron Status Affect Platelet Counts in Hemodialysis Patients? Kiyomi Koike,1 Kei Fukami,2 Kazumasa Shimamasu,1 Atsushi Kawaguchi,2 Seiya Okuda.1

Background: Normalizing hemoglobin (Hb) levels by ESAs has been reported to be associated with risk of cardiovascular death/events via thrombocytosis due probably to ESA-induced iron deficiency ‘platelet link hypothesis’ in CKD patients. However, whether or not disturbed iron status really affects platelet counts.

Methods: In our cohort, 117 HD outpatients followed for 4 years in a single center. Target Hb level was 11.0 g/dL. The outcome variable is increase in platelet counts. Potential predictors are iron indices such as transferring saturation (TSAT), serum iron and ferritin. We investigated the association between iron indices and increase in platelet counts by mixed effect model adjusted for time, age, gender, Hb, CrP, alb, a weekly ESAs dose and a monthly i.v. iron dose with non-linear analysis. Next, in the analysis for the first difference of a time series which is the series of changes from one period to the 3 months later (Δ), the correlation between iron indices and Apleptol counts was examined. Further, we analyzed whether or not ESAs dose was associated with iron status.

Results: Mean age; 61.9 yrs and mean Hb; 10.8 g/dL. In multivariate regression analyses, lower TSAT levels (increase in platelet counts 0.3+10^9/L per 10% decrease in TSAT, 95%CI -4.8 to -1.7; p<0.001 and higher ESAs dose (95%CI 0.03 to 0.22; p=0.077) were significantly correlated with larger increase in platelet counts independently of Hb, Alb, CrP and i.v. iron dose. ΔTSAT was negatively and Δferritin was positively correlated with Apleptol counts (95%CI -4.9 to -1.7; p=0.001 and 95%CI 0.007 to 0.004; p=0.003, respectively). Higher ESAs dose to keep target Hb levels was significantly associated with lower TSAT and ferritin (<330ng/ml levels) (p<0.001).

Conclusions: These observations suggest that iron status, especially decreased TSAT, may directly affect increased platelet counts and subsequently cause cardiovascular events in HD patients on ESAs treatment.

SA-PO381

IV Iron Is Not Associated with Change in CRP across Dose and Ferritin Levels: A DOPPS Study Laura H. Mariani, Keith McCullough, Mark R. Marshall, Patricia De Sequeira, Ananda Sen, Masaaki Inaba, Ronald L. Pisoni, Bruce M. Robinson.

Background: Inflammation and CRP levels are positively associated with mortality in hemodialysis patients. The sustained effects of IV iron on CRP levels are unclear, and may depend on patient iron and inflammatory status. This study examined the association between iron dose and change in CRP.

Methods: Observational DOPPS phase 4 (2009-11) data from facilities that measured CRP at least quarterly on 75% of patients, in seven European countries and/or New Zealand were used to determine IV iron dose over two consecutive months (iron dose measurement period, or IDMP). Baseline CRP was the most recent value prior to the IDMP. Final CRP was collected during the 2nd month of the IDMP or up to 1 month later. Linear measurement period, or IDMP). Baseline CRP was the most recent value prior to the IDMP.

Results: Change in CRP did not differ meaningfully across iron dose categories, overall or by ferritin levels.

Figure 1: Adjusted Change in CRP by Ferritin and IV iron

Table 1

<table>
<thead>
<tr>
<th>Subjects</th>
<th>&lt;30</th>
<th>30-100</th>
<th>&gt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td>ferritin, ng/mL</td>
<td>200</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Subjects (%)</td>
<td>11</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>subjects with Death (%)</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>subjects with Any SAE (%)</td>
<td>95</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>subjects with Any TEAE (%)</td>
<td>95</td>
<td>97</td>
<td>97</td>
</tr>
</tbody>
</table>

Conclusions: There was no evidence of an increase in adverse events associated with higher ferritin and TSAT levels.

SA-PO382

Achieved Iron Stores and Clinical Outcomes in a Trial of Ferric Citrate as a Phosphate Binder Kausik Umanath,1 Mohammed Sika,1 Mark Koury,1 Jamie P. Dywer,1 Julia Lewis,1 The Collaborative Study Group.1 1Vanderbilt Univ; 2Henry Ford Hosp; 3CMM.

Background: The safety of achieved iron stores in dialysis patients is controversial. Utilizing data from a multicenter, randomized trial in 441 dialysis subjects treated with ferric citrate (FC) or active control (AC) (calcium acetate, sevelamer carbonate, or a combination), we grouped subjects based on their achieved iron stores and examined their safety profiles.

Methods: Subjects were randomized: 2:1 to FC or AC, and followed during a 52-week safety assessment period (SAP). IV iron use was at the discretion of the site as long as the serum ferritin was ≤1000ng/mL and the transferrin saturation (TSAT) was ≤30%. All oral iron and vitamin C supplements were prohibited. Adverse events, ferritin, and transferrin saturation (TSAT) were collected and analyzed.

Results: In the SAP, baseline mean serum ferritin was 594 ± 279ng/mL. At week 52, mean ferritin was 776 ± 444 ng/mL. Mean TSAT at baseline was 31 ± 11%. At week 52, mean TSAT was 34 ± 14%. Treatment emergent adverse events (TEAE), death, and serious adverse events (SAE) by tertiles of mean ferritin and TSAT averaged over 52 weeks are shown in Tables 1 and 2.

Table 2

<table>
<thead>
<tr>
<th>TSAT, %</th>
<th>&lt;30</th>
<th>30-100</th>
<th>&gt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (N)</td>
<td>160</td>
<td>243</td>
<td>97</td>
</tr>
<tr>
<td>subjects with Death (%)</td>
<td>6</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>subjects with Any SAE (%)</td>
<td>97</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>subjects with Any TEAE (%)</td>
<td>97</td>
<td>97</td>
<td>97</td>
</tr>
</tbody>
</table>

Conclusions: There was no association between two-month IV iron dose (including doses suggestive of replacement IV iron dosing) and change in CRP across a range of markers indicative of iron and inflammatory status. Associations with longer-term IV iron dosing also merit study.
SA-PO384

A Mathematical Erythropoiesis Model Adjusted to Individual Hemodialysis Patients

Doris Helene Fuertinger,1,2 Franz Kappe,1 Stephan Thijssen,1 Peter Kotanko,1,3 Renal Research Institute, New York, NY, USA; 2Univ of Graz, Austria.

Background: Interindividual variability in red blood cell (RBC) lifespan, bone marrow response to erythropoietin (EPO), endogenous EPO production and half-life is high in hemodialysis (HD) patients. Routine measurement of these quantities is elusive, thus making it almost impossible to predict the individual response to EPO administration schemes. Here we describe the adaptation of a complex mathematical model of erythropoiesis to individual HD patients.

Methods: A mathematical model (Fuertinger et al, JMathBiol 2013) is adjusted to individual HD patients treated with EPO. The patient’s blood volume and number of stem cells are estimated based on height and weight. Crit-LineTM devices were used for intradialytic hemoglobin (Hgb) measurements. Hgb data is used to identify the RBC lifespan, bone marrow response to EPO, endogenous EPO production, and EPO half-life in individual HD patients.

Results: We studied 1,866 HD sessions in 36 patients (mean (range) age 59.8 (25.85) years; 66.7% Blacks; 52.8% females; 61.1% diabetes; body mass index (BMI) 26.3 (17.9-50.4) kg/m²). Independent of gender and BMI the mean (range) of the identified erythropoiesis parameters were biologically plausible: RBC lifespan 72.7 (50.5-103.4) days, and EPO half-life 6.98 (4.1-12.3) hours. The model accurately represented the Hgb dynamics in all patients. For an example for an adaption of the model to an individual HD patient, see Figure.

Conclusions: Our results indicate that this model can be adjusted to HD patients based on gender, height, weight, 3x weekly Hgb measurements, and EPO doses. The model quantitatively describes the specific dynamics of erythropoiesis and Hgb levels in EPO treated HD patients. The model can be used to investigate, compare, and improve EPO administration schemes based on metrics of accuracy, precision, and cost-effectiveness.

SA-PO385

Statin Therapy in Dialysis Patients and Its Effects on Erythropoietin Resistance Index

Jerome Pineault, Johannesburg; Jean-Philippe Lafriere, Montreal; Martin Leblanc, Georges Ouellet, Robert Zoël Bell, Michel Vallée, Vincent Pichette. Medicine, Div of Nephrology, Maisonneuve-Rosemont Hospital, Montreal, Canada.

Background: Erythropoietin (EPO) resistance and anemia is a burden among dialysis patients and efficient therapies are lacking. We studied the effect of statin therapy on EPO responsiveness in our dialysis population.

Methods: We reviewed the records of 676 patients receiving chronic dialysis from September 2008 to March 2011. We measured EPO resistance index (ERI) from the weekly doses of EPO/kg divided by Hgb (g/dL) each month. Association between statin use and ERI was estimated using a multivariable linear mixed-effects, adjusting for sex, age, diabetes, dialysis modality and ACEI/ARB use.

Results: A total of 503 patients underwent analysis after exclusion. The multivariate regression analysis showed that ERI was not improved with statin therapy (β = 0.97, with P = 0.05). Patients getting started on statins during the study (N=42) had increased ERI after statin exposure and those getting off statins (N=47) had their ERI decreased after statin was stopped, the exact opposite of what was expected, even though results were statistically significant. Male sex and peritoneal dialysis were associated with a lower EPO resistance. Also, ACEI/ARB and diabetes were associated (but not significantly) with higher EPO resistance.

Conclusions: Statin use was not associated with improved EPO responsiveness. Also, male sex and peritoneal dialysis appeared to be potential protectors from EPO resistance. However, a confirmation of these results is needed by larger randomized-controlled trials.

Funding: Clinical Revenue Support

SA-PO386

Hyporesponsiveness to Erythropoiesis-Stimulating Agent as a Prognostic Factor in Japanese Hemodialysis Patients: The Q-Cohort Study

Rieko Erguchi,1 Masatomo Taniguchi,2 Kazuhiko Tsuoryu,2 Hideki N. Hakarata,3 Satoru Fujimi,1 Takakiri Kitazono,2,3 Fukuoaka Renal Clinic, Fukuoka, Japan; 4Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ; Fukuoka, Japan; 5Div of Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan.

Background: Several longitudinal studies have shown that responsiveness to erythropoiesis-stimulating agent (ESA) is related to the prognosis in hemodialysis (HD) patients. We investigated the effects of hyporesponsiveness to ESA on mortality in Japanese HD patients, taking factors modifying its effects into account.

Methods: A total of 2,905 Japanese HD patients aged ≥18 years, who received ESAs, were prospectively followed up for 4 years. The responsiveness to ESA was estimated using an erythropoietin resistance index (ERI), defined as erythropoietin dosage for a week divided by the post-HD weight and hemoglobin value. Patients were divided into three groups with tertiles of ERI values; low ERI: ≤5.10, intermediate ERI: 5.11-9.43, and high ERI: ≥9.44. The risk estimates were calculated by using a Cox proportional hazards model.

Results: During the follow-up period, 482 patients died from any causes. The mortality rate for 4 years increased linearly with higher ERI levels, being 12.5%, 17.1%, 28.0% for low, intermediate, and high ERI levels (p for trend <0.001). Compared with those with lower ERI levels, the multivariate-adjusted hazard ratio (mHR) was significantly higher in patients with high ERI level (mHR, 1.59 [95%, confidence interval, 1.24-2.04]). Among high ERI group, patients with Kt/V≤1.57 had a significantly lower risk of death from any causes, than those with Kt/V>1.57 (mHR, 0.74 [0.55-1.00]).

Conclusions: Our findings suggest that ESA responsiveness can be considered a significant prognostic factor in Japanese HD patients, and higher dose of dialysis seems to be effective for improving prognosis of HD patients with hyporesponsiveness to ESA.

SA-PO387

Virdaglin, an Inhibitor of Dipeptidyl Peptidase-4 (DPP4-4), May Enhance the Effects of Continuous Erythropoietin Receptor Activator (CERA) in Treating Renal Anemia in Hemodialysis (HD) Patients

Yunichiro Hashiguchi,1 Satoshi Funakoshi,2 Yoshiaki Lee,1 Masatoshi Hayashida,1 Takashi Harada,1 Kenichi Miyazaki,1 Tomoya Nishino,1 Yoko Obata,2 Shigeru Kohno,3 Kazunori Utsuminomiy,11 Div of Blood Purification, Nagasaki Renal Center, Nagasaki, Japan; 2Dept of Internal Medicine, Nagasaki Univ Graduate School of Medicine, Nagasaki, Japan; 3Dept of Diabetology, Jikei Univ, Tokyo, Japan.

Background: DPP-4 (~CD26) is expressed on activated lymphocytes and poses hematopoietic effects via pathways for regulating cytokines (Jones B, et al. Blood 2003). Continuous erythropoietin receptor activator (CERA) is a long-acting erythropoiesis-stimulating agent, and the effects may possibly be enhanced by hematopoietic effect of DPP-4 inhibitor.

We evaluated the erythropoietic effects of DPP-4 inhibitor in HD patients treated with CERA when converted from sulfonyl urea (SU) or phenylalanine analogues (PA).

Methods: From September to December 2010, 15 HD outpatients were enrolled in a Phase II study after appropriate IC, and were monitored by various parameters including fasting plasma glucose (FPG), HbA1c, Hb, albumin or body weight. CERA doses had stayed the same.

Results: All the subjects were administered CERA at 134 ± 27.5 mg. FPG and HbA1c level had been stabilized after dose adjustment of virdaglin. As shown in Table 1, there was significant increase in Hb level (10.8 ± 1.49 to 11.6 ± 1.08, p=0.018) though CERA doses had been unchanged.

Other nutritional parameters stayed the same.

Conclusions: Virdaglin can potentially enhance the hematopoietic effects of CERA in the treatment of anemia for diabetic HD patients.

Funding: Private Foundation Support
SA-PO388
Human Erythropoietin Alfa Originator and Biosimilar: Safety, and Therapeutic Equivalence in a Cohort of Emodialysis Patients. A Pilot Study
Paolo Lentin.1 Luca Zanoli,2 Massimo de Cal,1 Stefania Rastelli,2 Anna Basso,2 Grazia Berlingo,2 Valentina Pellanda,3 Andrea Contestabile,1 Roberto Bell2 Aim: A previous study showed that the switch from human erythropoietin Alfa Originator (Eprex) and Biosimilar (Binocrit) to maintain haemoglobin and haematocrit levels in the therapeutic range and the monthly cost of each therapy.

Methods: 63 chronic haemodialized patients treated with Eprex were assigned to Eprex or Binocrit harm and followed up for 6 months. 42 subjects treated with Eprex and 11 subjects treated with Binocrit were included in this analysis. A general linear model for repeated measured adjusted for haemoglobin and haematocrit levels was used. In this analysis a cost of £55.31 for 10,000 UI of Eprex and £50.91 for 10,000 UI of Binocrit was used.

Results: Mean weekly erythropoietin Alfa dose was 12,078±1,440 and 12,981±2,677 UI in Eprex and Binocrit group; mean haemoglobin and haematocrit levels were comparable between groups. In multivariate analysis, adjusted for monthly cost of haemoglobin and haematocrit levels, erythropoietin Alfa dose was higher in Binocrit than Eprex group.

Conclusion: Eprex and Binocrit showed comparable safety and efficacy in this pilot study. However, Binocrit was 8% cheaper than Eprex, the monthly cost of erythropoietin Alfa to maintain haemoglobin and haematocrit levels in the therapeutic range was only 1% lower with Binocrit than with Eprex.

SA-PO389
Elevated Cobalt Levels in Chronic Hemodialysis Patients Are Not Associated with Increased Morbidity or Mortality, but Are Associated with Higher Hemoglobin Levels and Decreased Erythropoiesis Stimulating Agent Requirements
Rebecca Backenroth,1 Dvora Artouli.2 1Nephrology, Hadassah Univ Medical Center, Jerusalem, Israel; 2Pediatrics, Kaplan Medical Center, Rehovot, Israel.

Background: We have previously shown that chronic hemodialysis patients (CHD) have higher mean cobalt levels (Co) than healthy controls. The higher Co was associated with higher hemoglobin levels (Hb) and lower erythropoiesis stimulating agent (ESA) doses. Furthermore, ESA free patients with good Hb had strikingly higher Co. Since Co can be toxic, we evaluated possible detrimental effects of the spontaneously elevated Co.

Methods: Morbidity and mortality were evaluated retrospectively in all CHD who had Co determinations, with clinical and laboratory variables from charts and computerized lab records. Statistical analysis included T test, Mann Whitney, Chi Sq, Fisher’s Exact, Pearson correlation, Regression analysis, Kaplan Meier survival and the Log Rank tests. Numbers are mean ± SD.

Results: 150 CHD, 66% male, age 65±15, on dialysis for 6.4±2 yrs were studied. There was no difference in underlying or new onset of illnesses, hospitalizations or mortality between patients with Co lower or equal to the mean and those with higher levels, except the incidence of skin malignancy, which was less in CHD with lower initial Co. This relation disappeared when all Co levels were averaged. There were no melanomas or aggressive skin tumors. Kaplan Meier analysis was similar for low and high Co groups.

Conclusions: Our preliminary data showed that the switch from human erythropoietin Alfa originator to biosimilar is associated with an increase of erythropoietin dose during a follow-up of 6 months and with a comparable monthly cost of Binocrit and Eprex therapy.

SA-PO390
Bi-weekly Administration of a Continuous Erythropoietin Receptor Activator (CERA) is Recommended in the Treatment of Anemia in Hemodialysis (HD) Patients: A Longitudinal, Single Institutional Study
Satoshi Funakoshi,1 Junichihiro Hashiguchi,2 Yoshihiro Lee,1 Kenichi Miyazaki,1 Kenji Sawase,2 Takashi Harada,3 Tomoya Nishino,4 Yoko Obata,5 Shigeru Kohno,6 Kazunori Utsunomiya.1 1Div of Blood Purification, Nagasaki Renal Center, Nagasaki, Japan; 2Dept of Internal Medicine, Nagasun University Graduate School of Medicine, Nagasaki, Japan; 3Dept of Diabetology, Jikei Univ, Tokyo, Japan.

Background: CERA is a long-acting erythropoiesis-stimulating agent that is approved for the treatment of renal anemia, but data on routine use of either once-monthly or biweekly in HD patients are scarce. In several phase 3 trials CERA once every two weeks was approved compared to results with other ESA’s and other phase 3 trials evaluated the effects of once-monthly CERA.

Methods: This study to evaluate the efficacious intervals of CERA administration was a prospective, single-center trial with duration of up to 18 months. Seventy-eight HD patients receiving CERA in our facility were included, and CERA administration was converted from once-monthly to twice-monthly (with half CERA dose). Since there were 5-week months, the parameters were compared in once biweekly (Q2W), every 3 weeks (Q3W) and every 4 weeks (Q4W). The CERA doses were adjusted in each patients to maintain Hb levels in the range 10-12 g/dL.

Results: At the end of the 18-month study, CERA doses per month were reduced in 24 out of 78 patients. Mean Hb level was 10.5 ± 1.4 g/dL at baseline and 10.7 ± 1.7 g/dL at the end of the study. As shown in Figure 1, in biweekly administration of CERA, but not Q3W or Q4W, significantly higher reticulocyte counts and lowest ferritin levels were observed. Figure 2 shows that biweekly CERA was potentially the most efficacious in terms of red blood cell iron utilization or erythropoiesis.

SA-PO391
The Relationship between Serum Angiopoietin-Like Protein 2 Levels and Atherosclerosis Factors in Hemodialysis (HD) Patients
Terumasa Onoue,1 Teruhiko Mizumoto,2 Kohei Uchimura,3 Manabu Hayata,1 Yutaka Kakizoe,2 Kenichi Kitanura.2 Nephrology, Kumamoto Univ Graduate School of Medical Science, Kumamoto, Japan.

Background: Angiopoietin-like protein 2 (Angptl2), a proinflammatory protein, was recently revealed to contribute to the pathogenesis of atherosclerosis in mice. However, its role in humans still remains poorly understood. The purpose of this study is to identify factors associated with serum Angptl2 levels and to elucidate the relationship between serum Angptl2 levels and atherosclerosis in hemodialysis patients (HD).

Methods: Three hundred and eighty eight HD patients (men: 63%, mean age: 65±12 year, mean HD duration: 9.0±8.6 year) were enrolled. Serum Angptl2 levels and Hs-CRP levels were determined by the ELISA kit. Routine laboratory data, clinical history were collected. Cardio-ankle vascular index (CAVI) and carotid artery intima-media thickness were also measured.

Results: Mean serum Angptl2 level in all patients was 3.40±0.91 μg/mL, which was higher than in healthy subjects in Japan. In diabetic HD patients (N=136, mean age: 65±10 year, mean HD duration: 5.1±3.9 year, mean serum Angptl2 levels: 3.53±1.09μg/mL), CAVI, the frequency of percutaneous transluminal AV shunt angioplasty, and serum triglyceride levels were significantly associated with serum Angptl2 levels (R=0.54, P<0.001) in multiple regression analysis. In non-diabetic patients (N=220, mean age: 61.7±11.5 year, mean serum Angptl2 levels: 13.7±9.95 year, mean serum Angptl2 levels: 3.09±1.17μg/mL), HD duration, BMI, and Hs-CRP levels were significantly associated with serum Angptl2 levels (R=0.73, P<0.001). Cerebral infarction in non-diabetic patients was related to serum Angptl2 levels (R=0.02, P=0.01) in multiple regression analysis (R=0.54, P<0.01). Furthermore, in a multiple logistic regression, serum Angptl2 levels ≥ 4μg/mL was a significant risk factor for cerebral infarction in male diabetic HD patients (P=0.04, odds ratio: 2.09, 95%confidence interval: 1.03 - 8.02).

Conclusions: Serum Angptl2 levels are associated with several atherosclerosis factors, and it could be a biomarker for cerebral infarction in HD Patients.
Peripheral Monocytes May Be Predisposed to Uptake of Pro-Atherogenic Low-Density Lipoprotein through Genetically-Enhanced Expression of Scavenger Receptors in Hemodialysis Patients  Miki Nishida, Minoru Ando, Yusuke Iwamoto, Ken Tsuchiya, Kosaku Nitta, Debra F. Higgins, Yvonne M. O’Meara, Catherine Godson, UDCD Diabetes Complications Research Centre, UCD Conway Institute, Univ College Dublin, Dublin, Ireland; UCD School of Medicine and Medical Science, Univ College Dublin, Dublin, Ireland; Dept of Nephrology, Mater Misericordiae Univ Hospital, Dublin, Ireland.

Background: Atherosclerosis is accelerated in hemodialysis (HD) patients. Monocyte-macrophage scavenger receptor (SR) plays a pivotal role in promoting foam cell formation by binding and internalizing pro-atherogenic low-density lipoprotein (LDL).

Methods: Transcriptional levels of SR class A (SR-A) and class B (CD68) were simultaneously measured in peripheral monocytes by quantitative real-time PCR, using the comparative threshold (Ct) method. Peripheral monocytes were magnetically labeled and isolated using a MACS Separator (Miltenyi Biotec Inc). Subjects included 39 chronic HD patients (mean age, 72 years) and 14 healthy controls. Multivariate logistic analysis was used to determine an association of SR expressions with prevalence of cardiovascular disease (CVD), including myocardial and cerebral infarctions and peripheral artery disease.

Results: The relative expressions of SR-A and CD68 mRNA were significantly greater in monocytes from HD patients than in those from controls (mean [95% CI] of the mean): 3.14 [2.58-3.69] versus 1.09 [0.79-1.39], P < 0.001; and 4.45 [3.62-5.28] versus 1.15 [0.78-1.51], P = 0.0004, respectively. Each SR receptor expression was significantly higher in HD patients who had CVD than in those who did not: SR-A, 3.56 [2.89-4.22] versus 2.19 [1.29-3.10], P = 0.0137; and CD68, 2.43 [1.92-2.93] versus 1.65 [1.22-2.08], P = 0.0479, respectively. Moreover, each SR expression was significantly associated with prevalent CVD and adjustment by age, gender, presence of diabetes, HD vintage and serum LDL-cholesterol levels: odds ratio (95% CI), 1.95 (1.06-4.63) for SR-A and 4.18 (1.44-22.6) for CD68.

Conclusions: Transcriptional expressions of two SR types were enhanced in the HD patients, particularly those with CVD. Prospective studies are warranted to ascertain the association between SR expressions and incidence of CVD.

SA-PO393 Plasma Calprotectin Levels in Chronic Kidney Disease  Natalia Alvarez Borges, Amanda Barros, Lily Lobo, Denis Fouque, Federal Univ Fluminense, Niteroi, Rio de Janeiro, Brazil; Dept of Nephrology and Nutrition, CENS, Centre Hospitalier Lyon Sud, France.

Background: Calprotectin (MRP8/14) is the main neutrophil cytoplasmic protein, which exerts potent proinflammatory effects through activation of Toll-like receptor-4 (TLR-4). Elevated plasma MRP-8/14 predicts the risk of future cardiovascular events. The aim of this study was to evaluate calprotectin plasma levels in CKD patients without acute infection association between SR expressions and incidence of CVD.

Methods: Sixteen conservative treatment (CT) pts (44% men; 62.5±8.3 yrs; BMI 26.3±3.8 kg/m², CKD stage III - IV), nineteen hemodialysis (HD) pts (50.0% men; 59.4±15.8 yrs; BMI 23.1±2.4; dialysis vintage, 27.0 [20-52] months) and 16 healthy controls (43.7% men; 53.6±5.0 yrs; BMI 24.6±2.7) were studied. No correlation was found between plasma calprotectin levels and dialysis vintage.

Conclusions: The relative expressions of SR-A and CD68 mRNA (2-ΔΔCt) were enhanced in the HD patients, particularly those with CVD. Prospective studies are warranted to ascertain the association between SR expressions and incidence of CVD.

SA-PO394 Lipoxin A4 and Resolvin E1 Reduce Inflammatory Monocytes in Haemodialysis Patients Fileen Nolan, Debra F. Higgins, Yvonne M. O’Meara, Catherine Godson, UCD Diabetes Complications Research Centre, UCD Conway Institute, Univ College Dublin, Dublin, Ireland; UCD School of Medicine and Medical Science, Univ College Dublin, Dublin, Ireland; Dept of Nephrology, Mater Misericordiae Univ Hospital, Dublin, Ireland.

Background: An increase in CD16+ circulating monocytes occurs in haemodialysis (HD) and is associated with cardiovascular risk. CD16+ monocytes are pro-inflammatory and contribute to micro-inflammation. Lipoxin A4 (LXA4) and resolvin E1 (RvE1) are lipid mediators which promote the resolution phase of inflammation. Our hypothesis is that LXA4 and RvE1 may be a role in reducing inflammatory monocytes and cytokines in blood from HD patients. These agents may act through inhibition of the NF-κB signalling pathway. This study suggests that LXA4 and RvE1 have therapeutic potential in the management of inflammation in the haemodialysis population.

Funding: Government Support - Non-U.S.

Results: HD patients have higher levels of CD16+ monocytes (p<0.01) and higher plasma levels of TNF-a (p<0.001) and IL-6 (p<0.05) than healthy controls. Treatment of HD blood samples with LXA4 or RvE1 reduces CD16+ monocytes (p<0.05), while treatment of isolated monocytes with either agent reduces the production of TNF-a (p<0.01) and IL-6 (p<0.05). THP-1 monocytes cultured in uraemic plasma adopt an inflammatory phenotype with increased production of TNF-a compared to cells cultured in control plasma (p<0.01) that is attenuated by treatment with LXA4 and RvE1 (p<0.05). Treatment of stimulated THP-1 monocytes with LXA4 (p<0.001) or RvE1 (p<0.01) also leads to a reduction in p-IκB-alpha.

Conclusions: HD patients have evidence of inflammation and monocyte activation. Biologicals may therefore be useful in the treatment of inflammatory monocytes and cytokines in blood from HD patients. These agents may act through inhibition of the NF-κB signalling pathway. This study suggests that LXA4 and RvE1 have therapeutic potential in the management of inflammation in the haemodialysis population.

Funding: Government Support - Non-U.S.

SA-PO395 Upper Stream Reactions of Oxidative Stress in Hemodialysis Patients Aki Hiraya, Atsushi Ueda, Sohji Nagase, Hirofumi Matsui, Kazumasa Aoyama, Shigeru Owada, Asao Clinic, Kawasaki, Japan; 1Nephrology, Tsukuba Hospital, Tsukuba, Japan; 2Tsuchuba Univ Hospital; 3Hitachi Medical Education and Research Center, Hitachi, Japan; 4Nagase Naika Clinic, Moriya, Japan; 5Faculty of Medicine, Univ of Tsukuba, Tsukuba, Japan; 6Asao Clinic, Kawasaki, Japan.

Background: Upper stream reactions against oxidative stress that evoke following cellular responses still remain unclear. This study aimed to reveal the dynamics of multiple reactive oxygen and nitrogen species (ROS/RNS) which act as stimulators of oxidative responses in hemodialysis (HD) patients.

Methods: We investigated the interactions between inflammatory biomarkers (IL-6 and TNF-α) and IGF-1 as predictors of death over a 4 years of follow-up (median - 47 months, interquartile range - 17.5-7.5 months) in 96 prevalent HD patients (35% women, median age of 64.9±11.6 years).

Results: A significant interaction effect of low IGF-1 (defined as a level lower than median) and high IL-6 (defined as a level higher than median) on all-cause and cardiovascular mortality was found. The product termed IGF-1 X IL-6 were 3.06, with a 95% confidence interval (1.29-16.32) and 16.96, 95% CI 1.71 to 168.4, respectively. Across the four IGF-1 IL-6 categories, the group with low IGF-1 and high IL-6 exhibited the worse outcome in both all-cause and cardiovascular mortality (HR for the product termed IGF-1 X IL-6 were 3.06, with a 95% confidence interval (1.29-16.32) and 16.96, 95% CI 1.71 to 168.4, respectively)

Conclusions: The role of IGF-1 and IL-6 in the prediction of all-cause and cardiovascular mortality was found. The product of IGF-1 X IL-6 may be a more suitable outcome measure than either IGF-1 or IL-6 individually.
Fluid Retention in Hemodialysis (HD) Patients Is Associated with Endothelial Dysfunction through an Increased Pentranin 3 (PTX3) and ROS Production by Neutrophils

**Background:** Fluid retention in HD patients is associated with increased cardiovascular morbidity and mortality. PTX3, a marker of inflammatory responses, may be involved in endothelial dysfunction and is a predictor of mortality in HD patients. The aim of the study was to evaluate in vivo the association between fluid retention, pulmonary artery systolic pressure (PASP), endothelial dysfunction (flow-mediated dilation, FMD), PTX3 and ROS production in HD patients.

**Methods:** Sixty uremic patients (mean age 62.5 years; mean dialytic age 44.3 months) were placed on stable HD treatment with synthetic membranes and 20 healthy subjects were enrolled. Neutrophils activation (CD62L-) and PTX3 protein expression were evaluated by flow cytometry and ELISA. Intracellular ROS generation in neutrophils was measured by 2′,7′-Dehydrodihydrofluorescein. PASP and FMD of brachial artery were assessed non-invasively, using echocardiography and high-resolution ultrasound. The arterial stiffness was evaluated using carotid-ankle vascular index (CAVI).

**Results:** HD increased FMD from 4.23±3.18% (n=7:5±2.1%; p<0.01) to 7.03±0.73% (p<0.001). These changes returned to baseline by 24h (5.59±0.4%). FMD, observed pre- and post-HD, were significantly (p=0.002) and inversely correlated with PASP values (pre-HD: 27.7±2.4mmHg; post-HD: 18.1±1.6mmHg). The change in FMD and PASP were associated with a significant increase (p=0.0001) in neutrophil activation, intracellular and circulating PTX3 expression and ROS generation. Pre/post-HD (D) FMD was inversely correlated with CAVI (p<0.002) and P and PTX serum levels (p<0.02). PTX3, P serum levels and PASP were independent predictors of altered FMD.

**Conclusions:** In this single-centre case-control study, fluid retention in HD patients may contribute to endothelial dysfunction and arterial stiffness by increasing PTX3 and ROS production.

Incidence of Eosinophilia in a Hemodialysis Population: Longitudinal and Case Control Studies

**Background:** Eosinophilia associated with dialysis reaction was frequently reported in the 1980s which decreased with the use of more biocompatible membranes. Recent observations at a local level suggest a possible recurrence of eosinophilia amongst hemodialysis patients without apparent relationship to dialysis sessions.

**Methods:** Twenty-four patients (aged 31–81, 46% male) from a population of 510 were identified and paired with controls matched for age, gender and dialysis satellite facility. Comorbidity, dialysis and medication data were collected. A sample of patients on hemodialysis 5 years ago was examined whether fat mass or lean mass are associated with serum PTH.

**Results:** In multiple regression analyses after adjustment for age, gender, and HD vintage, HIV and hepatitis C status) were developed to study the relationship between monocyte-lymphocyte ratio (MLR), neutrophil-monocyte ratio (NMR) and NLR for toll-like receptors (TLR) with adverse outcomes. We investigated the predictive value of monocyte-lymphocyte ratio (NMR), neutrophil-monocyte ratio (NLR) and NLR for all-cause mortality and if death due to infectious causes is preceded by changes in MLR, NMR, and NLR.

**Conclusions:** We demonstrated, for the first time, that serum intact PTH correlated significantly, positively with body size in hemodialysis patients. Further, PTH was significantly, independently associated with fat mass and lean mass.

**SA-PO400**

Changes in Neutrophil-Monocyte Ratio Allow Prediction of Death from Infectious Causes in Incident Hemodialysis Patients: Results from a Retrospective Database Analysis

**Background:** Chronic systemic inflammation determines survival and disease progression in hemodialysis (HD) patients. Neutrophil to lymphocyte ratio (NLR) was previously proposed as predictor of all-cause mortality comparing well to established inflammatory markers. Immune dysfunction may be associated with decreased functional toll-like receptors (TLR) with adverse outcomes. We investigated the predictive value of monocyte-lymphocyte ratio (NMR), neutrophil-monocyte ratio (NLR) and NLR for all-cause mortality and if death due to infectious causes is preceded by changes in MLR, NMR, and NLR.

**Methods:** Relevant laboratory markers and white blood cell count were collected monthly. Fluid retention was measured by body size in hemodialysis patients, in whom PTH is abnormally regulated. We further examined whether fat mass or lean mass are associated with serum PTH.

**Results:** Changes in Neutrophil-Monocyte Ratio Allow Prediction of Death from Infectious Causes in Incident Hemodialysis Patients: Results from a Retrospective Database Analysis

**Conclusions:** In this single-centre case-control study, hemodialysis patients with eosinophil count greater than 1 x 10^9/litre during a 3 month period were identified and paired with controls matched for age, gender and dialysis satellite facility. Comorbidity, dialysis and medication data were collected. A sample of patients on hemodialysis 5 years ago was analysed to provide historical prevalence. Statistical analysis was performed using the Fisher exact test for categorical variables and t-test for continuous data.

**Results:** Twenty-four patients (aged 31–81, 46% male) from a population of 510 were identified as having eosinophilia with a mean level of 2.2 x 10^9/ (range 1.1-7.5 x 10^9/). Between cases and controls there were no differences in comorbidities, dialysis vintage or most medications. There was a significantly higher frequency of angiotensin converting enzyme inhibitors (ACEi) use in patients with eosinophilia (10/24 vs 24/24, p=0.049). There were no patients with an allergic syndrome related to dialysis sessions, and generally, intradialytic symptoms were more common in cases either. One patient did develop a dialysis-related febrile reaction 3 months after the onset of eosinophilia resolving with a change of dialysis membrane. A historical sample of 200 dialysis patients identified eosinophilia in only 3, demonstrating a significant increase in prevalence over time (1.5 vs 4.7%, p=0.049).

**Conclusions:** The prevalence of eosinophilia appears to have increased within this dialysis population over the last 5 years. No clear cause was identified in this study. More frequent use of ACEi may support a medication hypothesis for some patients. The development of intradialytic symptoms in one patient suggests components of the dialysis circuit as a possible cause so an empirical change of membrane is planned.

**SA-PO399**

Parathyroid Hormone (PTH) in Hemodialysis Patients Is Significantly, Positively Affected by Body Size: Both by Fat Mass and Lean Mass, Independently

**Background:** A significant positive relationship between PTH and body size has been reported in the general population (Eur J Endocrinol 2004) and in patients with primary hyperparathyroidism (J Clin Endocrinol Metab 2005). We hypothesize if PTH is affected by body size in hemodialysis patients, in whom PTH is abnormally regulated. We further examined whether fat mass or lean mass are associated with serum PTH.

**Methods:** Five hundred hemodialysis patients (age: 60.2±12.2 yr; median hemodialysis duration: 59.6 mo.; 343 males and 247 females; diabetics: 27.4%). We further examined whether fat mass or lean mass are associated with serum PTH.

**Results:** Intact PTH correlated significantly, positively with body weight and body mass index (p<0.001). Intact PTH correlated significantly and positively with fat mass and lean mass in males (p<0.01) and tended to correlate positively with fat mass and lean mass in females (p=0.1). In multiple regression analyses after adjustment for age, gender, hemodialysis duration, calcium, phosphate, vitamin D use and phosphate binder use, intact PTH was associated significantly with body weight, body mass index, fat mass and lean mass. Further, intact PTH was associated significantly and independently with both fat mass and lean mass after adjustment (R²=0.206, p<0.0001).

**Conclusions:** We demonstrated, for the first time, that serum intact PTH correlated significantly, positively with body size in hemodialysis patients. Further, PTH was significantly, independently associated with fat mass and lean mass.

**SA-PO397**

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

Underline represents presenting author/disclosure.

**References:**

2. Parathyroid Hormone (PTH) in Hemodialysis Patients Is Significantly, Positively Affected by Body Size: Both by Fat Mass and Lean Mass, Independently Eiji Ishimura,1 Senji Okuno,1 Akihiro Tsuda,1 Akinobu Ochi,1 Osaka City Univ Graduate School of Medicine; 2Shirasagi Hospital.

1. Simona Simone,1 Maria Pia dell'Oglio,1 Marco Ciccone,2 Roberto Corciuolo,1 Giuseppe Castellano,1 Cosima Balestra,1 G. Grandaliovà,1 Loreto Gesualdo,1 G. Pertosa. 1 DETO, Nephrology, Dialysis and Transplantation Unit; 2DETO, Cardiology Unit, Bari; 3Dept of Medical and Surgical Sciences, Nephrology, Dialysis and Transplantation Unit, Foggia, Italy.
SA-PO401
Importance of Food Labeling: Bromatological Study for Determination of Phosphorus and Potassium in Food Consumed by Hemodialysis Patients Camila Machado de Barros,1 Isabela Santos Areias,1 Bárbara Margareth Menardi Biavo,1 Edeli Simioni Abreu,1 Jacqueline Santos,1 Elzo Ribeiro Júnior,1 Carmen B. Tzanno-martins,1 Grupo CHR,2 Universidade Presbiteriana Mackenzie.2
Background: Adding nutritional information on food labels about these minerals becomes increasingly urgent, considering the growing population of patients on HD. Conduct chemical analyses of some processed foods in order to determine their amount of phosphorus and potassium, since this information does not appear on their label. Objective: Conduct chemical analyzes of some processed foods in order to determine their amount of phosphorus and potassium, since this information does not appear on their label.

Methods: The study was based on secondary data on food consumption by HD patients, from three hemodialysis clinics in São Paulo, Brazil. Laboratory tests were performed in the Bromatology Laboratory at the Mackenzie University. Each food was analyzed separately and twice. For the potassium measurement, it was used atomic absorption spectrophotometer; and for phosphorus, it was used phosphate by titration.

Results: We analyzed thirteen foods, Brazilian human ration; juice powder; milk pudding; hamburger; chicken nuggets; bis (a brazilian chocolate bar), instant soup, four cheese industrialized lasagna, industrialized bolognese lasagna; dark coca (a brazilian coconut candy); white coca; bread; goiabada (a brazilian guava candy). Regarding phosphorus concentration of per serving, the higher value foods were ready lasagna (39.2454 mg and 44.7886 mg), chicken nuggets (21.1259 mg) and milk pudding (19.2352 mg). When potassium concentration was analyzed, values shown were very low, even for patients undergoing hemodialysis, with recommended intake value of approximately 3900 mg daily.

Conclusions: Nutritional information with phosphorus content proved valuable and decisive in the choice of food for these patients. According to the foods surveyed, it was for patients undergoing hemodialysis, with recommended intake value of approximately 3900 mg daily.

SA-PO402
Nutrition Education as a Tool for Knowledge about Potassium in Hemodialysis Patients Camila Machado de Barros,1 Amanda Maifei,1 Fabiana Valverde,2 Luiza Saccoman,2 Edeli Simioni Abreu,2 Rosana Farah,2 Bárbara Margareth Menardi Biavo,1 Jacqueline Santos,1 Elzo Ribeiro Júnior,1 Carmen B. Tzanno-martins,1 Grupo CHR,2 Universidade Presbiteriana Mackenzie.2
Background: Potassium levels are generally high (hyperkalemia) in patients with chronic kidney disease (CKD) on hemodialysis (HD). Therefore it is important to control food with high potassium content.

Objective: To evaluate the effects of a nutrition educational program regarding potassium in food on the knowledge of a patient with hyperkalemia in HD treatment.

Methods: This was a longitudinal study with 243 patients with CKD who perform dialysis in three nephrology clinics, located in São Paulo, being 36% of them with chronic kidney disease. We evaluated the knowledge of a patient with hyperkalemia. In a given dialysis session, we have applied the group dynamics, “Potassium minefield”. The game consisted of a board with 60 squares in which there were food illustrations distributed randomly. Some of these foods were “bombs”, i.e. they contained high concentration of potassium and should be avoided. Other foods were low in potassium and are recommended to be consumed more often. Patients were asked to choose a food. Then we asked them if it was a “bomb” or not. After the answer, the square was turned. On the back of each card, the patient received a multiple choice question before and after the intervention.

Results: was observed that the knowledge on foods with high potassium content increased in the three units after completion of the nutritional dynamics. The percentage of correct answers increased from 63.3% (± 13.9) before the intervention to 73.5% (± 16.3) after the intervention.

Conclusions: These values showed a good level of knowledge about the consequences of hyperkalemia and its treatment, as well as the better understanding of the nutritional recommendations regarding diet.

SA-PO403
Effect of Citrate on the Proteome of the Secondary Protein Layer of the Dialysis Membrane Jaronim Eiselt, Jan Mares, Jiri Moravec, Lukas Kielberger. Internal Dept 1, Charité Univ.

Background: A secondary protein layer formed on the dialysis membrane affects the fluid permeability and fluid exchange. Those processes are influenced by the adsorption of plasma proteins and other macromolecules from the blood. Therefore it is important to control the composition of this secondary layer.

Methods: To clarify the immunnoloregulation of double filtration plasmapheresis in Maintenance Hemodialysis Patients with Chronic Hepatitis C Andreas H. Bock, Beatrice Paul. Nephrology Div, Kantonsspital Aarau, Aarau, Switzerland.

Background: Hemodialfiltration (HDF) removes high molecular weight solutes better than hemodialysis. This study compared three state-of-the-art high flux dialyzers in HDF maintenance hemodialysis (HD) patients affected by chronic hepatitis (18.6 kD) and phosphate. Improved 2M elimination is expected to delay 2M amyloidosis, and lowering leptin levels should increase appetite, which may help to improve nutritional status.

Results: During three consecutive weeks, each of 29 stable hemodialysis patients underwent a twice-weekly HDF session. Measurements were taken at hD (60/240 minutes) and cD, as well as 30 minutes after the end (270). Bloodsidea were performed using pre- and post-dialyzer blood samples at 60 and 240. Equilibrated removal ratios (eRR) were calculated from 0 and 270 samples. Dialysis obtained using a 1/2 split dialyzer collector was assayed for 2M, phosphate and albumin.

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>hD</th>
<th>cD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrate</td>
<td>201±89</td>
<td>204±84</td>
<td>0.033</td>
</tr>
<tr>
<td>K</td>
<td>89±19</td>
<td>103±27</td>
<td>0.008</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.9±0.5</td>
<td>4.9±0.5</td>
<td>0.96</td>
</tr>
<tr>
<td>Leptin</td>
<td>21.1±3.4</td>
<td>21.5±3.4</td>
<td>0.58</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.75±2.1</td>
<td>2.90±2.1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

The decrease of plasma leptin paralleled the height of baseline leptin (r = 0.62). eRR, clearance and dialysate removal for phosphate was high and similar for all three dialyzers. Conclusions: of HDF with modern high flux dialyzers removes significant amounts of phosphate substantially more than standard dialysis devices, all of which should be beneficial at longterm. The CorDiax dialyzer in these real-life conditions performed better than the two other dialyzers.

Funding: Pharmaceutical Company Support - Fresenius

SA-PO405
A Study of the Immunoregulation of Double Filtration Plasmapheresis in Maintenance Hemodialysis Patients with Chronic Hepatitis C Hao Henghe, Chunsun Dai, Junwei Yang. 2nd Affiliated Hospital, Nanjing Medical Univ, Nanjing, China.

Background: To clarify the immunoregulation of double filtration plasmapheresis (DFPP) in maintenance hemodialysis (MHD) patients with chronic hepatitis C (CHC).

Methods: DFPP were performed in 20 MHD patients with CHC (HCV-antibody positive and serum HCV-RNA >500 IU/mL more than 6 months). The serum titer of HCV-RNA was monitored and peripheral blood mononuclear cell (PBMC) was analyzed by flow cytometry at the time of hour 0, hour 3, day 1, day 3, day 7 and day 28 during the DFPP.

Results: Compared to MHD patients without CHC, the frequencies of innate immune cells were similar in MHD patients with CHC, while the ratio of Th1 to Th2 was elevated and the frequencies of Th17 cells and Treg cells were higher in MHD patients with CHC. Serum HCV particles could be removed partially by DFPP. The titers of serum HCV could remain in a lower level one month after the treatment. There were no significant changes of monocytes, NK cells, Th1, Th2 and Th1/Th2 in PBMC after DFPP in MHD patients with CHC. Single DFPP could reduce the frequency of Th17 cells in PBMC from 7 days after the therapy in MHD patients with CHC. Single DFPP could reduce the frequency of Treg cells in PBMC from 7 days after the therapy in MHD patients with CHC. Conclusions: DFPP could partially remove the serum HCV particles mechanically. The titer of HCV-RNA could remain in a lower level at least for one month probably due to the redistribution of the immunocytes in circulation.

Funding: Government Support - Non-U.S.

SA-PO404

Background: Hemodialfiltration (HDF) removes high molecular weight solutes better than hemodialysis. This study compared three state-of-the-art high flux dialyzers in HDF maintenance hemodialysis (HD) patients affected by chronic hepatitis (18.6 kD) and phosphate. Improved 2M elimination is expected to delay 2M amyloidosis, and lowering leptin levels should increase appetite, which may help to improve nutritional status.

Methods: During three consecutive weeks, each of 29 stable hemodialysis patients underwent a twice-weekly HDF session. Measurements were taken at hD (60/240 minutes) and cD, as well as 30 minutes after the end (270). Bloodsidea were performed using pre- and post-dialyzer blood samples at 60 and 240. Equilibrated removal ratios (eRR) were calculated from 0 and 270 samples. Dialysis obtained using a 1/2 split dialyzer collector was assayed for 2M, phosphate and albumin.

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>hD</th>
<th>cD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrate</td>
<td>201±89</td>
<td>204±84</td>
<td>0.033</td>
</tr>
<tr>
<td>K</td>
<td>89±19</td>
<td>103±27</td>
<td>0.008</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.9±0.5</td>
<td>4.9±0.5</td>
<td>0.96</td>
</tr>
<tr>
<td>Leptin</td>
<td>21.1±3.4</td>
<td>21.5±3.4</td>
<td>0.58</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.75±2.1</td>
<td>2.90±2.1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

The decrease of plasma leptin paralleled the height of baseline leptin (r = 0.62). eRR, clearance and dialysate removal for phosphate was high and similar for all three dialyzers.

Conclusions: of HDF with modern high flux dialyzers removes significant amounts of phosphate substantially more than standard dialysis devices, all of which should be beneficial at longterm. The CorDiax dialyzer in these real-life conditions performed better than the two other dialyzers.

Funding: Pharmaceutical Company Support - Fresenius

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

Underline represents presenting author/disclosure.
SA-PO406

Onodera’s Prognostic Nutritional Index May Be a Significant Predictor of Mortality in Hemodialysis Patients

Kiryong Park,1 Sangeon Gwooo,2 Ye Na Kim,1 Ho Sik Shin,2 Yeon Soon Jung,2 Hark Rim.2 1Internal Medicine, Changwon Fatima Hospital, Changwon; 2Internal Medicine, Kosin Univ College of Medicine.

Background: No standard method for assessing the nutritional status in HD patients exists. Onodera’s Prognostic Nutritional Index (OPNI) is a method that considers serum albumin level and total lymphocyte count. This simple method may involve common measures and can be applied rapidly in a large number of patients. Validation of OPNI has been performed for patients with end-stage liver disease, active tuberculosis, and gastrointestinal malignancies.

Methods: We examined the OPNI scores of 140 maintenance HD patients (59.8 ± 12.9 years; 64 men and 76 women) and followed these patients for 140 months. The OPNI is calculated based on the serum albumin level and total lymphocyte count and uses the following equation: OPNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (mL).

Results: The average OPNI value was 43.8 ± 6.5, and the values were negatively correlated with age. A total of 18 patients died during the 120-month follow-up period. OPNI values were normally distributed. Life table analysis revealed that patients with an OPNI < 40 (n = 31) had a significantly lower survival rate than those with an OPNI ≥ 40 (n = 109) (Wilcoxon test, P = 0.044).

Conclusions: These results suggest that OPNI is a significant predictor of mortality in HD patients. The simple OPNI method is a clinically useful marker for the assessment of nutritional status in Korean HD patients.

SA-PO407

Poor Nutritional Status Is Associated with Increased Calcifications and Higher Incidence of Hospitalization in Chronic Hemodialysis Patients

Paolo Lentini,1,2 Luca Zanolii,3 Stefania Rastelli,3 Massimo de Cal,1 Graziella Berlingò,1 Anna Bassal,4 Andrea Contestabile,1 Valentina Pellanda,1 Roberto Dell’Aquila.1 1Nephrology, San Bassiano Hospital, Bassano del Grappa, Italy; 2Internal Medicine, Univ of Catania, Catania, Italy.

Background: Calcifications are increased in chronic hemodialysis and associated with increased cardiovascular events. The nutritional status may influence, via the metabolism Ca/P, the outcome of the patients. We aimed to study the relations between the nutritional status, calcification score and hospitalization in chronic hemodialysed subjects during a follow-up of 1 year.

Methods: Body composition was evaluated with Bioimpedance spectroscopy technique (Fresenius BCM) and hospitalization was collected during follow-up; abdominal aortic calcifications (Kauppila score) were evaluated by lateral lumbar radiographs at baseline and after 1 year.

Results: 36 hemodialysed subjects (age 64±15 yrs; 50% males; hemoglobin 11.3±0.7 mg/dL; Ki/Vo ø Daugirdas 1.50±0.29) were enrolled.20 subjects (56%) were hospitalized.20 subjects (56%) were hospitalized. The average OPNI value was 43.8 ± 6.5, and the values were negatively correlated with age. A total of 18 patients died during the 120-month follow-up period. OPNI values were normally distributed. Life table analysis revealed that patients with an OPNI < 40 (n = 31) had a significantly lower survival rate than those with an OPNI ≥ 40 (n = 109) (Wilcoxon test, P = 0.044).

Conclusions: These results suggest that OPNI is a significant predictor of mortality in HD patients. The simple OPNI method is a clinically useful marker for the assessment of nutritional status in Korean HD patients.

SA-PO408

Tryptophan Metabolism in Hemodialysis Patients

Rakesh Malhotra,1 Vanja Perc,2 WeiFang Zhang,2 Garry J. Handelman,4 Mary Carter,4 Stephan Thijsse,4 Len A. Lissya,3 Fredric O. Finkelstein,3 Mark L. Unruh,4 Nathan W. Levin,4 Peter Kotanko,4 1Univ Medical Center Ljubljana; 2Univ of Massachusetts Lowell; 3Renal Research Institute; 4Yale Univ School of Medicine; 4Univ of New Mexico School of Medicine.

Background: Tryptophan (TRP) levels and augmented concentrations of its metabolites have been shown to be significantly lower in animal models of renal insufficiency. We sought to compare the levels of TRP and its metabolites between hemodialysis (HD) patients and healthy subjects and to examine the extent to which TRP metabolites are associated with inflammation in HD patients.

Methods: Venous blood samples were drawn in healthy subjects and HD patients. TRP, para-cresol sulfate (PCS) and kynurenine (KYN) metabolites were measured by reverse-phase high-performance liquid chromatography (HPLC), with appropriate detection wavelength for each compound. C-reactive protein (CRP) was measured with an immunoturbidometric technique. We used Spearman rank test for correlational analysis.

Results: We studied 30 HD patients (70% male; mean age 58.8±13.3 yrs) and 10 healthy control subjects (60% male; mean age 43.9±12.4 yrs). KYN and KYN/TRP (6.0±2.5 uMol/L vs. 2.1±0.5 uMol/L; p=0.002 and 0.17±0.06 vs. 0.03±0.01; P<0.0002, respectively) were significantly higher and TRP levels were significantly lower (35.3±18.1 uMol/L vs. 67.9±18.8 uMol/L; P<0.0001) in the HD patients than those in the controls. KYN/TRP ratio and CRP levels were positively correlated in HD patients (r=+0.14; P=0.05).

Conclusions: Low TRP and high metabolite levels were observed in HD patients, indicating increased TRP catabolism, possibly related to immune activation/inflammation. Further studies exploring the biological and functional consequences of increased TRP catabolism in HD patients are warranted.
Effect of Kibow Probiotic Renadyl™ on sCD30 Levels in Hemodialysis Patients

 Patients Subodh J. Saggi,¹ Eli A. Friedman,¹ Lorraine L.A. Thomas,¹ Natarajan Ranganathan,² Pari Ranganathan,³ Gary R. Briefel,¹ Mary C. Mallappallil,¹ of protein (CRP) and total indoxyl glucuronide levels. In order to link the reduction to markers of inflammation, we looked at one biomarker of T cell activation, sCD30. This marker has previously been shown to be elevated in patients with CKD and lower levels of sCD30 have been associated with better prognosis in kidney transplant patients.

 Methods: We conducted a prospective, double blind crossover trial with placebo and Renadyl™ for 8 weeks, followed by an 8-week washout period. Patient’s serum was taken at 3 time points (baseline, after probiotics, and after placebo) and sCD30 levels were measured by ELISA (Bender MedSystems). Patient adherence was assessed by pill count and stool culture to verify probiotic growth during study and absence during placebo period. Data were analyzed with ANOVA for a crossover design with a mixed model methodology in SAS to detect differences in least square means in treatment, period and sequence effect.

 Results: Mean sCD30 levels were 94.74/mg/mL and decreased to 89.84/mg/mL with probiotic administration. This difference is not statistically significant (p=0.49).

 Conclusions: Our results show that sCD30 levels are not affected with the administration of probiotics, which suggests that patients do not become immunocompromised by this treatment. Larger population studies or longer term studies might be needed to give a better insight into the role of sCD30 modulation by Probiotic Renadyl™.

 Funding: Pharmaceutical Company Support - Kibow Biotech, Inc

SA-PO410

Relationship between the Frequency of Monitoring Laboratory Parameters and the Outcome in Maintenance Hemodialysis Patients

 Patients: 310 MHD patients in our hemodialysis center were included with HD vintage from 13-216 months(58.78±39.68 months). We retrospectively analysed the status of hemoglobin,serum calcium,sodium,phosphorus,serum albumin,iPTH and the frequency of monitoring the status above from July 2010 to 2011.According to the KDOQI guidelines for CKD-anemia and the KDIGO guidelines for CKD-MBD,we calculated the qualified rate of the statuses above each patient. The relationship between the frequency and the status was analysed.

 Results: Patients were divided into 3 groups according to the frequency of monitoring(A group,frequency<3/year,B group,4-5/year,C group,frequency>6/year). There was no significant difference among the 3 groups in age,gender,and the course of HD.The B group was significantly lower in B than in B and C group(A vs B group,104.89±19.40g/L vs 111.06±15.37g/L,p<0.05).A group vs C group,104.89±19.40g/L vs 112.16±12.7g/L(p<0.05),and was not significantly different between B and C group(111.06±15.37g/L vs 112.16±12.7g/L,p=0.793). The same results were also observed in the qualified rate of quality of life A group 18.06±30.00% vs 24.39±22.00%,p=0.01 vs B group vs C group,18.06±30.00% vs 27.39±22.23%,p=0.01).serum calcium (A vs B group 40.20%±41.42% vs 43.86%±(31.46%,p=0.05,A vs C group 40.20%±41.42% vs 50.58%±32.37%,p=0.01,A group vs B group,48.63%±45.48% vs 50.81%±38.64%,p=0.03).serum phosphorus (A group vs B group,48.63%±45.48% vs 52.15%±36.33%,p=0.05).

 Conclusions: The frequency of monitoring laboratory parameters the KDOQI and KDIGO guidelines recommended was beneficial to MHD patients.Despite of the difficulties,the MHD patients should take clinical Lab test at least 4 times per year for better prognosis.

SA-PO413

Single Pulse-String Suture versus Double Pulse-String Sutures: Complications in Shorter Break-In Periods CAPD Patients

 Patients: We reviewed surgical catheter placement in our unit from January 2012 to March 2013. 100 patients without history of abdominal operation were enrolled and followed up at least two months. We defined break-in periods less than 14 days as shorter break-in periods. The single pulse string suture group comprised 27 patients who were using one pulse suture suture to fix peritoneum around the PD catheter, 44 patients with two string sutures were enrolled in double string suture groups, and 29 patients with two string sutures and break-in periods of 3-7 days,2 weeks as control group.

 Results: Time to initiation CAPD was shorter in single pulse string suture group(9.77±2.27 days)and double string sutures group(8.60±3.06 days) than control group(25.00±9.96 days)(P<0.001).The hospitalization after implantation was extended in single string string than single string suture group and double string sutures group(28.06±10.43, 21.26±7.11, 18.00±6.99)(P<0.01).single double pulse suture string group(7.41%), double string suture group(6.82%) and control group(3.43%) observed catheter related complications including migration, peritonitis and tunnel infection. Catheter related complications were restricted to men or women alone or to non-diabetic or diabetic patients separately.

 Conclusions: Shorter break-in periods of CAPD with single pulse string suture technique in Tenckhoff catheter placement did not increase catheter related complications in our patients. The hospitalization was significantly short when PD was initiated <14 days. We suggest that single pulse string suture and early initiation PD are applicable.
Future studies with long time follow-up and larger patient numbers are needed to validate the role of shorter break-in period and single string suture in PD practice.

SA-PO414
Non-Surgical Treatment to Reduce Periodontitis Associated Inflammation in ESRD Wilner Samson,1 George Fares,2 Effie Ioannidou.1 1Medicine, Univ of Connecticut School of Medicine, Farmington, CT; 2Medicine, Bay State Medical Center, Springfield, MA.

Background: Periodontitis (PDT) is a polymicrobial infectious disease affecting the hard and soft tissues that leads to tooth loss. PDT is prevalent in ESRD, and may contribute to systemic inflammation associated mortality. In a randomized clinical trial, we assessed clinical and systemic response to non-surgical periodontal treatment in ESRD subjects with PDT.

Methods: 12 ESRD subjects were recruited using the following criteria: presence of chronic PDT, > 15 teeth, no periodontal treatment within the past 6 months, and no use of systemic antibiotics within 30 days. All subjects received a full-mouth periodontal exam including clinical attachment levels (CAL), pocket depths (PD), bleeding on probing (BOP) and plaque scores (PS). Chronic PDT was defined by the presence of minimum of one site with 5mm or greater PD and minimum of 2 sites with 6mm or greater CAL. ESRD patients with PDT were randomized to two groups by a computer generated randomization list. The test group received oral hygiene instructions and scaling and root planning, whereas the control group received oral hygiene instructions and full mouth supragingival debridement. Subjects were recalled at 2 months for clinical periodontal measures and systemic inflammatory assessment (serum CRP).

Results: Baseline periodontal parameters and systemic inflammatory markers were compared between the two groups, no difference was found. The serum CRP levels decreased for the test group after treatment, however increased for the control group showing a trend to significance (p=0.1). When comparing the difference between pre- and post-therapy measures, CAL in the test group decreased but increased for the control group (p=0.02, p=0.06). BS was reduced in the test group, but in the control group PD showed increased trend (p=0.07). Reduction in serum CRP levels was significantly correlated with the improvement in PD, CAL, BOP and PS.

Conclusions: Non-surgical treatment for PDT in ESRD patients may improve gum disease as well as systemic inflammation, a marker of mortality.

Funding: Other NIH Support - NIH/ NIDCR K23 DE018689

SA-PO415
Abnormal Gastrointestinal Function in Chronic Kidney Disease: Role of Uraemia, Peritoneal Dialysis and Volume Status. Laura E.A. Harrison,1 Caroline Louise Hoad,2 Luca Marciani,2 Penny Anne Gowland,2 Chris W. McIntyre.1,3 1Renal Medicine, Royal Derby Hospital, United Kingdom; 2School of Physics and Astronomy, Univ of Nottingham, United Kingdom; 3Div of Medical Sciences & Graduate Entry Medicine, Univ of Nottingham, Derby, United Kingdom.

Background: Gastrointestinal (GI) dysfunction is common in chronic kidney disease (CKD), potentially driven by uremia, volume status and dialysis modality. We assessed postprandial changes in the upper GI tract in a cross-sectional CKD study utilising Magnetic Resonance Imaging (MRI) techniques.

Methods: Participants underwent serial T2-weighted MRI fasting and after a 331 kcal meal to assess small bowel water content (SBWC), a measure of free intraluminal water reflecting mucosal net intestinal secretion/absorption. 24 participants (9 Peritoneal Dialysis (PD), 6 CKD, 9 non-CKD) were recruited.

Results: Fasting SBWC was lowest in PD patients, less than half that of non-CKD, (PD 34 mL [IQR 10-63]; CKD 49 mL [IQR 22-138]; non-CKD 96 mL [IQR 50-157], p=0.04). Postprandially, SBWC fell to a nadir by T90 in all groups (PD 12mL, CKD 7 mL, non-CKD 9 mL, p<0.01). PD and CKD patients had a delayed increase in SBWC, in contrast to non-CKD which returned to fasting levels by T35. PD patients reported more postprandial abdominal pain and distension. AUC for total SBWC was significantly different between PD and non-CKD (PD 6772 mL/min vs non-CKD 16,430mL/min, p=0.001), suggesting reduced GI secretion or increased absorption. In PD patients, fasting SBWC was inversely related to NT-proBNP (r=-0.821, p=0.02), a marker of volume overload.

Conclusions: The altered GI physiological response to food in CKD patients is more marked in individuals receiving PD, and appears to be influenced by dialysis modality, in addition to uremia. Volume overload and bowel congestion may be crucial factors in this process and potential future therapeutic targets.

Funding: Pharmaceutical Company Support - Renal Discoveries Extramural Grant awarded by Baxter Healthcare

SA-PO416
Development and Validation of Novel Equations for Estimating Lean Body Mass and Evaluation of Their Prognostic Values for Mortality in Peritoneal Dialysis Patients Jie Dong,1 Rong Xu.1 1Renal Div, Institute of Nephrology, Peking Univ First Hospital, Beijing, China.

Background: Malnutrition is a strong predictor of mortality for dialysis patients. Early diagnosis and intervention for malnutrition is based on a simple surrogate marker in clinical practice. Lean body mass is a good marker for somatic protein store but is not easily determined by the golden standard. Our study is to develop and validate estimating equations for lean body mass (LBMI) in patients on peritoneal dialysis (PD), and then evaluate their prognostic value in a large prospective cohort.

Methods: Two equations for estimating LBMI based on midarm muscle circumference (MAMC) and hand grip strength (HGS) respectively were developed in 106 and validated in 107 PD patients with dual-energy x-ray absorptiometry (DEXA) as referenced gold method, as compared to LBMI estimated from creatinine kinetic (CKF) and anthropometry (A) method. The prognostic values of LBMI estimated from above four equations were further explored for all-cause mortality in 889 incident PD patients.

Results: Two new equations based on MAMC or HGS combined with gender, height and weight duration were developed. Bias of two new equations with LBMI-DX was smaller than those of LBMI-CKF and LBMI-A, with a median difference of 0.9 kg and -0.3kg between measured and estimated LBMI by LBMI-MAMC and LBMI-HGS respectively, as compared to 3.0kg with LBMI-CKF equation and -5.0kg with LBMI-A equation. Better precision and accuracy were achieved with LBMI-MAMC and LBMI-HGS equation reflected by smaller interquartile range of the difference and percentage of estimates that were 20% of measured LBMI. The prognostic value of LBMI-MAMC and LBMI-HGS was better than LBMI-CKF and LBMI-A with the higher Chi-square by Omnibus tests for models of all-cause mortality.

Conclusions: LBMI estimated from MAMC and HGS were verified to be more precise methods and reliable predictor of total mortality for PD population.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author/disclosure.
SA-PO418
Life in the Fishtank: AVF Monitoring for Dummies

David H. King,1 Asmaa Y.M. Al-Chididi,1 Michael Graeme Taylor,2 Mo Al-qasili,3 Sumith C. Abeygunasekara,1 Anthony Chan,1 Eric S. Chemla,1 William D. Paulson,1 Abdelgallil Abdellahm Ali.1 1Broomfield Hospital, Chelmsford, Essex, United Kingdom; 2Div of Imaging Sciences & Medical Engineering, Kings College London, London, United Kingdom; 3Div of Medicine & Cardiovascular Sciences, St. George’s Hospital, London, United Kingdom; 4Georgia Regents Univ, Augusta, GA.

Background: Time and resources tend to limit attempts at effective global monitoring for AVF (7 patients). Clinical monitoring appears to be a poor substitute. We have devised a non-invasive version of Static Pressure Ratio SpRn which features rapid ‘point and click’ data acquisition by BlueDop pocket Doppler (www.bluedeop.co.uk), paired with a smart database, the ‘Fishtank’ which allows patients with failing AVF to ‘loat’ to the top of the list for easy identification by the clinical team.

Methods: SpRn data was acquired during normal uninterrupted dialysis sessions using a unique algorithm to measure mean pressure at any desired point on the fistula, typically either distal brachial or radial artery. The SpRn algorithm is shown in Figure 1. Hospital number, Date, Time, BP and SpRn were automatically archived in the ‘Fishtank’ database. An SpRn value of greater than 0.64 was assumed to be associated with a > 60% (PSV:6) significant stenosis in the venous outflow segment.

Results: 340 measurements were made over a 10 week period on 73 patients. A further 60 patients formed a control group. 23% of the monitored group rose to the top of the ‘Fishtank’ of which 82% were subsequently shown by Duplex Ultrasound to have a significant venous stenosis of 60% or greater.

Conclusions: Retrospective analysis over 30 months of clinically initiated Duplex Ultrasound requests for AVF assessment showed that only 38% were candidates for intervention, 48% had excellent blood flow and 14% had already thrombosed. This compares with 82% suitable for planned procedures shown by the ‘Fishtank’. Figure 1. SpRn algorithm. SpRn = (1-PI/PIH). PI = (S-D) MAP derived from an automatic BP reading taken from the non fistula arm; Vf = (max-min)/mean derived automatically from the Doppler blood flow spectrum.

SA-PO419
Outpatient Dialysis Hospitalization Rates: A Comparison between Fellow (FL) and Non-Fellow (NF) Managed Units in NY State

George N. Coritsidis,1 Adedyoin G. Akitinde,1 Carol Lyden,2 Marie France R. DeLeon,1 Jasjit Singh.1 (FL) and Non-Fellow (NF) Managed Units in NY State for 2010 regarding demographics, emergency department (ED) visits and hospitalization and readmission rates. The hospitalization rates were then compared to 2009 data. Fellow units (29837 patients). Compared to the NF units, patients in the FL units were more likely to be African American (52.7% vs 38.5%, p<0.0001). Age, URR metrics, ethnicity and the incidence of diabetes and hypertension were similar.

Background: Hospitalization rates of dialysis patients are an important measure of proper care in ESRD patients. Renal fellows may provide for greater physician presence or possibly lower the threshold for hospital admission. We were interested to see how the presence of renal fellows impacts on this measure, and whether it provides for more efficient care.

Methods: We reviewed the de-identified records of Network 2 which includes all of NY State for 2010 regarding demographics, emergency department (ED) visits and hospitalization rates. The hospitalization rates were then compared to 2009 data. Fellow managed units (FL) were compared with non-fellow managed units (NF). Data was corrected for the number of patients per unit (pt).

Results: We identified a total of 24 fellow managed units (4412 patients) and 196 Non fellow units (29837 patients). Compared to the NF units, patients in the FL units were more likely to be African American (52.7% vs 38.5%, p<0.0001). Age, URR metrics, ethnicity and the incidence of diabetes and hypertension were similar.

Conclusions: There was a significantly higher percentage of African Americans in the fellow managed units. ED visits, hospitalization and readmission rates were similar regardless of the presence of a renal fellow.

SA-PO420
In Vitro Characterization of High-Flux and High Cut-Off Membranes

Mauro Atti, Luca Corazza, Marialuisa Caiazzo, Luisa Sereni, Giuseppe Palladino. Scientific Affairs, Bellco S.r.l., Mirandola, Modena, Italy.

Background: The conventional dialysis membranes are classified as low-flux or high-flux membranes, depending on their permeability. Today a new class of High cut-off blood purification membranes are commercially available and this represent a challenge for traditional rejection of different pathologies treatable with extracorporeal therapy.

Dextran sieving experiments is an achievable and simple method, to classify High flux and High cut off membranes. Here we present preliminary results based on vitro method, obtained from six different membranes.

Methods: Dextrans (Sigma-Aldrich; Average MW 17,9, 35.6 and 73.4 kDa) solutions were prepared in distilled water at concentration of 1 g/L for each dextran. The dextran solution was recirculated at 300 ml/min flow rate and 50 ml/min as ultrafiltration flow. Feed (blood side entrance), retentate (blood side exit), and filtrate (dialysate exit) samples were taken at 15 and 60 min. Relative concentration of the samples were analyzed by spectrophotometric analyzer. The sieving coefficient SC was calculated according to Eq 1. SC = Cf/(Cf×Cf) where Cf is the concentration of the solute in the filtrate, Cf its concentration in the permeate and C its concentration in the retentate.

Results: Six different commercially available dialyzer were characterised and results are summarized in fig 1.

SA-PO421
Prevalence of Hypercalcemia and Hyperparathyroidism with Two Dialysate Calcium Concentrations

Patricia Coral Ruiz Palacios, Manolo Ramos Gordillo, Juan Francisco Fernandez-pellon, Jose C. Pena. Nephrology and Mineral Metabolism, Centro de Diagnostico Angeles, Mexico, Distrito Federal, Mexico.

Background: The “calcium and alkaline” syndrome is a frequent complication in hemodialysis(HD) patients. The aims were to identify the presence of hypercalcemia in HD patients and to evaluate the effect of both a high dialysate calcium concentration compared to a low dialysate calcium concentration upon the serum calcium and PTH concentrations.

Methods: From January 2010 to March 2011, 447 patients, age 52.6 ± 16 years old, 269 men(60%), were treated with high flux HD during 3 to 4 hours, 3 times per week, with a high dialysate calcium concentration(3.5 mEq/L). Then, during 14 months in the same cohort, the dialysate calcium concentration was lowered to 2.5 mEq/L. Oral calcium intake was kept constant in all patients during both periods. (1163 ± 757 mg/day). Hypercalcemia was defined as serum corrected calcium > 10.5 mg/dL. Serum calcium, PTH and mortality were evaluated in all patients during both study periods. Results are expressed as mean ± SD. Mean values were compared with paired t test, hypercalcemia prevalence was compared with chi-squared test. Survival analysis was performed by Kaplan Meier curves and Log Rank (Mantel-Cox) test.

Results: Hypercalcemia prevalence was higher with high dialysate calcium(81 patients, 18.1 %) than with low dialysate calcium(15 patients, 3.3 % p < 0.01). With high calcium dialysate, mean serum corrected calcium was higher(9.61 ± 1.07 vs 9.24 ± 0.84 mg/dL p < 0.01) and mean PTH was lower(988 ± 71.7 vs 992 ± 75.9 pg/mL p = 0.02) compared to low calcium dialysate. Survival rate was lower with high calcium dialysate compared to low calcium dialysate.

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

Underline represents presenting author/disclosure.
SA-PO422

Comparing Accuracy of Assessment of Clotting of Dialyzer during Heparin Anticoagulation for Hemodialysis

Ki-won Kwon,1 Young Hye Song,1 Eun Hye Seo,2 Jung-Hwan Park,2 Jong-Ho Lee,2 Young-II Jo,2 1Dialysis Center, Konkuk Univ Medical Center, Seoul, Republic of Korea; 2Div of Nephrology, Konkuk Univ Medical Center, Seoul, Republic of Korea.

Background: Clinical assessment is useful for identifying coagulation problems during anticoagulation for hemodialysis (HD), the accuracy of visual assessment has yet to be clarified. This study was designed to evaluate the accuracy of visual assessment of clotting within dialyzer during heparin anticoagulation for HD.

Methods: Adult ESRD patients who received maintenance HD were recruited. At the end of each dialysis session, the dialyzer was inspected for visible signs of thrombus formation and scored semiquantitatively (0=no clotting, 1=minimal, 2=moderate, 3=heavy, 4=complete clotting). The clotting volumes in dialyzer were calculated as follows: total blood compartment volumes (TBCV) of dialyzer before HD - TBCV after HD. The area of clotting in cross-section of dialyzer was measured by using squared paper. Each parameter was compared.

Results: A total of 244 dialyzer from 82 adult patients (male:female 41:41, age 62.6±11.6, DM 49%) were assessed and assorted into five groups (G-0:G-1:G-2:G-3:G-4=98:33:8:43:34:3) according to visual assessment of clotting within dialyzer. The grades of clotting within venous chamber estimated by visual inspection (G-0:G-1:G-2:G-3:G-4=239:4:1:0:0) were not correlated with the degrees of clotting within dialyzer. However, there were significant correlation (p<0.001) between the clotting within dialyzer and the clotting volumes in dialyzer and the area of clotting in cross-section of dialyzer.

Conclusions: These results suggested the grade of clotting within dialyzer estimated by visual assessment may be useful indicator in decision of heparin dose for anticoagulation during HD.

SA-PO423

Ratios of Plasma Bicarbonate Increase to Dialysate-Plasma Bicarbonate Gradient at Early and Late Hemodialysis on 34 and 40 mEq/L Dialysate Bicarbonate Concentrations

David Tovchin, Roberto Fudin, Nayel Mohamed Habbashe,1 Yakov Kuperman,2 Saher Srur,3 Alla Reitman,1 Amir Abd Elkadir,1 1Department of Nephrology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; 2Department of Nephrology, Meir Medical Center, Kfar Sava, Israel; 3Department of Nephrology, Assaf Harov Medical Center, Haifa, Israel.

Background: Acidosis correction in hemodialysis (HD) requires bicarbonate (BIC) transfer to expanded extra-plasma compartments through narrow plasma compartment (P-E transfer). Dialysate-plasma (D-P) transfer depends on D-P BIC concentration gradient (DBIC-PBIC). Intra-dialytic BIC increase reach alkalotic range & counters gradient, D-P transfer & acidosis correction. We hypothesized that in pre-HD PBIC<22 mEq/L, on standard BIC (SDBIC-34mEq/L), high DBIC (HDBIC-40 mEq/L) corrects inter-dialytic acidosis. We evaluated the ratios of PBIC increase/DBIC-PBIC and found significant increases.

Methods: We assessed intra-dialytic BIC increase & their ratios/relations with PBIC-PBIC gradients on SDBIC & HDBIC.

Results: In a prospective bi-center study, 15 patients were assessed for 3 weeks on SDBIC & HDBIC. Blood gases/electrolytes were assessed weekly after, at 2 hours (mid-HD) & end HD. 3rd week data is presented as mean (SD) & evaluated using non-parametric tests.

Conclusions: Acidotic patients develop intra-dialytic alkalosis on SDBIC & more on HDBIC, which corrects inter-dialytic acidosis. Late HD decreased PBIC increase/DIBC-PBIC ratios suggest larger P-E transfer for gradient. Thus, smaller gradient & DBIC are needed, which may limit alkalosis.

SA-PO424

Effects of Peritoneal Dialysis Using Icodextrin Dialysis Solution in Patients with Chronic Renal Failure Complicated by Refractory Congestive Heart Failure

Masahito Tamura, Tetsu Miyamoto, Yota Serino, Yumi Furuno, Kenichiro Bando, Yoko Fujimoto, Akihiro Kuma, Emi Hasegawa, Yutaka Otsuki. Dept of Nephrology, Univ of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan.

Background: Chronic heart failure is likely to cause renal failure and often becomes resistant to conventional treatments. We evaluated the usefulness of peritoneal dialysis (PD) using icodextrin solution in patients with refractory congestive heart failure (CHF) complicated by chronic renal failure.

Methods: In patients at CKD stage 5 who presented with symptoms of NYHA III or above CHF resistant to conservative therapy and had a medical history of hospitalization for CHF using icodextrin solution, we has invited to prospectively evaluate its usefulness. One bag of icodextrin dialysis solution was administered overnight as the basal dose, and dextrose dialysis solution was added as renal function declined.

Results: Four patients classified as NYHA IV were enrolled to this study. The mean estimated GFR level was 7.12 ml/min/1.73m2 in the PD initiation period. The mean amount of PD fluid removal was 817 ml/day. Urinary output increased from 812 ml/day before to 1,083 ml/day after PD initiation. The NYHA classification showed improvement to class II in all patients. Duration of hospitalization due to CHF decreased from 29 days/ year before to 0 days/year after PD initiation. Improvements of the following parameters were observed after as compared to before PD initiation: atrial natriuretic peptide, from 294.1 to 12.7 pg/ml; left ventricular ejection fraction, from 37.5 to 48.3%; end-diastolic left ventricular diameter, from 56.5 to 46.6 mm; and end-systolic left ventricular diameter, from 42.8 to 31.9 mm. Body weight showed significant change from 55.1 kg before to 57.2 kg after PD initiation. In 1 patient, residual renal function declined after PD initiation, and hemodialysis was used in combination due to poor body fluid control.

Conclusions: It was suggested that PD with icodextrin dialysis solution might be useful in patients with chronic renal failure complicated by refractory CHF. Improvement of the NYHA classification might be attributable to improved cardiac function.

SA-PO425

NeutroPhase Shows Improvement in the Infections Associated with Peritoneal Dialysis Catheters

Allan G. Kavalich,1 Dmitri Debabov,2 Ramin (ron) Najafi,2 Russell Hoon,2 Thomas Paulson,2 1Medical Director, San Bernardino Valley Home Dialysis Center, Inc., San Bernardino, CA; 2NovaBay Pharmaceuticals, Emeryville, CA.

Background: S. aureus accounts for most exit site and tunnel infections associated with peritoneal dialysis catheters. Gram negative bacteria and fungi are also less common, but difficult to eradicate and frequently lead to peritonitis if catheter removal is delayed.

Methods: NeutroPhase spray (a stabilized 0.01% pure hypochlorous acid in a NS solution) was used to treat five patients with infections associated with peritoneal catheters.

Results: A 59 year old male with exudative tunnel infection due to heavy growth of multi-resistant E.coli was treated with Levequin. After 10 days he was re-tested and grew resistant E.coli and started on NeutroPhase. Patient was brought into unit TID, NeutroPhase was induced into tunnel via 30cc syringe and flexible IV catheter to bathe area with 5cc for 10 minutes repeated X four. NeutroPhase was allowed to dry, catheter was anchored and dressing was applied. Process was repeated 2 X weeks, then at home bunched 2 X days for six weeks. With complete resolution. 55 year old female developed a Candida Albicans PD exit site infection; was treated with IV Difilcan and Nystatin cream. Culture remained positive. Treated with NeutroPhase 4 sprays to the exit site BID X six weeks with complete resolution. Continues to use spray daily at exit site X six months with no further infections. A 64 year old male with MRSA exit site infection was treated solely with NeutroPhase spray TID for eight weeks with complete resolution. 55 year old female with chronic staph epi exit site infections in the past treated with Vanco and Rifampin. NeutroPhase spray started. Exit site clean after six weeks. Continued spray QD without infection X six months. 29 year old female with recurrent exit site infections treated with NeutroPhase spray QID with complete resolution X four weeks.

Conclusions: NeutroPhase was the only treatment showing improvement in these patients. Our data show that there is a clear utility for the use of NeutroPhase for treatment of infections associated with peritoneal dialysis catheters.

Funding: Pharmaceutical Company Support - NovaBay Pharmaceuticals

SA-PO426

Encapsulating Peritoneal Sclerosis in PD Patients or on Renal Transplantation after Peritoneal Dialysis

Valerio Vizzardi, Massimo Sandrini, Luigi Manili, Silvio Sandrini, Gisella Setti, Laura Econimo, Giovanni Cancarini. UO Nefrologia, Spedali Civili and Uni of Brescia, Brescia, Italy.

Background: Encapsulating Peritoneal Sclerosis (EPS) is one of the most severe complication of peritoneal dialysis (PD). Prevalence of EPS after PD discontinuation has been increasing in the last years, mainly after kidney transplantation (50% of cases).

Methods: Retrospective analysis of EPS diagnosed in our Center from Jan 2008 to Dec 2012.

Results: 13 cases of EPS(2.5%) occurred in 517 non-TX patients still on PD. In the same period, 81 PD patients received a TX and two of them (2.5%) developed EPS. TX Pt: 53 yrs old man: hemodialysis (HD) from 1982 to 1987. 1st TX from 1987 to 2002 [cyclosporine (Cys) and steroids (ST)]. APD from 2002 to 2005. In 2005 he received a 2nd...
TX (Mycophenolate (Myc) and ST). In 2009 renal failure failed and the pt started PD. EPS was diagnosed on peritoneal biopsy obtained during the placement of the Tenckhoff catheter. Clinical history: no episode of bowel obstruction. The patient was shifted to HD and continued Myc and ST (8mg/day). Abdomen CT scan (2011 after an episode of intestinal sub-obstruction) showed “distention of bowel loops, some focal thickening along the parietal peritoneum (previously absent).” The pt started Tamoxifen 20 mg/day. In the following months the clinical condition deteriorated and in December 2012 parenteral nutrition was started. TX P2: 57 yrs old man, on APD for 79 months. On April 2007 he received a TX. Therapy: Myc, ST and Tacrolimus (after 36 months shift to Cys). The patient is still on Cys, Myc and ST. 2003, abdomen CT-scan: “calcifications of the parietal peritoneum”, peritoneal biopsy: “chronic peritonitis with fibrosis and sclerosis.” 2005, abdomen CT-scan: no peritoneal calcification. In the 2007 the pt underwent enterolysis surgery for bowel obstruction. He continue on 5 mg of ST and, at present, six years after enterolysis, is asymptomatic.

Conclusions: In literature EPS prevalence increases after PD discontinuation mainly after TX. In our experience the incidence of EPS do not differ between TX and non-TX PD patients. The evolution of the two cases was acceptable after 3 and 6 years since the time of diagnosis.

SA-PO427
Effect of Peritoneal Dialysis Modality and Peritoneal Membrane Characteristics on Phosphorus Level and Management
Rafael Garcia, Sherali Kansal, Martin J. Schreiber. Hypertension & Nephrology, Cleveland Clinic Foundation, Cleveland, OH.

Background: Hyperphosphatemia is highly prevalent in peritoneal dialysis (PD). Prior studies have suggested that phosphate (P) removal in continuous ambulatory PD (CAPD) and automated PD (APD) was regulated by peritoneal membrane (PM) transport type. The current study examined the impact of PD modality and PM transport type on P values, P binder equivalent doses (PBED), calcium and PTH values.

Methods: In this retrospective and single cohort study, we included 40 patients (24 M, 16 F, mean age 53 y/o) all new to PD dialysis. Baseline PM transport type, PD modality, duration and TCrCl significance were evaluated. Longitudinal data analysis on repeated measures of outcomes by mixed effects models for nation-wide prospective cohort from September 1, 2008 to June 30, 2011 were analyzed. 29% of causative organisms were gram +ve, 32% gram -ve, 3% fungal and 32% had no cations of the causative organisms. In total anuric PD patients, non-survived patients showed significantly higher PBED than APD. RRF and TCrCl but not PCrCl also significantly affected P levels but not PBED whereas TCrCl significantly correlated with P level. PD type was significant for PBED; CAPD demonstrated significantly higher PBED than APD. RRF and TCrCl but not PCrCl also significantly affected PBED.

Results: 65% of patients utilized APD and 35% CAPD. PM transport distribution: low-low average: 17, high-average-high: 23. At baseline (mean): RFF 6.57 ml/min, PCCI 39.39 L/wk, TCrCl 143.58 L/wk, Kt/V 2.55, P4 mg/dL, PBED 166.6 mg/dL. At 12 months, P and PBED were higher at 5.1 mg/dL and 2653 mg/dL PM transport type did not affect P levels or PBED. The slope of P change was not affected by PD modality, however, PMCI and TCrCl significantly correlated with P level. PD type was significant for PBED; CAPD demonstrated significantly higher PBED than APD. RRF and TCrCl but not PCrCl also significantly affected PBED.

Conclusions: The change in P level or PBED was not significantly impacted by PM transport type. Patients on CAPD have higher PBED suggesting an advantage to APD for phosphate control. PCCI significantly affected P levels but not PBED whereas TCrCl significantly affected both suggesting cointaneous clearance may be a better measurement of adequacy with regard to phosphate control as compared to Kt/V and should be examine in all patients to optimize P control. Prescription design focused on achieving the highest TCrCl should be a priority in settings of hyperphosphatemia.

SA-PO428
Survival Predictors in Anuric Korean Peritoneal Dialysis Patients: Prospective Multicenter Propensity Score Matched Cohort Study
Jang-Hee Cho,1,2 Hye Min Jang,1,3 Yon Su Kim,1,3 Shin-Wook Kang,4 Chul Woo Yang,4 Nam Ho Kim,1,5 Ji-Young Choi,1,2 Sun-Hee Park,1,2 Chan-Duck Kim,1,2 Yong-Lim Kim.1,2

Clinical Research Center for End Stage Renal Disease in Korea; Kyungpook National Univ School of Medicine; Seoul National Univ College of Medicine; Yonsei Univ College of Medicine; Catholic Univ of Korea College of Medicine; Chonnam National Univ Medical School.

Background: This study aims to evaluate predictors of survival in the absence of residual renal function using anuric peritoneal dialysis (PD) patients.

Methods: Anuric PD patients (n=505, <100 ml of daily urine) enrolled in Korean nationwide prospective cohort from September 1, 2008 to January 31, 2013 (all new to PD dialysis. Baseline PM transport type, PM modality, duration and presence of diabetes. The change in P level or PBED was not significantly impacted by PM transport type. Patients on CAPD have higher PBED suggesting an advantage to APD for phosphate control. PCCI significantly affected P levels but not PBED whereas TCrCl significantly affected both suggesting cointaneous clearance may be a better measurement of adequacy with regard to phosphate control as compared to Kt/V and should be examine in all patients to optimize P control. Prescription design focused on achieving the highest TCrCl should be a priority in settings of hyperphosphatemia.

Conclusions: The change in P level or PBED was not significantly impacted by PM transport type. Patients on CAPD have higher PBED suggesting an advantage to APD for phosphate control. PCCI significantly affected P levels but not PBED whereas TCrCl significantly affected both suggesting cointaneous clearance may be a better measurement of adequacy with regard to phosphate control as compared to Kt/V and should be examine in all patients to optimize P control. Prescription design focused on achieving the highest TCrCl should be a priority in settings of hyperphosphatemia.

Conclusions: There was a wide variation of peritonitis among PD centres. Staphylococcus aureus nasal carriage was the most important factor for peritonitis while automated PD reduced the risk.

SA-PO430
Effects of Walking Ability on Risk of Hospitalization for Cardio-Cerebrovascular Events in Hemodialysis Patients
Yoshifumi Ab,1 Atsuhiho Matsunaga,2 Ryota Matsuazawa,3 Akira Ishii,3,4 Kei Yoneki,1 Manae Harada,1 Toshiki Kutsuna,1 Yukia Takata,2 Atsushi Yoshida,3 Yasuo Takeuchi,1 Kouji Kamata.1,5

Kitasato Univ, Sagamihara, Japan; SagamiJunki Clinic, Sagamihara, Japan.

Background: Hemodialysis (HD) patients are at high risk for cardiovascular and cerebrovascular events, yet very few studies have examined physical activity and function as a way to reduce the risk of cardio-cerebrovascular events among HD patients. We investigated the prognostic significance of walking ability on cardio-cerebrovascular events requiring hospitalization among HD patients.

Methods: A total of 148 Japanese outpatients undergoing maintenance HD three times per week at a HD center from October 2002 to August 2012 were followed up to 5 years. We measured maximum walking speed and characteristics (age, sex, body mass index, HD duration, conorbid conditions, serum albumin, and serum C-reactive protein) at baseline. HD patients were divided into two groups based on maximum walking speed: the fast speed group (women, 1.35 m/s; men, ≥1.50 m/s) and the slow speed group. A Cox proportional hazard regression was used to assess how walking speed affected hospitalization from all-cause, cardio-cerebrovascular events and non-cardio-cerebrovascular events.

Results: Median (25th, 75th percentile) age of this study population was 64 (56, 72) at baseline, and 57.4% of the patients were women. Sixty percent of the patients were included in the fast speed group. There were 35 hospitalizations for cardio-cerebrovascular events and 21 hospitalizations for other causes. After adjusting for the effects of clinical characteristics, the hazard ratios for hospitalization from all-cause, cardio-cerebrovascular events and non-cardio-cerebrovascular events in the fast speed group were 0.48 (95% CI: 0.25-0.93; P = 0.03), 0.33 (95% CI: 0.15-0.74; P = 0.01) and 0.89 (95% CI: 0.31-2.56; P = 0.83), respectively, compared with those in the slow speed group.

Conclusions: Walking speed is closely associated with physical activity of daily living. The results suggest that specific instruction on how to improve and maintain walking ability may be necessary to reduce the risk of cardio-cerebrovascular events among HD patients.
SA-PO431
Low Serum Magnesium Is Related with Vascular Stiffness in Patients on Maintenance Hemodialysis (MHD) but Not in Non-Dialysis Chronic Kidney Disease Patients (ND-CKD)

Background: Recent clinical studies have shown that lower serum magnesium (Mg) levels are associated with vascular calcification and cardiovascular mortality in MHD. In this study, we evaluated the factors affecting Mg in MHD or ND-CKD. Furthermore we evaluated the relationship between Mg and the markers of arteriosclerosis in these patients.

Methods: We measured blood levels of Mg, hemoglobin (Hb), total cholesterol, creatinine (Cr), ura nitrogen (UN), 24microglobulin (MG), albumin (alb), Calcium (Ca), phosphate (P), intact parathyroid hormone (int-PTH), and tumor necrosis factor (TNF)-α in 69 patients with different stages of ND-CKD and 125 HD. Furthermore, we measured brachial-ankle pulse wave velocity (ba-PWV) and ankle-brake index (ABI).

Results: There was no significant difference in Mg between ND-CKD (2.19±0.26 mg/dl) and MHD (2.34±0.35 mg/dl). In Mg, Hb was significantly correlated with age (r=0.004, p<0.25), Ca (r=0.02, r=0.27), TNF-α (r=0.005, r=0.25), alb (r=0.001, r=0.32) and ba-PWV (r=0.001, r<0.29). In multiple regression analysis, alb (β=0.0001, β=0.31) and Cr (r=0.005, β=0.18) were selected as the significant predictors of Mg in MHD. In the analysis for determining the factors affecting vascular stiffness of Mg, Hb (r=0.001, r=0.02) was selected as the significant predictor of ba-PWV as well as systolic blood pressure (ß=0.0001, β=0.32) and age (ß=0.005, β=0.25). In ND-CKD, Mg did not correlate with Cr, UN, β2MG, alb, Ca, P, and int-PTH, ba-PWV and ABI.

Conclusions: Mg were associated with the index of vascular stiffness (ba-PWV) in MHD, and not correlated with several levels of Ca and alb. In ND-CKD, we could not show any parameters associated with Mg level.

SA-PO432
Neutrophil/Lymphocyte Ratio as a Predictor of Cardiovascular Events in Japanese Patients Starting Renal Replacement Therapy

Background: Previous studies have suggested that a high neutrophil/lymphocyte ratio (NLR) is related to worse outcome in patients with cardiovascular diseases (CVD). Patients with chronic kidney disease (CKD) have an increasing risk for premature mortality, primarily as a result of CVD; however, the association between NLR and CVD risk is not known.

Methods: Eighty seven incident Japanese dialysis patients (58 males, age 58 ±11 years) without acute infections and severe liver dysfunction were enrolled and followed for a median of 38.7 months (range 1-68.9 months). Laboratory biomarkers including white blood cell count (WBC) and its differential count, were checked.

Results: NLR was 3.72 (1.19-24.4). NLR positively correlated to WBC (R²=0.16, P<0.0001), neutrophil count (R²=0.55, P<0.0001) and CRP levels (R²=0.07, P<0.001), and negatively to lymphocyte count (R²=0.51, P<0.0001). The duration from start of dialysis therapy to the first CVD events was significantly shorter in patients with higher NLR (Log rank 6.95, P=0.0084). The patients with high NLR had a significantly increased relative risk (Cox hazard model; 3.07 95% CI; 1.32-8.00) of CVD compared with those with lower NLR, even after adjustments for age, gender and presence of diabetes, while the relations between WBC, neutrophil and lymphocyte count and CVD events respectively were much weaker. The number of CVD events per year during the observation period was higher in patients with higher NLR (28.5 events per 100 person-years) than in patients with lower NLR (10 events per 100 person-years).

Conclusions: A higher NLR associates with increasing risk of cardiovascular events and is a stronger predictor of future CVD events compared with WBC, neutrophil, and lymphocyte counts.

Funding: Government Support - Non-U.S.

SA-PO433
Importance of Brain Natriuretic Peptide in Assessing Overhydration in Patients on Maintenance Hemodialysis: A Validation Study Using Three-Dimensional Echocardiography

Background: Therapeutic decisions in patients undergoing intermittent hemodialysis (HD) are based on the determination of fluid removal and an estimation of the intravascular fluid volume. Brain natriuretic peptide (BNP) has been suggested as a valuable marker for the evaluation of fluid status in patients on maintenance HD. BNP measurement provides objective information which can be correlated with hydration status. However, measurement of BNP has not become a standard practice in clinical routine.

Methods: In our cohort study forty-four prevalent HD patients on maintenance hemodialysis (HD) were enrolled. Exclusion criteria were medical history of coronary artery disease, diabetes mellitus, any cardiomyopathy or significant valvular disease. Prior to regular HD session, overhydration percentage (OHP) was assessed with bioimpedance (Freibruner Body Composition Monitor) and blood sample was collected for BNP measurement. 3D echocardiography was performed both before and after HD (GE Vivid E9). End-diastolic (EDV), end-systolic (ESV) volumes indexes to body surface area, ejection fraction (EF) and sphericity were measured using dedicated software (4D Analysis, GE, 4DImaging). Data are presented as mean±SD or median (interquartile range).

Results: EDV and ESV were reduced, while EF increased after ultrafiltration [pre- vs. post-HD; EDV: 56.3(17.2) vs. 55.6(13.9), ESV: 19.8(6.8) vs. 19.3(5.7) mm³/m², EF: 36.3(9.5) vs. 60.10 %, all p<0.001]. 3D sphericity describing full shape of the left ventricle decreased with fluid removal [pre-HD vs. post-HD; P=0.001], OHP (%) correlated with pre-dialysis values of EF (Spearman's rho=-0.478, p=0.491), OHP (%)<0.484, all p<0.01. In a multivariate linear regression model BNP (β=0.455) and sphericity (β=0.456) were found to be independent predictors of EF.

Conclusions: Brain natriuretic peptide implies overhydration through the alterations of cardiac geometry and function. 3D echocardiographic assessment of the left ventricle provides valuable and instantaneous information on intravascular fluid load.

Funding: Clinical Revenue Support

SA-PO434
Amputation-Free Survival in Dialysis Patients Undergoing Angioplasty of the Lower Limbs: Is Vascular Intervention Futile?

Background: Previous studies have shown that dialysis patients are at increased risk for peripheral arterial disease. With improvement in interventional technology, more patients are undergoing angioplasty of the arterial tree to try to avoid amputation, and to maintain mobility and quality of life. However, there are few studies that have examined the outcome of lower limb angioplasty in these patients.

Methods: A retrospective analysis of all dialysis patients evaluated and treated by the interventional radiology department at a large referral hospital from January 2005 to August 30 2012 with at least one-year follow up was conducted using electronic patient records. The Kaplan-Meier method was used to assess the main time-to-event outcomes (mortality and amputation) in comparison to non-dialysis patients during the same period of time. Cox proportional hazards models were fitted to examine the independent association among comorbidities, the use of antplatelet and lipid-lowering agents, ACE/ARB and time-to-event outcomes.

Results: We evaluated 153 patients with lower limb angioplasty or stent of whom 51 (33.33%) were in dialysis (2/1D and 49 HD) and 102 (66.7%) were not on dialysis. Mean time on dialysis was 76.9 months (SD 49.2). In the dialysis group there were 33(64.7%) deaths and 26(51%) amputations vs. 22 (21.6%) and 31(30.4%) in the non-dialysis group, with a P value of 0.004 and 0.01 respectively. Almost half the deaths occurred within the first year after angioplasty: 16(34.6%) for the dialysis group vs. 108(9.8%) for the non-dialysis group, P=0.001. All patients in the dialysis group who had an amputation within a year of angioplasty died within that year.

Conclusions: This study shows a remarkably higher mortality and amputation rates in dialysis vs. non-dialysis patients who underwent lower limb angioplasty and/or stenting. This suggests that vascular intervention in dialysis patients may not be as effective as in those not on dialysis. A shift may be needed to focus on the benefits of early diagnosis, preventive measures, and the need for involving the palliative service early in the course along with nephrology and vascular teams.

Funding: Clinical Revenue Support

SA-PO435
Association of Physical Activity with HDL-C Level in Hemodialysis Patients

Background: The Japanese Society for Dialysis Therapy reports that decreased high-density lipoprotein cholesterol (HDL-C) levels are associated with increased mortality in dialysis populations. Although physical activity increases HDL-C levels in the general population, this remains unclear in hemodialysis patients. After confirming the relationship between HDL-C levels and survival, we investigated the effect of physical activity on HDL-C levels in hemodialysis patients.

Methods: First, 266 hemodialysis patients (age; 64±13 years; duration of hemodialysis; 9.8±8.8 years, mean±SD) were monitored prospectively for 5 years. Serum lipid levels were obtained at baseline. Cox proportional-hazards regression was used to confirm the contribution of HDL-C level to mortality. Second, before investigating the association between physical activity and HDL-C level, we excluded patients who had severe comorbidities or who needed help in walking. As a result, 116 patients (age, 67±9 years; duration of hemodialysis; 9.9 years, HDL-C; 42.8±12.8 mg/dl) were recruited in the cross-sectional study. We evaluated their physical activity and characteristics including age, sex, body mass index, duration of hemodialysis, comorbid conditions, serum albumin and creatinine levels, smoking habit, and use of antipilems. Physical activity was evaluated with an accelerometer as the number of steps per day for a consecutive 5-day period. We used multiple regression analysis to evaluate the association between physical activity and HDL-C level.

Results: During the follow-up period, 77 patients died. We confirmed that HDL-C level was a significant predictor of all-cause mortality (hazard ratio, 0.975; 95% CI, 0.954-0.997; P = 0.03). After adjustment for patient characteristics, physical activity was independently associated with HDL-C level (adjusted β coefficient, 0.244; adjusted R², 0.235; P = 0.005).

Conclusions: Physical inactivity was strongly associated with decreased HDL-C level in hemodialysis patients.

Funding: None
SA-PO436

Decline of Peripheral Resistance over Time in Patients with End Stage Renal Disease. Results from the CONvective TRAnsport Study (CONTRAST) Irina Mostovaya,1 Michiel Bots,2 Muriel Grooteman,2 Marinus A. Van Den Dorpel,2 Pieter M. Ter Wee,3 Peter J. Blankstein,1 1Nephrology, Univ Medical Center Utrecht, Utrecht, Netherlands; 22 Julius Center for Health Sciences and Primary Care, Univ Medical Center Utrecht, Utrecht, Netherlands; 3Nephrology, VU University Medical Center, Amsterdam, Netherlands; 4Internal Medicine, Maassieder Hospital, Rotterdam, Netherlands.

Background: Peripheral resistance is a well established marker of sympathetic activity in cardiovascular disease (CVD). Previous studies have shown variability of peripheral resistance over time. The aim of this study was to examine changes over time of peripheral resistance (PR), cardiac output (CO), mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Methods: A subpopulation of 84 patients from the CONvective TRAnsport Study (CONTRAST), a randomized trial comparing online hemodiafiltration with low-flux hemodialysis, received echocardiography and simultaneous blood pressure measurements on a non-dialysis day at baseline, 6 months, 12 months and annually thereafter. PR was computed as MAP/CO. A total of 190 measurements were thus performed over a follow-up period of 3 years. The rate of change over time of PR, CO, MAP, SBP and DBP was estimated using linear mixed effects models.

Results: At baseline, patients had a mean age of 62 ± 14 years and 55% were male. Median PR was 17.7 (IQR 15.3 – 22.5) mmHg/gmin/L, mean CO was 5.5 ± 1.5 L/min, mean MAP was 97 ± 15 mmHg and mean SBP and DBP were 137 ± 29 and 76 ± 12 mmHg respectively. PR (A-1.6 95%CI:-3.0 to 0.2 mmHg/gmin/L per year), MAP (A-4.2 95%CI:-7.5 to -0.8 mmHg per year) and DBP (A-3.8 95%CI:-6.7 to -0.9 mmHg per year) decreased over time, while CO (A0.3 95%CI:-0.1 to 0.7 L/min per year) and SBP (A-4.3 95%CI:-10.3 to 0.9 mmHg per year) remained stable.

Conclusions: In ESRD patients MAP decreases over time, mainly due a decrease in DBP. As CO remained stable, this decline can be explained by a decrease of PR over time. Previous cross-sectional investigations were not performed, but a decrease in renin-angiotensin system activity and renal sympathetic nerve activity could be a plausible explanation.

SA-PO437

Influence of Methodology on Left Ventricular Mass Measurement by Cardiac Magnetic Resonance in the Frequent Hemodialysis Network (FHN) Nocturnal Trial Gerald J. Beck, Glenn M. Chertow, Paul W. Egers, Tom Greene, Brett Larive, Nathan W. Levin, Sanjay Rajagopalan, Michael V. Rocco, Javier Sanz, Tam Tran, Christopher Kramer, Alan S. Kliger, The FHN Trial Group. NIH, NIDDK.

Background: The FHN previously reported in the Daily Trial that left ventricular (LVM) by cardiac magnetic resonance (CMR) declined more over 12 months (unadjusted mean difference 13.9g) among patients randomized to 6x/week in-center hemodialysis (CONTRAST) compared to conventional 3/week HD controls. In the smaller Nocturnal Trial (n=87 vs. 245), although LVM declined by 8.8g in the 6x/week nocturnal (NIH) vs. conventional HD (CHD) patients, these results were not significant. In the FHN trials, baseline and month 12 CMR studies were centrally read sequentially during the trial by 3 trained readers blinded to treatment group. Readers had rigorous training in standardized assessment of LVM and volumes.

Methods: Given the two trials’ similar LVM effect sizes, we explored the impact of a single reader vs. concurrent evaluating LVM for all Nocturnal Trial patients using matched baseline and 12 month MRIs (n=76) while blinded to treatment and time of visit.

Results: The standard deviation of the change in LVM was 28.2g using sequential measurements and 23.8g with concurrent measurements; a reduction of 16.6%. LV volumes showed closer agreement between sequential and concurrent readings. The original reported primary outcome (change in LVM or death) did not differ between the NIH vs. CHD arms: hazard ratio (HR) of 0.69 (95% CI 0.44 to 1.07, p=0.095). Use of concurrent readings showed closer agreement between sequential and concurrent readings. The original reported analysis of speckle tracked imaging (STI) echocardiography can be used to examine both global and segmental contractile function. In this study, we examined the relationship of HD induced circulatory stress with overall ventricular function (assessed as global longitudinal strain (GLS), segmental distribution of strain and their impact on patient survival).

Methods: Averaged values of segmental and GLS were determined from peak–peak diameters (225 minutes) echocardiography of 104 conventional HD patients. These values were compared to the reference values of healthy individuals. Impact on survival was assessed over a follow up period of up to 7 years.

Results: The segmental and global strain values were −8.65 to −16.51 ± 4.91 to 8.13 and −11.48 ± 4.42, respectively. Significant HD induced changes to segmental strain were restricted to the mid- and apical-septal segments (r=0.29 to -0.33; p<0.05). Global and most of the segmental (10 of 12) contractile function was reduced in HD patients c.f. normal controls, with segmental and global strain values significantly higher than healthy individuals (2.70-9.83, p<0.001). Of the forty-six patients who died, there were statistically significant negative correlations between survival time and the GLS (r=0.30, p=0.04) and the apical, inferior and septal segments (r=0.31 to -0.32, p=0.04).

Conclusions: Global and segmental strain as measured from STI provides additional information relating to the effects of HD induced cardiac injury. The clustering of dialysis induced segmental strain abnormalities to the apical, inferior and septal watershed area of the left ventricle suggests a higher degree of vulnerability to demand ischemia in this part of the uremic heart to challenged perfusion.

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

Underline represents presenting author/disclosure.

SA-PO439

The Prevalence of Oral Lesions in People on Hemodialysis: Oral-D Study Giovanni F.M. Strippoli1,2,3 Suettonia Palmer,1 Marinella Ruospo,2,1 Patrizia Natali,1 Valeria Maria Saglimbene,1,3 Michela Sciancalepore,1 Letizia Gargano,1 Fabio Pellegrini,2 David W. Johnson,6 Pauline J. Ford,6 Jonathan C. Craig,4 Paul Stroumza,1 Luc Franzen,1 Miguel Rodrigues Leal,1 Marietta Torok,1 Anna Bednarek,1 Jan Dulawa,1 Eduardo Jorge Celia,1 Ruben Gelfman,1 Jorgen B.A. Hegbrant,1 Charlotte Wollheim,1 Staffan Schón,1 Michele De Benedittis,1 Massimo Petruzzi,1 Diviersom; 2Mario Negri Sud Consortium; 3Univ of Bari; 4Univ of Sydney; 5Univ of Otago; 6Univ of Queensland.

Background: It has been shown that oral diseases are common in the general population and are associated with socioeconomic status. The prevalence of oral diseases could be increased in people on hemodialysis, but this has not been formally established.

We conducted a systematic prospective survey of oral lesions in hemodialysis and are also evaluating their association with death and adverse vascular outcomes.

Methods: ORAL-D is a multinational prospective cohort study. We consecutively enrolled adults receiving hemodialysis in 75 outpatient clinics selected randomly from a collaborative dialysis network in Europe and South America. A dental surgeon conducted a standardized oral examination. We analyzed prevalence of oral diseases using descriptive statistics and will analyze prospective association with death and adverse vascular outcomes with a Cox regression.

Results: 4324 (mean age 61 years (SD 16) adults on hemodialysis in the participating clinics received a complete oral examination. Of these, 868 (20%) were edentulous, 996 (30%) had dental erosion. The mean decay/missing/filled teeth (DMFT) score was 22 (9), salivary pH was 7.3 (1.4). Salivary flow rate before dialysis was 0.5 ml/min (0.8), versus 0.4 ml/min (0.8) post dialysis. 1880 (43%) patients reported mouth dryness and 304 (7%) reported mouth pain. Periodontitis was present in 3036 (91%) of 3340 dentate patients. Analysis of association with death and adverse vascular outcomes is in progress.

Conclusions: Oral diseases prevalent in people receiving hemodialysis may indicate impaired healthcare practices, although further research on the predictors of oral disease in this population is needed.

SA-PO440

Oral Hygiene Habits in People on Hemodialysis and Association with Death and Adverse Vascular Outcomes: Oral-D Study Giovanni F.M. Strippoli1,2,3 Suettonia Palmer,1 Marinella Ruospo,2,1 Patrizia Natali,1 Valeria Maria Saglimbene,1,3 Michela Sciancalepore,1 Letizia Gargano,1 Fabio Pellegrini,2 David W. Johnson,6 Pauline J. Ford,6 Jonathan C. Craig,4 Paul Stroumza,1 Luc Franzen,1 Miguel Rodrigues Leal,1 Marietta Torok,1 Anna Bednarek,1 Jan Dulawa,1 Eduardo Jorge Celia,1 Ruben Gelfman,1 Jorgen B.A. Hegbrant,1 Charlotte Wollheim,1 Staffan Schón,1 Michele De Benedittis,1 Massimo Petruzzi,1 Diviersom; 2Mario Negri Sud Consortium; 3Univ of Bari; 4Univ of Sydney; 5Univ of Otago; 6Univ of Queensland.

Background: Oral hygiene habits in people with end end-stage kidney disease on hemodialysis are poorly described. We prospectively surveyed global oral hygiene habits in a large outpatient hemodialysis population, evaluating association with death and adverse vascular outcomes.

Methods: ORAL-D is a multinational prospective cohort study of oral diseases in people on hemodialysis. We enrolled adults on hemodialysis in 75 outpatient clinics selected randomly from a collaborative dialysis network in Europe and South America. A dental surgeon conducted a standardized oral examination. We analyzed prevalence of oral diseases using descriptive statistics and will analyze prospective association with death and adverse vascular outcomes with a Cox regression.

Results: 4324 hemodialysis patients in the participating clinics from Italy, Hungary, Poland, Argentina, Portugal, France and Spain responded to the questionnaire. Of these, 2327 (52%) did not remember when they had last dental visit or reported they did not have a regular dental practitioner. 1171 (27%) reported their first dental visit at 30 years or older, 494 (11%) never brushed their teeth, 1570 (36%) used mouthwash and only 295 (7%) used a toothbrush. Only 1339 (31%) spent more than 2 minutes on daily oral hygiene care. Analysis of association with death and adverse vascular outcomes is in progress.
Conclusions: Using validated instruments to evaluate oral hygiene, nearly half of adults on hemodialysis do not regularly visit a dentist practitioner and many have poor oral hygiene habits. Additional studies of whether these variables on oral hygiene have any influence on clinical outcomes may be warranted.

SA-PO441
Association of Periodontal Disease and All Cause and Cardiovascular Mortality in Hemodialysis Patients: Oral-D Study
Giovanni F.M. Strippoli,1,2,3,4 Sutonia Palmer,3 Marinela Ruoso,1,2 Valeria Maria Saglimbene,2 Patrizia Natoli,1 Michelle Sciancalepore,1 Letizia Gargano,1 Fabio Pellegrini,2 David W. Johnson,4 Pauline J. Ford,4 Jonathan C. Craig,4 Paul Stroumiza,1 Luc Frantzen,5 Miguel Rodrigues Leal,1 Marietta Torok,1 Anna Bednarek,1 Jan Dalawa,1 Eduardo Jorge Celia,1 Ruben Gelfman,1 Jorgen B.A. Hegbraut,1 Charlotte Wollheim,1 Staffan Schol,1 Michele De Benedettis,1 Massimo Petruzz1,2 1Diaverum; 2Mario Negri Sud Consortium; 3Univ of Barri; 4Univ of Sydney; 5Univ of Otago; 6Univ of Queensland.

Background: Periodontal disease is associated with increased cardiovascular mortality according to several studies done in the general population. We evaluated the association between periodontal disease and all-cause and cardiovascular mortality in hemodialysis.

Methods: ORAL-D is a multinational prospective cohort study of consecutive adults receiving hemodialysis in 75 outpatient clinics selected randomly from a dialysis network in Europe and South America. A dental surgeon evaluated presence of periodontitis during a standardized oral examination. We are assessing survival at 12 months using centralized mortality data. We conducted analysis with Cox regression controlling for age, gender, previous cardiovascular event, income status, clinical performance measures, dialysis prescription and performance indicators.

Results: 3324 dentate hemodialysis patients in the participating clinics received a complete evaluation for periodontitis and completed follow up. Median follow up was 8.0 (6.5 to 8.7) months. 3036 patients (91%) had periodontitis and 344 (10%) died during follow up. While unadjusted analysis suggested an association between periodontitis and mortality, adjusted analysis had shown no associations with risks of all-cause (HR 1.11 [95% CI 0.68-1.82]) or cardiovascular (HR 2.20 [95% CI 0.94-5.11]) mortality.

Conclusions: Contrary to data in the general population, periodontitis at present follow-up of 8 months has uncertain associations with all-cause or cardiovascular mortality in patients on hemodialysis. ORAL-D will be completed at the end of 1 year follow up by September 2013.

SA-PO442
Left Ventricular Mass Is a Powerful Risk Factor for All-Cause and Cardiovascular Death in End Stage Kidney Disease (ESKD) Patients on Dialysis but Does Not Contribute to Prognosis: An Analysis in Two European Cohorts
Giovanni Tripepi,1 Bruno Pannier,1 Francesca Mallarnaci,1 Gerard M. London,2 Carmine Zoccali.1 1Nephrology Unit, CNR-IBIM, Reggio Calabria, Italy; 2Service d’Hémodialyse, Hôpital F.H. Manhé, Fleuré-Mérogis, INSERM, Nancy, France.

Background: Left Ventricular Hypertrophy (LVH) is one of the strongest risk factors for death and CV events in end stage kidney (ESKD) patients. Causality apart, the concept that LVH is useful for risk stratification in ESKD has never been formally tested by state-of-art statistical analyses [risk discrimination(ROC curve area, AUC), calibration and reclassification].

Methods: We re-analysed the prognostic power of LVMI for all-cause and CV mortality in 2 independent ESKD cohorts in Italy and in France, the Cardiovascular Risk Extended Evaluation cohort (CREED, n=254) and the Hospital Manhes cohort (HM, n=270). In both cohorts, LVMI predicted all-cause [CREED, hazard ratio(HR):1.05; HM:HR:1.03] and CV death [HR:1.06 and 1.05] (P<0.001). In these cohorts, the AUCs of LVMI for all-cause death were 0.71 (CREED) and 0.67 (HM) and in 2 independent ESKD cohorts in Italy and in France, the Cardiovascular Risk Extended Evaluation cohort (CREED,n=254) and the Hospital Manhes cohort (HM,n=270).

Results: In both cohorts, LVMI predicted all-cause [CREED, hazard ratio(HR):1.05; HM:HR:1.03] and CV death [HR:1.06 and 1.05] (P<0.001). In these cohorts, the AUCs of LVMI for all-cause death were 0.71 (CREED) and 0.67 (HM) and in 2 independent ESKD cohorts in Italy and in France, the Cardiovascular Risk Extended Evaluation cohort (CREED,n=254) and the Hospital Manhes cohort (HM,n=270). All predictive models were calibrated. In the CREED cohort a predictive model including Framingham factors, anti-hypertensive treatment, CV morbidity, heart rate, Hb and albumin produced an AUC of 0.89 for all-cause and 0.76 for CV death, figures similar to those in the HM cohort (0.92 and 0.87). The inclusion of LVMI did not improve the discrimination power of these models (all-cause death, CREED 0.89 vs.0.89; HM: 0.93 vs. 0.92; CV mortality, CREED:0.76 vs.0.76; HM:0.88 vs.0.87). In an aggregate analysis of the 2 cohorts (n=524) the net reclassification index (NRI) by LVMI was not significant both for all-cause (NRI:1.45%,P=0.11) and CV death (NRI:1.4%,P=0.33).

Conclusions: LVMI is a strong risk factor in ESKD. However, the prognostic power of LVMI is by far lower than that by age alone or combined with standard risk factors. While LVH remains a fundamental treatment target in ESKD, measurement of LVMI solely for prognosis is unwarranted in these patients.

Funding: Government Support - Non-U.S.

SA-PO443
Longitudinal Change in Ultrafiltration Rate in the First Year and Survival Len A. Usykta,1 Peter Kotanko,2 Franklin W. Maddux,1 Eduardo K. Lacon.1 1FMCNA, Waltham, MA; 2RRI, NY, NY.

Background: Higher ultrafiltration rate (UFR) during HD may be associated with poor outcomes. As UFR is measured in mL/hr/kg, interdialytic weight gain, HD time, and body size all contribute towards differences in mortality. We aim to determine association b/n changes of UFR at different levels of baseline UFR and survival.

Methods: All incident HD patients in FMCNA who initiated dialysis b/n Jan 1, 2010 and May 1, 2012, survived>365 days, with Kru<0.1 ml/min at the initiation were included. UFR (in mL/hr/kg) was calculated for 1st 6 months of dialysis [baseline-1] and in months 7 to 12 [baseline-2]. Patients were stratified into 4 groups at baseline 1 and 2 by UFR: <8, 8-10, 10-13, and >13 mL/hr/kg. Mortality was tracked until May 1, 2013. The Cox model adjusted for age, gender, DM status, race, ethnicity, and baseline BMI levels were constructed to assess survival after the first year on dialysis in 16 combinations of UFR categories at Baseline 1 and 2.

Results: Among 26099 incident patients, 16132 (62%) had stable UFR at both baseline 1 and 2. Mean age was 62.3±14.8; 52% male. The median survival follow-up time was 650 (range 1-851) days. We found significant negative correlation between UFR and BMI in baseline: r=-0.28 (P=0.001). Mortality risk tended to increase not only with an increment in UFR but also with decline of UFR in univariable and adjusted models, for patients with baseline-1 UFR<28 mL/hr/kg.

Conclusions: This analysis demonstrates that patients with both increasing and decreasing UFR have a trend toward poorer survival than stable UFR (particularly >8 mL/hr/kg). These larger patients have better outcomes, inverse correlation b/n UFR and BMI signals residual confounding. Further analyses are needed to determine contributions of the patients’ body size, HD time, interdialytic weight gains, and/or changes in those parameters to the survival differences.

SA-PO444
Non-Traditional Blood Pressure Medications (BPM) Instructions for Hemodialysis (HD) Patients Sana Waheed,1 Stephen M. Sozio,1 Wendy L. St. Peter,2 Patti Ephraim,1 Jason Luly,1 L. Ebony Boulware,1 Tariq Shaikh.1 1Dept of Medicine, Johns Hopkins Univ, Baltimore, MD; 2Dept of Pharmacy, Univ of Minnesota, Minneapolis, MN.

Background: Most studies of BPM use in HD patients assume that they take BPM similar to non-HD patients. However, with blood pressure (BP) fluctuations in HD patients, BPM are sometimes held before HD (HOLD) or administered as needed (PRN). Our study describes the frequency of the non-traditional instructions of (HOLD and PRN) in HD patients.

Methods: We performed a retrospective cohort study of patients starting HD at Dialysis Clinic, Inc. facilities from 2003-2008 who were on a BPM at 6 months. Three independent abstractors reviewed medication instructions from free text comments entered in electronic medical records. We assessed distribution of HOLD and PRN instructions across patient demographics, dialysis related factors and BPM regimens.

Results: Of 11,291 incident HD patients who were on a BPM at 6 months, mean age was 62 years; 55% were men and 53% White. At 6 months, there were 30,212 BPM prescriptions of which 1,683 (5.6%) prescriptions had non-traditional instructions (HOLD: 1,191 (3.9%); PRN: 496 (1.6%)). HOLD orders were commonest with β-blockers (5% of all β-blocker prescriptions) whereas PRN orders were commonest with clonidine (12.7% of all clonidine prescriptions). Patients with HOLD orders were likely to be older, white, had greater comorbidities and lower pre- and post- dialysis systolic BP whereas those with PRN orders where younger, less likely to be white and had higher pre and post dialysis systolic BP and greater BP variability (all p<0.05).
SA-PO445

Association of Age and Blood Pressure Variability with Long-Term Mortality in Hemodialysis Patients

Ha Yeon Kim, Kang Hee Lee, Chang Seok Kim, Joon Seok Choi, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim. Dept of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea.

Background: Blood pressure (BP) variability is known as a poor prognostic factor for cardiovascular disease and mortality. This study assessed the prognostic significance of BP variability in association with increasing age in hemodialysis patients.

Methods: We retrospectively analyzed 2,174 patients on hemodialysis at Chonnam national university hospital between January 2000 and December 2012. BP data were collected three times in each hemodialysis session at start and finish times. Highest and lowest points of BP over the first month of dialysis initiation were collected as well. Intradialytic systolic BP variations over 20 mm Hg and diastolic BP variation over 10 mm Hg were defined as BP variability, respectively. Intradialytic systolic BP variations over 10 mm Hg and diastolic BP variation over 5 mm Hg were defined as BP variability, respectively.

Results: In patients aged <55 years, Kaplan-Meier survival curves for 5-year cumulative mortality showed significant higher mortality in patients with higher intradialytic systolic and diastolic BP variability as well as interdialytic systolic and diastolic BP variability (log-rank p=0.006, 0.001, 0.018 and 0.001). Cox proportional analysis revealed that 5-year mortality was associated with intradialytic diastolic BP variability (HR, 2.034 CI, 1.246-3.321). On the other hand, in older patient groups, 5-year mortality has no significant association between intradialytic systolic and diastolic BP variability as well as interdialytic systolic and diastolic BP variability by Cox proportional analysis (p=0.383, 0.828, 0.708 and 0.642 in 55 ± age < 75 group, p=0.335, 0.246 0.272 and 0.059 in 75 ± age group, p=0.290).

Conclusions: For patients aged <55 years, the mortality was significantly higher in patients with BP variability. The association of BP variability with long-term mortality was weaker with increasing age, indicating that the prognostic significance of BP variability in hemodialysis patients is age dependent.

SA-PO446

Outcomes of Dialysis Patients after Coronary Revascularization: A Nationwide Cohort Study in Taiwan

Te-Chao Fang,1,2 Chulin Chou,2 Tsung-cheng Hsieh.1 1Dept of Internal Medicine, Buddhist Tzu Chi General Hospital, Hualien, Taiwan; 2Institute of Medical Sciences, Tzu Chi Univ, Hualien, Taiwan; 'School of Medicine, Tzu Chi Univ, Hualien, Taiwan.

Background: The outcomes of Chinese patients undergoing dialysis after coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), or coronary stenting.

Methods: Using data from the National Health Institutes Research Database, we determined the outcomes of 1,287 dialysis patients who underwent initial coronary revascularization between 1997 and 2008.

Results: The 7-year all-cause survival rates were 69% ± 4%, 68% ± 3%, and 57% ± 2% for the CABG, stent, and PTCA patients (P = 0.001), respectively. After demographic and comorbidity adjustment, the hazard ratios (HRs) for all-cause death in the CABG (versus PTCA) and stent (versus PTCA) patients were 0.695 (P = 0.015) and 0.721 (P = 0.009). Additionally, no significant difference in all-cause death was found between the CABG and stent patients (P = 0.906). Moreover, the ≥65-year-old CABG group patients and the <65-year-old coronary stent group patients showed better survival than the PTCA group patients. Compared with the PTCA and CABG groups, the coronary stent group was significantly associated with a higher risk for a recurrent AMI based on age stratification, the ≥65-year-old stent group had a higher risk for a recurrent AMI than PTCA group (HR, 1.49, 95% CI, 1.05-2.10).

Conclusions: Chinese patients undergoing dialysis who underwent CABG or coronary stenting had better survival than those who underwent PTCA. Moreover, being ≥65 years old, CABG has better survival compared with PTCA; being <65 years old, coronary stenting has better survival compared with PTCA.

Funding: Private Foundation Support

SA-PO447

Hybrid Myocardial Imaging for Risk Stratification prior to Kidney Transplantation: Added Value of Coronary Calcium and Epicardial Adipose Tissue Analysis

Antonio Belli,1 Cristian E. Karohl,2 Luis D’Moura,3 Paolo Raggi.1 1Dept of Nephrology, Ospedale Sant’Anna, Como, Italy; 2Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; 3Nephrology, Hospital Universitario Raúz y Páez, Universidad de Oriente, Ciudad Bolivar, Venezuela; 4Mazankowski Alberta Heart Institute, Univ of Alberta, Edmonton, Canada.

Background: Patient selection and what clinical or imaging markers may help improve risk stratification prior to kidney transplantation remain uncertain. We looked for imaging markers that help predict an abnormal result in screening nuclear stress testing prior to surgery.

Methods: Cross-sectional study of 411 consecutive chronic kidney disease (CKD) stage 4-5D patients awaiting kidney transplantation referred for risk stratification. PET-computed tomography (PET-CT) or SPECT-CT were used to assess myocardial perfusion and quantify coronary artery calcium (CAC) and epicardial adipose tissue (EAT). Abnormal myocardial perfusion was defined as a perfusion defect involving >5% of the left ventricular myocardium.

Results: Fixed (necrotic myocardial) or reversible myocardial perfusion defects (ischemia) were present in 41 patients (10%). Male sex, smoking, and history of cardiovascular disease were more prevalent and age, CAC and EAT were greater in patients with myocardial perfusion defects than in those with normal myocardial perfusion (all p-values<0.05). On multivariate logistic regression, EAT and CAC were independent predictors abnormal myocardial perfusion while diabetes mellitus was of borderline significance (P=0.08). EAT added incremental diagnostic value to a model including age, CAC and diabetes mellitus [AUC 0.73 (95% CI: 0.64-0.81) to 0.76 (95%CI: 0.68 – 0.84); P=0.07]. For the prediction of abnormal perfusion, further refinement of the model containing EAT showed improved diagnostic discrimination (integrated discrimination improvement, IDI).

Conclusions: Abnormal myocardial perfusion on screening stress testing appears to be rare in patients awaiting kidney transplantation suggesting an excess of testing. EAT and CAC may help predict what patients are at higher risk of having an abnormal myocardial perfusion.

SA-PO448

Left Atrial Volume and Dialysis Induced Cardiac Injury

Lisa E. Crowley,1 Adam Kirk,1 Richard J. Fluck,2 Maarten W. Taal,3 Chris W. McIntyre.2 1Dept of Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; 2Div of Medical Sciences and Graduate Entry Medicine, School of Medicine, Univ of Nottingham, Nottingham.

Background: Left atrial volume (LAV) has been demonstrated to be a powerful determinant of cardiovascular mortality in HD patients. Haemodialysis (HD)-induced myocardial stunning driven by ischaemia is a recognised complication of HD and a pivotal pathophysiology of the observed excess in CV mortality. We aimed to assess the hierarchy of importance of ventricular hypertrophy, increased LAV and presence/severity of dialysis induced cardiac injury.

Methods: 60 established HD patients underwent echocardiography at rest assessing cardiac structure and function. Dialysis induced cardiac stunning was detected and quantified from the measurement of left ventricular wall motion abnormalities (RWMA) under dialytic stress.

Results: 38/60 patients experienced dialysis induced cardiac stunning. Higher LAV was significantly correlated with severity of stunning (as measured by number of RWMAS (>0.37, p=0.004) and humoral evidence of volume overload (NT-proBNP=0.56, p=0.001). Both increased LAV and dialysis induced stunning were associated with reduced survival. There was a clear hierarchy of effect demonstrated in multi-variable Cox Proportional Hazard modelling. Stunting was most strongly associated with mortality (HR 4.92 [1.0-23.1] p=0.04), followed by LAVI (HR 1.065 [1.001-1.1000] p=0.038) and LVMRI (HR 0.99 [0.97-1.00] p=0.36).

Conclusions: This study demonstrates the hierarchical relationship (stunning>LAVI>LVMRI) between the principal recognised morphological and functional echocardiographic determinants of increased CV mortality in HD patients and suggests that dynamic echocardiographic parameters may be more predictive of outcome than structural measures.

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

Underline represents presenting author/disclosure.
SA-PO449

Association between Cardiac Valvular Calcification and Myocardial Ischemia in Asymptomatic High Risk Patients with End Stage Renal Disease

Soo Jin Kim,1 Young Rim Song, Jwa-kyung Kim, Sung Gyun Kim, Jeun Oh, Jong-woo Yoon, Jung-woo Noh, Ja-Ryong Koo. Internal Medicine, Hallym Univ, Hallym Kidney Research Institute, Seoul, Republic of Korea.

Background: Valvular calcification is associated with significant morbidity and mortality in patients with end stage renal disease (ESRD). This study examined the hypothesis that valvular calcification is a marker of myocardial ischemia in asymptomatic high-risk patients with ESRD.

Methods: Echocardiography and myocardial perfusion single-photon emission computed tomography were performed in 285 asymptomatic high-risk patients with ESRD at initiation of dialysis. We evaluated the extent and severity of myocardial ischemia by the sum of perfusion score (SDS) and defined the presence of myocardial ischemia as SDS ≥ 3 and moderate to severe ischemia as SDS ≥ 8. The presence of cardiac valvular calcification was assessed by echocardiography and defined as aortic valve calcification or mitral valve calcification.

Results: Eighty-four (29.9%) patients had echocardiographic evidence of cardiac valvular calcification. The presence of myocardial ischemia was significantly associated with aortic valve calcification (odds ratio [OR] = 3.19; 95% confidence interval [CI] = 1.76–5.78; p < 0.001), mitral valve calcification (OR = 3.31; 95% CI = 1.74–6.28, p < 0.001), and cardiac valvular calcification (OR = 3.18; 95% CI = 1.79–5.65; p < 0.001). The presence of moderate to severe myocardial ischemia (SDS ≥ 8) was independently associated with cardiac valvular calcification (OR = 2.86; 95% CI = 1.12–7.27; p = 0.028).

Conclusions: Valvular calcification was significantly associated with the presence of ischemia in asymptomatic patients with ESRD, and may be a potential marker of patients at high-risk for the presence of silent myocardial ischemia.

SA-PO450

Experience of Antegrade Traseptal Percutaneous Transcatheater Aortic Valvuloplasty in Hemodialysis Patients

Manabu Asano,1 Kenichi Oguchi,1 Masahiro Shimoyama,1 Tokuya Nakahara,2 Machiko Okamoto,1 Hitoshi Iwabuchi,1 Yoshitaka Sakata.2 1Renal Unit, Ikegami General Hospital, Tokyo, Japan; 2Heart Center, Ikegami General Hospital, Tokyo, Japan.

Background: Aortic stenosis (AS) due to accelerated sclerotic-calcific degeneration of valve is one of prevalent cardiovascular comorbidities in chronic dialysis patients. Percutaneous trans-catheter valvuloplasty (PTA V) is expected to function as an alternative utilization of Inoue balloon (Ante-PTA V) has been reappraised in terms of its improved therapeutic effect, procedural safety and possibly long-term symptomatic palliation. In this study, we evaluated the clinical efficacy of Ante-PTA V particularly on hemodialysis (HD) patients in order to define its therapeutic role.

Methods: Total 16 HD patients with severe AS (age 76.3±8.8 years old; 56.3 % males and 12.5 % diabetics) underwent Ante-PTA V with Inoue balloon (mean balloon size 20.5mm). Trans-Aortic valve gradients (AP) and valve area (AVA) were measured both by catheterization and echocardiography. Hemodynamic data were obtained in all treated patients, and symptomatic improvement over Ante-PTA V was evaluated and early clinical outcomes were followed up.

Results: From 1/2009 to 12/2012, 16 HD patients successfully underwent Ante-PTA V in our unit. The mean dialysis vintage of those patients was 119.9±110.4 months (range 11–390 months; median 90 months). Critical aortic valve calcification was present in 94% of patients. The mean AVA increased from 0.65 ± 0.31 cm² to 1.28 ± 0.59 cm² (p < 0.05). The mean AP decreased from 17.0 ± 9.15 mmHg to 11.8 ± 7.47 mmHg (p = 0.05) over Ante-PTA V. In the short-term follow-up (within 3 month after Ante-PTA V), hemodynamic stability and tolerance during HD was remarkably increased in over 80% of treated patients. The median hospital stay was 4 days. No significant complications were noted.

Conclusions: Ante-PTA V is a useful and safe procedure to treat symptomatic AS in HD patients who are high risk for surgical valve replacement or ineligible for trans-catheter valve implantation.

SA-PO451

The Impact of Non-High-Density Lipoprotein Cholesterol Levels on the Clinical Outcome in Incident Hemodialysis Patients

Chang Ho Kim,1 Mi Jung Lee,1 Hye-Young Kang,2 Hyeong Jung Oh, Tae-Hyun Yoo,1 Shin-Wook Canada, 2Dept of Internal Medicine, College of Medicine; 3Brain Korea 21, Yonsei Univ, Seoul, Korea; 4On Behalf of the Clinical Research Center for End Stage Renal Disease Investigators.

Background: Even though hyperlipidemia is a well-established risk factor for cardiovascular disease (CVD) in the general population, the association between abnormal lipid levels and CV disease in ESRD patients remains unclear. Recently, non-high-density lipoprotein cholesterol (NHDL-C) has been demonstrated as a risk factor for CV events in patients with combined dyslipidemia. In this study, we investigated the impact of NHDL-C on the clinical outcome in incident hemodialysis (HD) patients.

Methods: A prospective cohort of 867 incident HD patients from 36 centers of the CRF for ESRD in Korea was selected for this study. The subjects were divided into ‘high’ and ‘low’ groups based on the baseline NHDL-C concentrations (≥ 2 and <100mg/dL). Primary outcome was defined as a composite of all-cause mortality or CV events. Cox proportional hazard analysis was performed to determine the independent prognostic value of NHDL-C for the clinical outcome.

Results: The mean age was 57.6 years and 59.5% were male. During a median follow-up duration of 23 months, 53 patients (6.1%) died and CV events occurred in 78 patients (9.0%). The composite outcome was observed in 81 patients (15.1%) in the ‘high’ NHDL-C group compared to 35% in the ‘low’ NHDL-C group, but this difference did not reach statistical significance (P=0.06). However, after adjustment for demographic and clinical characteristics, and parameters related to inflammation and malnutrition, the risk for reaching the composite outcome was significantly higher in the ‘high’ NHDL-C group compared to the ‘low’ NHDL-C group (HR = 5.89; 95% CI = 1.03–2.44; P=0.038). In subgroup analyses, a significant association of NHDL-C with adverse clinical outcome was observed in patients with diabetes, patients without CV disease, and patients with increased high sensitivity C-reactive protein levels.

Conclusions: Serum NHDL-C at the time of HD commencement was a significant independent risk factor for adverse clinical outcomes in incident HD patients.

Funding: Government Support - Non-U.S.
SA-PO454

Association of Sleep Apnea and Sleep Quality with Left Ventricular Mass in Hypertensive Hemodialysis Patients in Blood Pressure in Dialysis (BID) – SLEEP Study

Manisha Jhamb,1 D. Miskulin,2 Jennifer J. Gassman,3 David W. Ploth,3 Brigitte Schiller,2 Raymond Y. Kwong,4 Cynthia A. Kendrick,4 Jose L. Vega,5 John W. Kusek,7 P. Zager,6,8 Mark L. Unruh.8

Background: Sleep apnea (SA) and short and fragmented sleep may contribute to cardiovascular morbidity and mortality in hemodialysis patients. The association between SA severity and LV mass in these patients is not well described.

Methods: Maintenance HD patients joined this ancillary SLEEP study after enrolling in the Blood Pressure in Dialysis (BID) Pilot, a randomized trial of two levels of BP control. SA was monitored for 1 night with a portable home monitor (ApneaLink with oximetry). Sleep-wake behavior was assessed by actigraphy over a 5-day period. Subjective sleep quality was assessed with Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale. LV mass was measured centrally by MRI.

Results: Currently 27 patients (52±13.3 yrs, 63% male, 41% AA) have completed baseline sleep study. 23 had SA (85%) and of those 9 had mod-severe SA (AHI ≥ 15). Actigraphy showed 13 (57%) of patients slept <6 hrs/night. Most had poor sleep efficiency (87%) and poor sleep quality (86% with PSQI score ≥ 5). Body mass index, systolic BP, diastolic BP, heart rate, number of antihypertensive medications, inter-dialytic weight gain, hemoglobin level, history of myocardial ischemia, and MRI characteristics did not differ between those with no-mild SA (AHI ≤ 15) as compared to those with mod-severe SA (AHI ≥ 15).

Conclusions: Sleep apnea and poor sleep quality were common among hypertensive HD patients we studied. Based on preliminary data we did not observe a relationship between severity of sleep apnea and LV mass.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc., Private Foundation Support

SA-PO455

Accelerated Atherosclerosis in Hemodialysis Patients; Correlation of Epicardial Fat Tissue Thickness with Coronary Artery Flow Reserve

Elif Ari Bakir,1 Beyza Macunluglu.2 Nephrology, Kartal Research and Training Hospital, Istanbul, Turkey; 2Nephrology, Uskudar State Hospital, Istanbul, Turkey.

Background: The aim of this study was to evaluate the relation between epicardial fat tissue (EFT) thickness and coronary artery flow reserve (CFR) in HD patients as an indicator of accelerated atherosclerosis.

Methods: Seventy-one chronic HD patients and 65 age and sex-matched healthy controls were included in the study. EFT thickness and CFR were assessed by transthoracic Doppler echocardiography.

Results: EFT thickness was higher (6.53±1.01 mm vs 5.79±1.06 mm, p=0.001); CFR was lower (1.73±0.11 vs 2.32±0.28, p<0.001) in HD patients compared to controls. There was a significant negative correlation between EFT thickness and CFR (r=−0.287, p<0.05).

Conclusions: Sleep apnea and poor sleep quality were common among hypertensive HD patients we studied. Based on preliminary data we did not observe a relationship between severity of sleep apnea and LV mass.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc., Private Foundation Support

SA-PO456

Antihypertensive Medication Regimens and Hospitalization Risk in Incident Hemodialysis (HD) Patients

Tariq Shah,1 Stephen M. Sozio,2 Wendy L. St. Peter,3 Karen J. Bandeen-roche,1 Patti Ephraim,1 Jason Luly,1 L. Ebony Boulware.3 Johns Hopkins Univ; 4Univ of Minnesota.

Background: Optimal strategies to reduce hospitalizations, a frequent occurrence in HD patients, are not known. We compared the effectiveness of different blood pressure medication (BPM) regimens on reducing hospitalizations in HD patients.

Methods: We performed a retrospective cohort study of all adult patients initiating HD at Dialysis Clinic, Inc. facilities from 2003-2008 and prescribed a BPM at 6 months. We linked their dialysis electronic medical records to USRDS data, and the National Death Index. We categorized BPM use as 4 mutually exclusive regimens: β-blockers (BB), renin-angiotensin system agents (RAS), BB+RAS or OTHER regimens not including BB or RAS. Patients with BPM discontinued during follow-up constituted the DC group. We used discrete time proportional hazards marginal structural models accounting for repeated events, confounding and mediation by numerous clinical and demographic factors including blood pressure and HD session volume removal to quantify the association between BPM regimen and hospitalizations [all cause and cardiovascular (CV)] censoring for death.

Results: Of the 11,291 patients, mean age was 62 years, 55% were male and 53% were White: 22,384 hospitalizations (7,070 from CV causes) occurred during follow-up (median, 22 months). Compared to BB, patients treated with a RAS had lower risk of hospitalizations, particularly among those with CV disease at baseline [HR 95%CI for all-cause: 0.92 (0.85-0.99); CV: 0.90 (0.80-1.01)]. DC group had lower risk of hospitalization but higher risk of death [1.5 (1.1-2.06)] compared with BB group.

Conclusions: Our data have demonstrated that HD patients exhibit increased EFT thickness and decreased CFR. To our knowledge this is the first study to demonstrate the inverse relationship between EFT thickness and CFR in HD patients.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO457

Prognosis of Dialysis Patients with Normal Stress Myocardial Perfusion Imaging at the Initiation of Dialysis: Long-Term Outcome and Predictors

Jwa-kyung Kim, Soo Jin Kim, Sun Ryoung Choi, Jong-woo Yoon, Jung-woo Noh, Sang Gyun Kim. Dept of Internal Medicine, Hallym Univ Sacred Heart Hospital, Kidney Research Institute, Gyunggi-do, Korea.

Background: Normal myocardial perfusion is closely associated with very low rates of cardiac events and better long-term outcomes in general population. However, little is known about its prognostic value in patients with end-stage renal disease (ESRD).

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc., Private Foundation Support

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

Underline represents presenting author/disclosure.

730A
SA-PO458

National Study of Acute Stroke in Patients on Renal Replacement Therapies

Alfred J. Power,1 Retha D. Steenkamp,2 James Fotheringham,1 Damian G. Fogarty,1 *Imperial College London, United Kingdom; †UK Renal Registry, Bristol, United Kingdom; ‡Sheffield Kidney Institute, United Kingdom.

Methods: We studied all patients incident to RRT in England [Jan 2002–Dec 2006] with follow up to Dec 2009 [n=21175, 62% male, 47% diabetic, 74% hemodialysis, 23% PD]. Demography & comorbidity at the start of RRT and hospitalization for first acute stroke were derived from ECD-10 codes in national Hospital Episode Statistic [HES] datasets linked to UK Renal Registry data.

Results: Overall 12% of the study cohort [n=2848] experienced first acute stroke [40% events prior to RRT start] compared to 2.3% in the general population. During RRT, 77% strokes occurred in hemodialysis (HD), 10% on PD & 4% in renal transplant patients.

Conclusions: Stroke affects a significant proportion of patients on all RRT modalities and remains over-represented in dialysis cohorts particularly HD. Current ongoing analyses of national patient- & treatment-level stroke risk factors will allow for interventions to reduce stroke burden in all RRT populations.

SA-PO459

Ventricular Diastolic Function before, during and after Hemodialisation

Israel Campo González, Sujail Estrada, Patricia Zarate Rojas, Magdalena Madero, Armando Vazquez-Rangel, Hector Perez Grovas.

Div of Nephrology/Echocardiography, National Heart Institute, Mexico City, Mexico.

Methods: Prospective study conducted between May-August 2011 in HDF patients. Tissue Doppler & 3D Echocardiography were captured pre, during & post-HDF. Dyssynchrony index and ADP parameters were measured and the change in measurements was evaluated at different time points.

Results: 11 patients were included, the median age was 34±12y and 72% were female. The mean HDF duration was 23±18min. Blood flow (BQ) was 442±37 mL/min, substitution volume was 17.4±1.2 L, weight gain was 2.63±0.58 Kg. Left ventricular ejection fraction was 52±0.3%, 51±0.2%, 51±0.5% for pre, during and post HDF(p<0.05). There were significant changes in diastolic function parameters at different time points.

### PHASE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-HDF</th>
<th>During-HDF</th>
<th>Post-HDF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV (mL)</td>
<td>93.1±14</td>
<td>87.1±12</td>
<td>97.3±12</td>
<td>0.001</td>
</tr>
<tr>
<td>LV stroke work (mJ)</td>
<td>115.2±37</td>
<td>124±35</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>LV filling pressure (mmHg)</td>
<td>0.9±0.4</td>
<td>0.8±0.3</td>
<td>0.227</td>
<td></td>
</tr>
</tbody>
</table>

### PHASE 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-HDF</th>
<th>During-HDF</th>
<th>Post-HDF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV (mL)</td>
<td>93.1±14</td>
<td>87.1±12</td>
<td>97.3±12</td>
<td>0.001</td>
</tr>
<tr>
<td>LV stroke work (mJ)</td>
<td>115.2±37</td>
<td>124±35</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>LV filling pressure (mmHg)</td>
<td>0.9±0.4</td>
<td>0.8±0.3</td>
<td>0.227</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Diastolic dysfunction occurred in 44% of the patients in the Pre-HDF phase and increased to 82% during & post HDF (p<0.05). Diastolic & systolic diameter, telesystolic, telediastolic and stroke volume(SV) had significant changes(p<0.001). There was significant correlation between SV & BQ (r=0.63, p<0.003) and SV & transmembrane pressure (r=0.94, p<0.001).

Conclusions: Diastolic dysfunction is prevalent in HDF patients but increases dramatically during & after HDF. In contrast, systolic function remains intact throughout. These findings may contribute to understand CV disease in HDF. Larger studies are needed to confirm our findings.

SA-PO460

Mean Platelet Volume as a Predictor for Coronary Artery Disease in Chronic Hemodialysis Patients


Methods: Mean platelet volume (MPV), as a marker of platelet activation, has been shown to be related to coronary artery disease and mortality after myocardial infarction. However, the effects of MPV on cardiovascular complication and vascular access failure in hemodialysis (HD) patients is not known.

Results: 180 chronic HD patients (age 59.1±12.1 years, male 47.8%, diabetes 53.9%, mean dialysis duration 48.3±51.0 months) were enrolled. After baseline evaluation, all patients were monitored continuously for the development of coronary artery disease, cerebrovascular disease, vascular access failure and death.

Conclusions: MPV was 9.14±0.78 fl (range 7.7 to 12.0). Patients were grouped according to half-tile values of MPV (>9.0fl, group 1 [n=98]; ≤9.0 fl, group 2 [n=89]). Patients with higher MPV had a higher level of platelet count (p<0.001) and a lower level of triglyceride (p<0.001). Vitamin D was total (p<0.03). During a follow-up period of median 127 weeks, 133 composite events (31 deaths, 33 coronary artery disease, 9 cerebral artery disease, and 60 vascular access thrombosis or stenosis) occurred. The Kaplan-Meier curve showed significant difference in the cumulative events of coronary artery disease between two groups (23.5% vs 12.3%; log-rank test, p<0.05).

Conclusion: While a significant minority of ESRD pts begin dialysis without prior nephrologic care and CKD is known to be associated with insulin resistance, A1c measurement is not routinely performed in ESRD pts without a history of DM. In a single center experience, we (Desiraju et al, ASN 2005) identified NDM ESRD pts maintained on HD with abnormal A1c>5.6%.

Methods: We explored the distribution of A1c in a national sample of 1454 NDM Pts from 26 FMCNA facilities distributed across the US. Relative blood from routine monthly draws was analyzed. We report on mean casual blood glucose and A1c in these pts for the period January-March 2013. Pts were classified as unclassified (Undx/c) if A1c<6.5% and pre-diabetic (PreDx) if A1c=5.6 but ≤6.5%.

Results: The A1c values were administered without DM diagnosis in 99% of pts. However, ~16% met pre-diabetic A1c range and are potentially at risk for increased future morbidity (Table). Pre-diabetic status was associated with age, male gender, shorter dialysis vintage, and peritoneal dialysis (PD) modality (all p<0.05). A1c≥5.6%, while race and ethnicity were similar. Undiagnosed DM was similarly associated with even shorter dialysis vintage and with use of PD.

### Table

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
<th>Mean A1c (%age)</th>
<th>Median</th>
<th>Mean glucose mg/dL</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undx/c</td>
<td>227</td>
<td>5.7±(3.5-6.4)</td>
<td>5.7</td>
<td>107±(88-123)</td>
<td>107</td>
</tr>
<tr>
<td>PreDx</td>
<td>119</td>
<td>5.8±(3.6-6.4)</td>
<td>5.8</td>
<td>116±(99-126)</td>
<td>116</td>
</tr>
<tr>
<td>ESRD</td>
<td>1199</td>
<td>5.2±(3.8-6.5)</td>
<td>5.2</td>
<td>102±(85-121)</td>
<td>102</td>
</tr>
</tbody>
</table>

Conclusions: While the absence of a diagnosis of DM was consistent with A1c values for most patients, physicians should be vigilant in detecting rare cases of undiagnosed DM. One in every 7 dialysis patients may be pre-diabetic and it is not clear if this finding is associated with worse outcomes. We will prospectively follow these patients to determine the prognostic significance of the pre-diabetic range of A1c.

SA-PO462

Impact of Nephrological Care on Dialysis Initiation and Survival

Laura Sola,1 Maria Carlota Gonzalez-Bedat,2 Alejandro Ferreiro. 21 Renal Healthcare Program, Montevideo, Uruguay; 2Uruguayan Registry of Dialysis, Montevideo, Uruguay.

Background: While significant improvement in dialysis technology, mortality rate (MR) in chronic dialysis (CD) patients (Pts) still remains extremely high. Late referral to nephrologist has been linked to higher morbidity and short term mortality. The objective of the study is to analyze the impact of predialysis nephrological care (PN) on selected clinical indicators and first year survival on CD.

Methods: Data from the Uruguayan Registry of Dialysis of Pts beginning CD between 11/1/2008-12/31/2011 were analyzed. PNC was assessed by stage 4 Pts included in the CKD Registry with follow-up ≥ 3 months. Quality of care indicators at CD initiation
Included: hemoglobin (Hb) ≥10 g/dL, fistula ≥60 days (FADV60) and hepatitis B (HB) immunization. Initial CD modality was assessed. Hospitalization time at CD initiation and first year survival were compared regarding PNC, including PNC time and number of visits. Logistic regression analysis age, gender and diabetes adjusted was performed for hospitalization <5 days and Cox regression analysis for MR risk factors. Significant differences were considered as p<0.05.

Results: Of 1666 Pts that began CD, 194 (11.6%) had PNC. Pts with PNC had older age (mean 66.1 ± 60.5 years) and were more commonly women (49.5% vs 40.1%) than those without PNC. PNC was significantly associated to higher Hb (61.0 vs 61.5%), HB immunization (54.6 vs 23.1%), and FADV60 (34.6 vs 17.3%), but not to PTD choice (149.3 vs 9.8%). Hospitalization time was significantly lower in PNC Pts (8.5 ± 14.5 vs 15.6 ± 20.2 days) and didn't differ with PNC duration or number of visits. Less hospitalization was associated to PNC and Hb ≥10g/dL. First year survival was higher in Pts with PNC (Kaplan Meier). Adjusted to age, gender and diabetes, PNC reduced 34.8% mortality risk. Adjusted to FADV60, PNC didn't significantly improved survival.

Conclusions: Pts with PNC had better quality of care indicators, lower initial hospitalization time CD and of most importance greater first year survival allowing timely fistula confection. Our study emphasizes the importance predialysis care in order to reduce costs and improve outcomes.

SA-PO463

Serum Phosphorus Is Associated with Ankle-Brachial Index in Maintenance Hemodialysis Patients: A Different Reference Range? Ziyong Tang, Yue Wang, Ning Zhang, Haijiejie Ge, Xinhong Loo. Renal Div; Peking Univ Third Hospital, Beijing, China.

Background: Abnormally low ankle-brachial index (ABI) values (ABI<0.9) and high ABI (ABI>1.3) are associated with high cardiovascular morbidity and mortality in maintenance hemodialysis (MHD) patients. This study is aimed to assess the relationship of serum phosphorus level with ABI in MHD patients.

Methods: A total of 89 MHD patients were included in this retrospective study. ABIs were measured using an ABI-form device. The patients’ serum phosphorus in the past 6 months were recorded. Other clinical and laboratory data were also collected.

Results: The mean of past six months’ serum phosphorus levels in this group ranging from 2.45mg/dl to 12.34mg/dl, with the median 6.36 mg/dl. As normal homeostasis doesn’t reach significantly different of low ABI among the levels (p=0.020), but the difference of high ABI among the levels (p=0.406).

Conclusions: In MHD patients, low ABI is prevalent in the phosphorus level lower than 4.5mg/dL, and high ABI is prevalent in the phosphorus level higher than 6.5mg/dL. The reference range of serum phosphorus level in MHD patients may be different from that of general population.

Funding: Government Support - Non-U.S.
Methods: Patients enrolled in the NHD training program at a single tertiary care centre were invited to participate in the study between 2009-2011 inclusive. Eligible patients had a life expectancy greater than 12 months and had no reliable expectation of receiving a kidney transplant within 12 months. Participants underwent TTE and CMR at baseline and after one year of NHD. Data regarding blood pressure, mineral metabolism and degree of anemia were also collected and analyzed.

Results: A total of 11 patients were included in the study (6 male, mean age 48±16 years). Left ventricular mass index (LVMI) decreased significantly at one year by both TTE (152.7±129.8 g/m², p<0.05) and CMR (162±142.4 g/m², p<0.05). There were also significant reductions in left and right atrial volume as well as right ventricular mass index. Diastolic dysfunction, graded from 0 to 4, improved from a baseline of 2.8±1.2 to 1.0±0.4 at one year follow-up. There was no significant effect of NHD on blood pressure, mineral metabolism, or degree of anemia.

Conclusions: Long-term nocturnal hemodialysis leads to favorable cardiovascular remodeling with a reduction in cavity dimensions, regression of LVH, and improved diastolic function as assessed by both TTE and CMR.

SA-PO469

Improvement in Left Ventricular Hypertrophy and Diastolic Dysfunction in Patients on Nocturnal Home Hemodialysis as Assessed by Echocardiography and Cardiac Magnetic Resonance Imaging

Background: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Left ventricular hypertrophy (LVH) is present in more than 70% of ESRD patients and is an independent risk factor for cardiac death in this patient population. Nocturnal home hemodialysis (NHD) is a form of renal replacement therapy whereby hemodialysis is performed for six hours overnight at least four days per week. NHD has several benefits over conventional hemodialysis (CHD) including improved blood pressure control, mineral metabolism, and degree of anemia. Limited studies are conflicting however, about the effects of NHD on cardiovascular remodeling as assessed by transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (CMR).

Methods: Patients with elevated Ca125 (n=40) had significantly lower albumin, RWT, LVEF, FS while B-type natriuretic peptide levels, LTFD, LVEF were significantly higher. Correlation analysis showed that CA 125 was positively related prolNIP(r=0.596, P < 0.05), CrP (r=0.439, P < 0.05), LVDd(r=0.599, P < 0.001), LVEF(r=0.750, P < 0.001), LVMi(r=0.378, P < 0.05). But serum Ca 125 levels were negatively correlated with Hb (r=0.513, P < 0.05), hemoglobin (r=0.475, P < 0.05), HDL(r=-0.336, P < 0.05), EF (r=-0.878, P < 0.0001). Presence of depressed ejection fraction (8<1.121, p<0.0001) and increased CRP levels (8<0.247, p<0.035) were independent predictor of high Ca125 levels in whole group in multivariate-model.

Conclusions: Our study demonstrated an association between Ca125 and LV systolic dysfunction in patients with ESRD treated with HD. We conclude that Ca125 appears to be useful in establishing the presence of systolic heart dysfunction in HD patients.

SA-PO468

Relationship between Serum Cancer Antigen 125 (Ca125) and Left Ventricular (LV) Function in Patients on Maintenance Hemodialysis

Background: The aim of the study was to analyze associations between serum Ca125 levels and LV function in patients on maintenance hemodialysis.

Methods: The study group included 110 patients (54 women, 56 men) aged 65.2±15.7 years, 47.9% diabetic, dialysing with calcium concentrations of 1.0, 1.25, 1.35 and 1.40 mmol/l (9.64±1.94 vs 10.45±1.98 mmol/l, p<0.002) and 1.35 mmol/l (9.75±1.96 vs 10.21±2.18 mmol/l, p=0.02).

Conclusions: Our study demonstrated an association between Ca125 and LV systolic dysfunction in patients with ESRD treated with HD. We conclude that Ca125 appears to be useful in establishing the presence of systolic heart dysfunction in HD patients.
Conclusions: The increase in pulse wave velocity observed over time with the lowest calcium dialysate group suggests that factors other than the dialysate calcium balance determined by the dialysate calcium concentration, may be more important in promoting vascular stiffness in hemodialysis patients.

SA-PO470
Relation between Diastolic Dysfunction, Physical Function and Body Composition in Hemodialysis Patients
Jim Hee Jeong1, Pei-tzu Wu1, Peter J. Fitschen2, Brandon Kistler1, Hae Ryong Chung1, Annabel Biruete1, Ken Wilund1, Mohamed Ali1, Bo Fernhall1, Shane Phillips2.

Background: Cardiovascular (CV) complications are the main cause of death in hemodialysis (HD) patients. Although metrics related to left ventricular systolic dysfunction (LVSD) such as ejection fraction (EF) are commonly used to predict adverse CV outcomes, LV diastolic dysfunction (LVDD) measures provide better diagnostic values in HD patients because they are less sensitive to blood volume changes. Additionally, muscle wasting and declines in physical function are common in HD patients. This can result from abnormalities in cardiac function, which can be further worsened by physical deconditioning. Little is known about the relationship between cardiac function and physical function in HD patients. Aim: To evaluate the prevalence of LVDD and to assess its relationship to physical function and body composition in HD patients.

Methods: Walking performance, leg strength, and whole body lean mass (WBLM) by DXA were measured in 83 HD patients (age=52.9±11y). Echo was used to assess LVDD classiﬁed by LVDD classiﬁcation (E/A<0.8, E'<8cm/s, E/E'<8, and DT<200ms) and 2) advanced DD (E/A>0.8, E'<8, E/E'<8, and DT<200ms). BMI was signiﬁcantly higher in patients with LVDD (p=0.017). After adjusting for age, gait speed, right leg peak strength, and WBLM% were signiﬁcantly higher in the group without LVDD than with LVDD (p=0.006, 0.001 and 0.007, respectively). However, there was no signiﬁcant difference in any measure of physical function or body composition between patients with and without LVSD.

Conclusions: This data indicates that LVDD is more closely related to physical function and body composition than LVSD in HD patients, and suggests that LVDD may be an important therapeutic target.

Funding: NIDDK Support

SA-PO471
Bradycardia as a Cause of Hypotensive Episodes during Routine Hemodialysis
D. Miskulin1, Klemens B. Meyer1, John E. Moran2,3,4.'Nephrology, Tufts Medical Center, Boston, MA; 1Intelemed, Inc, Pittsburgh, PA; 2Nephrology, Stanford Univ School of Medicine, Stanford, CA.

Background: Patients on maintenance hemodialysis (HD) have a high cardiovascular (CV) mortality and often suffer CV events such as hypotension during HD. One calculation of CV stress is the appearance of arrhythmias which may be associated with hypotension.

Methods: 25 patients with a history of frequent hypotensive episodes during routine HD were monitored during 4 HD treatments using the CV Insight device (Intelemed, Inc), which captures and processes the signal from a standard pulse oximeter (Nonin Medical, Inc) to provide real-time display of CV status based on rate of change of pulse rate and of pulse amplitude. Bradycardia was defined as a 15% decrease in pulse rate during treatment.

Results: 8 patients experienced 18 episodes of bradycardia during the study; 3 patients had episodes in all 4 HD treatments studied, 1 patient experienced 2 episodes, and 4 patients 1 episode. 15/18 episodes (83%) were associated with a defined CV event requiring intervention; in 2 of the other 3 episodes the systolic BP fell by more than 60 mm Hg. Four of the 8 patients were receiving beta blocker therapy. In 7 patients the fall in pulse rate was gradual over the course of treatment; in 1 patient there was an abrupt fall in all 4 treatments which was preceded by a fall in BP.

Conclusions: Some HD patients have an inappropriate fall in pulse rate during HD treatment, not necessarily related to beta blockade. Real-time monitoring will allow recognition of such events and facilitate intervention.

Funding: Pharmaceutical Company Support - Intelemed, Inc

SA-PO472
Mortality Rates among Prevalent Hemodialysis Patients in Turkey: A Comparison with USRD Data
Gulay Ass1, Daniele Marcelli2, Aygül Cetlik1, Aileen Grassmann3, Mustafa Yaprak1, Abdulkermi Furkan Tamer1, Mehmet Nuri Turan1, Mehmet S. Sever2, Ercan Ok1, 1Nephrology, Ege Univ, Turkey; 2Fresenius Medical Care, Germany; 3Nephrology, Istanbul Univ, Turkey.

Background: There are significant differences between countries in mortality rates of hemodialysis patients (HD). We compared mortality rates in Turkey and the US and analyzed potentially related differences in patient-treatment characteristics.

Methods: All patients undergoing HD or hemodiafiltration in March 2009 for >3 months(n=4041) in the Turkish clinics of the NephroCare network were enrolled. Data were prospectively collected for 2 years through the database EutClID. Mean age was 58.7±14.7 years, 45.9% female, 22.9% diabetic. Comparison with US data was performed by applying indirect standardization technique, using as reference specific mortality rates for patients on HD by age, gender, race and primary diagnosis as provided by the 2012 USRDS Annual Data Report.

Results: Crude mortality rate was 9.5 per 100 pt-yrs. Comparison of specific unadjusted mortality rates(per 1000 pt-yrs) of Turkish Patients with US whites is reported in table.

The mortality advantage for Turkish patients was present in all subgroups. Standardized mortality rate of Turkish cohort was 0.50 (95%CI 0.46-0.54, p=0.001) compared to US. The differences in treatment characteristics between two populations are given in figure.

Conclusions: Annual mortality rate is significantly lower in Turkish cohort than US HD patients. Higher use of AV fistula, longer treatment time, better volume control and hemodiafiltration treatment are possible contributing factors.

Funding: 1Nephrology, Ege Univ, Turkey; 2Fresenius Medical Care, Germany; 3Nephrology, Istanbul Univ, Turkey.

SA-PO473
Acute Effects of Isolated Ultrafiltration and Isolated Dialysis on Myocardial Perfusion and Function Assessed by Intra-Treatment Positron Emission Tomography (PET)
Jolives Assa1, Johanna J. Kuipers2, Esmee M. Ettema2,1, Judith J. Dasselaar1, Yoran M. Hummel2,3, Adrian A. Voors2, Paul E. de Jong2, Ralf Westerhuis2, Rene A. Tio2, Riemer Hja Start1, Casper P.M. Franssen1,1Nephrology; 2DCG; 3Cardiology; Nuclear Medicine, UMCN, Netherlands.

Background: Previous studies showed that hemodialysis with combined dialysis and ultrafiltration (UF-only) and dialysis (dialysis-only) on myocardial perfusion and development of regional left ventricular (LV) systolic dysfunction. We studied the effect of isolated ultrafiltration (UF-only) and dialysis (dialysis-only) on myocardial perfusion and function.

Methods: 8 patients (7 male, 55±18 years) underwent 1h UF-only (UF-rate 11h) and dialysis-only (zero fluid balance). Myocardial perfusion and LV ejection fraction (EF) were assessed by 123I-NIH, PET before and during the last 15 min of treatment. Regional LV systolic function was assessed by echocardiography.

Results: Blood pressure, heart rate and body temperature were comparable during treatments. Global myocardial perfusion did not change during UF-only and dialysis-only, however, during dialysis-only a non-significantly greater number of LV segments showed a 1 segment improvement in perfusion compared with UF-only (7.9%±5.3 vs 5.0±5.1). LVET rose during UF-only (p=0.06) and did not change during dialysis-only. Two patients developed regional LV hypokinesia only during isolated dialysis (3 segments in both); 1 other patient developed regional LV hypokinesia during both UF-only and dialysis-only (in 4 and 2 segments, respectively).

Conclusions: Annual mortality rate is significantly lower in Turkish cohort than US HD patients. Higher use of AV fistula, longer treatment time, better volume control and hemodiafiltration treatment are possible contributing factors.
In addition, whether sodium setpoint can be altered prospectively will be determined. Personalization of dialysate sodium alters the stability of the sodium setpoint. Be compared between each three month period and 2. Sodium setpoint, to determine if 17, 2013. Results will be considered in two categories: 1. Clinical outcomes, which will sodium slope and difference across each 3 month interval.

The most recently recorded pre-dialysis sodium setpoint. Clinical outcomes were compared with dialysate sodium concentration that was 3 mmol/L above then below (or vice versa) frequency and duration. Each patient was treated with two consecutive three month periods program were included in a randomized crossover design. Patients differed in dialysis arterial disease requiring medical or surgical intervention.

In this group, 72% were African Americans, 24% Hispanics, and 4% were end stage renal disease (ESRD). Although arterial stiffness is now recognized as an independent predictor of cardiovascular mortality in ESRD, there are no data on arterial stiffness in minorities with ESRD and its impact on cardiovascular outcomes.

Background: Personalized dialysate sodium alters blood pressure, interdialytic weight gain, and perhaps mortality. We have previously shown that the Post- to Pre-dialysis sodium gradient (PPNa+) predicts clinical outcomes in home hemodialysis population. Moreover, modifiable factors affecting interdialytic weight gain in this population include dialysis duration and frequency, and dialysate sodium concentration, while patient age, sex and pre-dialysis serum albumin also have a role. Our objectives were to validate prospectively our equation for predicting interdialytic weight gain, and to confirm our retrospective data that pre-dialysis sodium setpoint is modifiable.

Method: All patients in the Southwestern Ontario regional home hemodialysis program were included in a randomized crossover design. Patients differed in dialysis frequency and duration. Each patient was treated with two consecutive three month periods with dialysate sodium concentration that was 3 mmol/L above then below (or vice versa) the most recently recorded pre-dialysis sodium setpoint. Clinical outcomes were compared between each three month interval. Clinical outcomes considered included pre-dialysis systolic and diastolic blood pressure (mm Hg), interdialytic weight gain (Liters). We also evaluated the stability of the pre-dialysis sodium setpoint by comparing the pre-dialysis sodium slope and difference across each 3 month interval.

Results: Data for this trial will be collected and analyzed completely by October 17, 2013. Results will be considered in two categories: 1. Clinical outcomes, which will be compared between each three month period and 2. Sodium setpoint, to determine if personalization of dialysate sodium alters the stability of the sodium setpoint.

Conclusions: The results of this trial will determine if and how dialysate sodium should be chosen in hemodialysis patients with increased dialysis frequency or duration. In addition, whether sodium setpoint can be altered prospectively will be determined.

Funding: Government Support - Non-U.S.

SA-PO475

Arterial Stiffness and Cardiovascular Outcomes in Minorities with End Stage Renal Disease  Kalvani Perumal, 1 Peter D. Hart, 1 James P. Lash. 2 1Nephrology, John H Stroger Hospital, Chicago, IL; 2Nephrology, Univ of Illinois at Chicago, Chicago, IL.

Background: Cardiovascular disease is the leading cause of mortality in patients with end stage renal disease (ESRD). Although arterial stiffness is now recognized as an independent predictor of cardiovascular mortality in ESRD, there are no data on arterial stiffness in minorities with ESRD and its impact on cardiovascular outcomes.

Methods: We therefore conducted a prospective study to investigate the measures of arterial stiffness (pulse wave velocity, PWV) and reflected wave (augmentation index, Aix) in a predominately minority cohort of 77 patients on hemodialysis and its effect on composite outcome - cardiovascular event or all-cause mortality. PWV and Aix were determined from arterial waveforms recorded by SphygmoCor® device. 80% of measurements were taken prior to dialysis sessions. Cardiovascular events were defined as new onset myocardial infarction, congestive heart failure, arrhythmia, acute cerebrovascular event, peripheral arterial disease requiring medical or surgical intervention.

Results: In this group, 72% were African Americans, 24% Hispanics, and 4% were non-Hispanic whites. Mean age was 55 yrs, 61% were male. Major causes of ESRD were diabetes (58 %) and hypertension was present in 91 %. Mean duration of dialysis was 41 mos. Mean PWV was 11 m/s and mean Aix was 24% in this cohort. All patients were followed for a mean of 36 mos. A total of 4 fatal and 24 non-fatal cardiovascular events occurred in 19 patients. In multivariate regression analysis, age and diabetes were identified as significant predictors of PWV (p < 0.05). In multivariate Cox analysis, after adjustment of confounding factors, the risk ratio for each 10% increase in PWV was 1.12 (CI 1.00- 1.23, p<0.05) for composite outcomes. Survival analysis showed that the group in lower tertile of PWV (PWV< 12 m/s) had a mean survival event free survival when compared to the group in upper tertile (PWV> 12 m/s) (p < 0.01).

Conclusions: Thus, our study provides the first direct evidence that PWV is a significant predictor of cardiovascular morbidity and mortality in the minority population on hemodialysis.
SA-PO478
Stroke and the “Stroke Belt” in Dialysis: Contribution of Patient Characteristics to Ischemic Stroke Rate and Its Geographic Variation
James B. Wetmore,1 Edward F. Ellerbeck,2 Jonathan D. Mahnken,2 Milind A. Phadnis,3 Sally K. Rigler,2 John Spertus,4 Purna Mukhopadhyay,2 Theresa I. Shireman,1,2 Medicine, Div of Nephrology, Hennepin County Medical Center, Minneapolis, MN; 3Biostatistics, Univ of Kansas Medical Center, Kansas City, KS; 4Preventive Medicine and Public Health, Univ of Kansas Medical Center, Kansas City, KS.

Background: Geographic variation in stroke rates is well-established in the general population, with higher rates in the south than in other areas of the U.S. End-stage renal disease (ESRD) is a potent risk factor for stroke, but whether regional variations in stroke risk exist among dialysis patients is unknown.

Methods: Medicare claims from 2000-05 were used to ascertain ischemic stroke events in a large cohort of incident dialysis patients. A Poisson generalized linear mixed model was generated to determine factors associated with stroke and to ascertain state-by-state geographic variability in stroke rates by generating observed-to-expected (O/E) adjusted rates for stroke.

Results: A total of 265,685 Medicare-eligible incident dialysis patients were studied. Older age, female sex, African-American race and Hispanic ethnicity, unemployed status, diabetes, hypertension, history of a previous stroke, and permanent atrial fibrillation were all significantly associated with ischemic stroke, while body mass index > 30 kg/m2 had an inverse association with stroke (P < 0.0001 for each). After full multivariable adjustment, the 3 states with O/E rate ratios > 1.0 were all in the south: North Carolina, Mississippi, and Oklahoma.

Conclusions: Regional efforts to increase primary prevention in the “stroke belt,” or to better educate dialysis patients on the signs of stroke so that they may promptly seek care, may improve stroke care and outcomes in dialysis patients.

Funding: NIDDK Support, Private Foundation Support

SA-PO479
Race and Ethnicity Largely Account for State-by-State Geographic Variation in Hemorrhagic Stroke in Dialysis Patients
James B. Wetmore,1 Milind A. Phadnis,3 Jonathan D. Mahnken,2 Edward F. Ellerbeck,2 Sally K. Rigler,2 Theresa I. Shireman,1 Medicine, Div of Nephrology, Hennepin County Medical Center, Minneapolis, MN; 3Biostatistics, Univ of Kansas Medical Center, Kansas City, KS.

Background: Geographic variation in stroke rates is well-established in the general population, with higher rates in the south than in other areas of the U.S. A similar pattern of geographic variation in ischemic strokes has also recently been reported in chronic dialysis population, with higher rates in the south than in other areas of the U.S. A similar pattern of geographic variation in ischemic strokes has also recently been reported in chronic dialysis population, with higher rates in the south than in other areas of the U.S.

Methods: Medicare claims from 2000-05 were used to ascertain ischemic stroke events in a large cohort of incident dialysis patients. A Poisson generalized linear mixed model was generated to determine factors associated with stroke and to ascertain state-by-state geographic variability in stroke rates by generating observed-to-expected (O/E) adjusted rates for stroke.

Results: A total of 265,685 Medicare-eligible incident dialysis patients were studied. Older age, female sex, African-American race and Hispanic ethnicity, unemployed status, diabetes, hypertension, history of a previous stroke, and permanent atrial fibrillation were all significantly associated with ischemic stroke, while body mass index > 30 kg/m2 had an inverse association with stroke (P < 0.0001 for each). After full multivariable adjustment, the 3 states with O/E rate ratios > 1.0 were all in the south: North Carolina, Mississippi, and Oklahoma.

Conclusions: Regional efforts to increase primary prevention in the “stroke belt,” or to better educate dialysis patients on the signs of stroke so that they may promptly seek care, may improve stroke care and outcomes in dialysis patients.

Funding: NIDDK Support, Private Foundation Support

SA-PO481
Fibroblast Growth Factor 23 and the Risk of All-Cause Mortality and Cardiac Hospitalizations and Death in Hemodialysis Patients: Results from the HEMO Study
Kristen L. Jablonski,1 Jessica B. Kendrick,1 Alfred K. Cheung,2 Tom Greene,3 Michel Chonchol,3 1Univ of Colorado Denver, Aurora, CO; 2VASLCHS, Salt Lake City, UT; 3Univ of Utah, Salt Lake City, UT.

Background: Elevated serum levels of fibroblast growth factor 23 (FGF23), have been associated with adverse outcomes in patients requiring long-term dialysis therapy. Although the values of FGF23 often evolve over time, no study has examined the accumulated effects on important clinical end points.

Methods: The HEMO Study was a randomized multicenter study evaluating the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Serum intact FGF23 levels were measured in stored serum samples obtained at baseline and at 12 months in 1,340 patients in this cohort. Quartiles of FGF23 concentrations were chosen as the primary predictor variable, with the lowest quartile serving as the reference category. Time-dependent Cox proportional-hazards models were used to examine the association between FGF23 levels with all-cause mortality (ACM) and a composite of first cardiovascular hospitalization or death.

Results: Participants had a mean age of 57±14 years, 55% were females and 46% were white. During a median follow-up of 3.0 years, 582 (43%) died from any cause, and 514 (41%) had a cardiac event. Median (IQR) serum FGF23 level was 3118 [72, 12928] pg/mL. Overall, median levels of FGF23 rose during follow-up (p<0.01). After adjustment for potential confounders available in the database, including inflammatory markers and usage of calcitriol, the highest quartile of FGF23 was associated with an increase in risk of ACM (HR, 1.51; 95% CI 1.05-2.15; p=0.02) and cardiac events (HR, 1.51; 95% CI 1.07-2.13; p<0.02) when compared to the lowest quartile. Similarly, when FGF23 was evaluated as a continuous variable, higher levels of FGF23 were associated with an increased risk of ACM and cardiac outcomes (HR, 1.10; 95% CI 1.01-1.13 per doubling of FGF23; p<0.01).

Conclusions: In the HEMO study, higher serum FGF23 levels were independently associated with all-cause mortality and cardiac hospitalizations and death in time-dependent Cox regression models.

Funding: NIDDK Support

SA-PO482
Interaldiabetic Weight Gain Is an Independent Risk Factor for All-Cause Mortality and Cardiovascular Events in Incident Hemodialysis Patients
Hye-Young Kang,1 Shin-Wook Kang,2,3 Mi Jung Lee,2 Chan Ho Kim,3 Hyung Jung Oh,2 Seung Hyok Han,2 Tae-Hyun Yoo,2 1Department of Internal Medicine, College of Medicine, Yonsei Univ, Seoul, Korea; 2On Behalf of the Clinical Research Center for ESRD in Korea was selected for this study. The cohort consisted of 1,013 incident HD patients from 36 dialysis centers of the Clinical Research Center for ESRD in Korea was selected for this study. The percentage of IDWG (IDWG%) was expressed as a ratio of absolute IDWG to dry weight, and thus it is associated with unfavorable clinical outcome. Meanwhile, the amount of food intake also contributes to IDWG, which can reflect nutritional status. Such a paradoxical meaning of IDWG requires further investigation, particularly in terms of its prognostic value for adverse clinical outcomes.

Methods: A prospective cohort of 1,013 incident HD patients from 36 dialysis centers of the Clinical Research Center for ESRD in Korea was selected for this study. The percentage of IDWG (IDWG%) was expressed as a ratio of absolute IDWG to dry weight, and thus it is associated with unfavorable clinical outcome. Meanwhile, the amount of food intake also contributes to IDWG, which can reflect nutritional status. Such a paradoxical meaning of IDWG requires further investigation, particularly in terms of its prognostic value for adverse clinical outcomes.

Results: The mean IDWG% was 2.7±1.8%. During a mean follow-up duration of 18.7 months, 84 patients died and 99 cardiovascular events occurred. Compared to patients with IDWG% of 1.0-1.9, the adjusted hazard ratios (HRs) of IDWG% <1.0, 2.0-2.9, 3.0-3.9, and ≥4.0 groups were 1.30 [95% confidence interval (CI), 0.73-2.31; p=0.37], 1.37 [95% CI 0.78-2.42; p=0.27], 1.91 [95% CI 1.10-3.33; p=0.02], and 1.81 [95% CI 1.04-3.16; p=0.03], respectively. In addition, sensitivity analysis revealed that a significant impact of IDWG% for primary outcome, a composite of all-cause mortality or cardiovascular events.

Conclusions: High IDWG% (≥3.0) was a significant independent predictor of all-cause mortality and cardiovascular events in incident HD patients.

Funding: Government Support - Non-U.S.
SA-PO483

Atrial Natriuretic Peptide Prophylaxis Does Not Improve Short-Term Survival or Contrast-Induced Nephropathy: A Meta-Analysis

Sayyad F. Kyazimzade,1 Daniel M. Pearlman,1 Vinay Rao,1 Alex L. Yerukhimov,2 Jeremiah R. Brown.1 1The Dartmouth Institute for Health Policy and Clinical Practice at the Geisel School of Medicine, Lebanon, NH; 2Dartmouth College, Hanover, NH.

Background: Atrial natriuretic peptide (ANP) has been shown to improve renal function in individual randomized controlled trials (RCTs). Yet, other studies have not replicated this finding. To determine the true effect of ANP, we performed a systematic review of existing studies that assessed renal function and/or its relationship to patient survival. We hypothesized that prophyllactic administration of ANP would improve the risk of contrast-induced nephropathy (CIN) and 21-day dialysys-free survival.

Methods: We conducted a meta-analysis of published RCTs involving prophyllactic administration or treatment with ANP in participants who had renal failure. Eligible studies reported the number of participants experiencing 21-day dialysis-free survival or CIN among the total number of study participants. Our search identified 71 records, of which 5 RCTs, including 1288 patients, met our pre-specified eligibility criteria. We calculated random-effects summary estimate odds ratios (OR) and 95% confidence intervals (CI) for the CIN and 21-day dialysis-free survival, and for the 2 trials that reported ANP occurrence.

Results: Pooled analyses revealed a nonsignificant difference in the odds of CIN occurrence among participants receiving ANP relative to those receiving placebo (1.13% vs. 12.3%; OR: 0.77; 95% CI: 0.30–2.02). Odds of 21-day dialysis-free survival in pooled ANP versus placebo study arms were also nonsignificant (9.2% vs. 14.3%; OR: 0.62; 95% CI: 0.34–1.11).

Conclusions: Existing trials show a nonsignificant improvement in the odds of both CIN and 21-day dialysis-free survival following prophylactic administration and treatment with ANP.

SA-PO484

Muscle and Fat Mass and Their Relationship to Survival in Hemodialysis Patients

Stephan Thijsen, Nathan W. Levin, Peter Kotanko. Renal Research Institute, New York, NY.

Background: Mortality among dialysis patients is strongly associated with anthropometric measures, such as body mass index (BMI) and lean body mass, estimated as the volume of distribution of urea. In contrast to the general population, in dialysis patients a high body mass index is associated with improved survival. We have previously developed a set of regression equations for estimation of subcutaneous adipose tissue (SAT) mass and muscle mass (MM) in African-American hemodialysis (HD) patients (Thijsen, WCN 2007; R² ranging from 0.85 to 0.98). In this study, we applied these equations to elucidate the relationship between body composition and survival.

Methods: SAT and MM were estimated at baseline in 1,598 incident African-American HD patients who started HD between 1/1/2000 and 12/31/2010. For the purpose of run-in stability, only patients who survived for at least 120 days were analyzed. Crude time to death was compared between tertiles of fat and muscle mass by Kaplan-Meier analysis and log-rank test for consecutive 2-year segments up to 6 years after start of HD.

Results: There was a significant relationship between tertiles of SAT and mortality, with better survival in patients with greater SAT. The association was lost after the first 2 years on HD (Figure, top 3 plots). Similarly, greater MM was associated with significantly better survival, but this relationship was retained for the first 4 years on HD and only then disappeared (Figure, bottom 3 plots).

Conclusions: SAT and MM are significantly related to survival in HD patients, and it appears that the improved survival related to greater MM can be traced substantially longer than that related to SAT. Future studies dealing with the relationship between body composition and outcomes in HD patients should focus on individual components of body composition (like fat and muscle mass) rather than vague surrogates such as BMI.

Funding: Pharmaceutical Company Support - Renal Research Institute

SA-PO485

Opioid Analgesic Use among Dialysis Patients

Eric D. Weinhandl,1 Akcem Yusuf,1 Yi Peng,1 Wendy L. St. Peter.1,2 1USRDs Coordinating Center, MMRF, Minneapolis, MN; 2Univ of Minnesota, Minneapolis, MN.

Background: Pain is a common and potentially debilitating symptom among dialysis patients. Although opioid analgesics are frequently prescribed in the United States, there are relatively few data regarding use among dialysis patients. We used Medicare Part D data to describe utilization of opioid analgesics (OAs) among adult dialysis patients between 2007 and 2011.

Methods: For year 1, included patients initiated dialysis no later than March 31 of year Y-1; received dialysis and carried Medicare Parts A and B as primary payer from June 1 to December 31 of year Y-1; and carried Part D coverage from January 1 of year Y to the earliest of kidney transplant, death, or December 31 of year Y. Patients were categorized as having received the low-income subsidy (LIS) or not having received the subsidy (non-LIS).

Results: Between 2007 and 2011, the percentage of patients with ≥1 OA fill ranged from 60.8% to 62.2%, while the percentage of patients with ≥2 fills increased from 21.7% to 24.3%. Among users, cumulative OA supply increased from 108 days per patient-year in 2007 to 130 days in 2011. In 2011, most widely prescribed OAs were hydrocodone/acetaminophen (APAP) (42.1%), oxycodone/APAP (17.9%), tramadol (13.5%), codeine/APAP (7.1%), and oxycodone (6.1%). Other agents with use in >1% of patients were fentanyl, hydromorphone, morphine, and tramadol/APAP. Use of propoxyphene was negligible, following withdrawal of branded formulations in November 2010. The prevalence of patients with ≥6 OA fills was relatively high with age <65 years, Native American race, and polycystic kidney disease as primary cause of end stage renal disease; and relatively low with Asian race and peritoneal dialysis. Furthermore, 27.1% of LIS versus 15.0% of non-LIS patients had ≥6 OA fills.

Conclusions: Opioid analgesic use is widespread among dialysis patients, exceeding estimates of 5% to 36% in a recent systematic review (CJASN, 6:326-333). Among users, the duration of use is increasing. Hydrocodone and oxycodone, each in combination with acetaminophen, are most commonly prescribed. Studies investigating the potential for opioid analgesic overuse and the relative safety of opioid analgesics in dialysis patients are needed.

Funding: NIDDK Support

SA-PO486

Widespread Opioid Use in the U.S. End-Stage Renal Disease Population

Anne Mobley Butler,1 Abhijit V. Khirsarag,2 M. Alan Brookhart.1 1Dept of Epidemiology, Univ of North Carolina at Chapel Hill; 2UNC Kidney Center, Univ of North Carolina at Chapel Hill.

Background: Almost half of patients with end-stage renal disease (ESRD) report chronic pain, and over three-quarters rate it moderate to severe. The etiology of the pain is multifactorial, often related to comorbidities, renal osteodystrophy, and complications of the dialysis procedure. Because non-steroidal anti-inflammatory drugs have adverse effects on renal function, opioids may be perceived as the preferred analgesic agents in this population. We sought to quantify the magnitude of opioid use among U.S. ESRD patients.
Methods: Using data from the United States Renal Data System (USRDS), a national registry of patients in the Medicare ESRD program, we identified patients ≥ 18 years receiving dialysis on January 1, 2008 represents both A, B, and D coverage. Information on opioid use was ascertained from Medicare part D claims. We calculated the proportion of patients receiving opioid prescriptions. Patients were censored at: end of continuous enrollment in Medicare Parts A, B, and D; loss-to-follow-up; kidney transplantation; death; and end of study on June 30, 2008.

Results: During the 6-month study period, there were 335,888 opioid prescriptions. Of 156,476 eligible dialysis patients, 77,697 (50%) patients used an opioid. Hydrocodone, oxycodone, and propoxyphene were prescribed to 30%, 14%, and 10% of the study population, respectively. The study population was predominantly aged (mean age 66 years), 52% male, 50% white, 43% black, and 8% low income subsidy status. Opioid use was higher among patients of younger age, female gender, black or white race, and without low income subsidy status. Opioid use varied by primary cause of ESRD, years on dialysis, and dialysis modality. In a separate analysis with similar eligibility criteria, quarterly opioid use increased slightly from quarter 3 of 2006 (38%) to quarter 4 of 2008 (39%).

Conclusions: We document widespread and increasing use of opioids in the U.S. ESRD population. Given increasing concerns about opioid safety in the elderly, research is needed to better understand the safety and effectiveness of opioids in ESRD patients.

SA-PO487
Depressive Affect in Incident Hemodialysis Patients Is Associated with Increased Hospital Days and Hospital Admissions

Kathryn A. McDougall, John W. Larkin, Michael D. Isvyat, Rebecca L. Wingard, Edward J. Costello, Franklin W. Maddux. Fresenius Medical Care North America (FMCNA), Waltham, MA.

Background: Depression is a key disorder that affects chronic dialysis patients. However, it is not consistently recognized and outcomes related to the disease have not been well-defined, particularly for the first 120 days in incident hemodialysis (iHD) patients. This study investigated the associations between depressive affect (DA) in iHD patients and hospital days/hospital admissions.

Methods: Among a random selection of 108 dialysis centers, 429 iHD patients in the first month of chronic outpatient dialysis at FMCNA clinics from Jan-Mar 2013 were identified and telephone contact was attempted for up to three times to administer the Patient Health Questionnaire 2 (PHQ2). The PHQ2 has two questions screening for DA in the previous two weeks. Scores range from 0-6 with a positive DA score defined as ≥3. Hospital admissions and clinical parameters were captured for 120 days after the patients initiated dialysis (up to 30 Apr 2013). Multivariate Poisson regression models were constructed to determine whether hospital days and hospital admissions differ for depressed patients.

Results: Among 172 screened iHD patients, DA was detected in 23.3%. Increased hospital days of 15.8 versus (vs) 7.4 days per patient year (ppy) occurred in DA vs non-DA patients. Hospital admissions were also greater with 2.9 vs 1.5 events ppy, respectively. Poisson regression identified DA as an independent predictor of hospital days (p=0.001) and a trending predictor of hospital admissions (p=0.096) even after adjustment for covariates typically associated with depression (figure 1).

Figure 1: Poisson regression outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estimate (95% CI)</th>
<th>Rate Ratio (95% CI)</th>
<th>% Change vs Pre</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital days</td>
<td>-0.19 (-0.30 to -0.09)</td>
<td>0.81 (0.72 to 0.91)</td>
<td>-19%</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>0.12 (0.00 to 0.24)</td>
<td>1.12 (1.00 to 1.24)</td>
<td>12%</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Conclusions: DA in iHD patients was significantly associated with higher hospital days after adjustment for covariates. Further studies are needed to elucidate if interventions would reduce DA improve outcomes.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO488
Increased Depression and Anxiety Are Associated with Decreased Adherence in ESRD Patients

Daniel Cukur,1 Nisha Ver Halen,2 Yvette Fruchter,2 Subodh J. Desai,1 Psychiatry and Behavioral Science, SUNY Downstate Medical Center; Brooklyn, NY; 1Medicine, SUNY Downstate Medical Center, Brooklyn, NY.

Background: A significant relationship between depression and medical outcome has been demonstrated in ESRD patients in hemodialysis (HD). There may be a direct, neurobiological relationship between depression and medical outcome or the association may be mediated by adherence behaviors. The current study investigates depression, anxiety, and adherence at a Brooklyn dialysis center that serves a predominantly African American population.

Methods: Fifty-seven hemodialysis patients completed questionnaires during dialysis sessions. Depressive and anxious symptoms were assessed with the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI), respectively. Higher scores on the BDI and STAI indicate lower levels of depression and anxiety, respectively. Opioid use increased significantly from quarter 3 of 2006 (38%) to quarter 4 of 2008 (39%).

Results: Depressive symptoms (r = -0.36, p = .01), state anxiety (r = -0.38, p = .01), and trait anxiety (r = -0.43, p = 0.003) negatively correlated with adherence. Utilizing a regression with a model correcting for age and gender, the Beck Depression Inventory explained 24% of the variance in adherence (r = 0.49, p = .01). Separate regressions were run with state and trait anxiety to examine their predictive abilities for adherence behaviors when correcting for age and gender. State anxiety explained 19.1% of the variance in adherence (r = -0.27, p = .045) and trait anxiety explained 25.7% of the variance in adherence (r = -0.73, p = .01).

Conclusions: Depressive and anxiety play an important role in treatment adherence, a known predictor of medical outcome.

SA-PO489
NOTICE Initiative Post- versus Pre-Infection Control Evaluation (ICE) Results

Erik Ross, Natalie Scholz, Casey Parrotte, John Kalbfleisch, Rajiy Saran, Carol Chenoweth, Joseph M. Messana. Univ of Michigan, Ann Arbor, MI.

Background: The National Opportunity to Improve Infection Control in ESRD (NOTICE) project was developed to test similar declines in matched US dialysis facilities, to identify areas for quality improvement, and to reduce infections. Infection rates were measured before and after use of procedural and audit checklists, along with an on-site ICE.

Methods: Monthly NHSN vascular access-related infection (VAI), NHSN positive blood culture (PBC), and Medicare claims vascular access-related infection (ICD-9) data were collected from 34 facilities over 12 months with ICE visits occurring at 4-6 months. Generalized linear mixed models were used to assess changes in infection rates. Poisson mixed models and log binomial regression were used to determine the number of patients in the facility each month. Random effects for provider were included. The ICD-9 rates for NOTICE facilities were compared to controls matched on size, ownership, infection rate, and SES.

Results:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre (Mean)</th>
<th>Post (Mean)</th>
<th>% Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAI</td>
<td>0.69</td>
<td>0.69</td>
<td>0%</td>
<td>0.91</td>
</tr>
<tr>
<td>PBC</td>
<td>4.58</td>
<td>2.35</td>
<td>-48%</td>
<td>0.02</td>
</tr>
<tr>
<td>ICD-9</td>
<td>0.22</td>
<td>0.08</td>
<td>-63%</td>
<td>0.04</td>
</tr>
<tr>
<td>VAI (N) vs matched controls (C)</td>
<td>0.42/0.48</td>
<td>0.31/0.42</td>
<td>-35%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

The avg rates for all measures decreased from pre to post periods. VAI and ICD-9 rates were reduced by 28% and 18%, respectively. Differences were statistically significant (p<0.03). The reduction in PBC was not significant. When the change in ICD-9 rates were compared between NOTICE and control facilities, no difference was identified (RR=1.01, p=0.92).

Conclusions: Improvement in VAI and ICD-9 rates was statistically significant, and based on the post pre rates alone would suggest a marked improvement during the project. However, the ICD-9 rates showed similar declines in matched controls. The national decline in reported ICD-9 suggests that factors other than those included in NOTICE likely contributed to the pre-post changes reported here.

SA-PO490
Urgent-Start Peritoneal Dialysis: A Multicenter Clinical Trial

Arshia Ghaffari,1 Tracey L. Milligan,2 Mark H. Shapiro,3 Michelle Cassin,2 John E. Moran,4 Nephrology, Univ of Southern California, Los Angeles, CA; 2DaVita HealthCare Partners, Inc, Denver, CO; 3‘Univ of California, San Diego, La Jolla, CA; 4Nephrology, Stanford Univ School of Medicine, Stanford, CA.

Background: Patients who present with advanced chronic kidney disease (CKD) in need of urgent dialysis are usually started on hemodialysis (HD), most commonly via a central venous catheter (CVC). Very few patients are given the option of peritoneal dialysis (PD) in this situation due to a number or issues, including nephrologists’ unease and inexperience in urgently starting PD in unplanned, late-presenting patients. We initiated this study to demonstrate urgent-start PD can be safely applied in a protocol-driven, outpatient model.

Methods: Protocols were developed to standardize patient selection and management in the urgent-start period. Patients were provided with small-volume, in-center, supine PD thrice weekly less than two weeks after PD catheter placement. Catheters were placed by local available methods.

Results: 181 patients (55% male, average age 54 ± 16 years, 49.4% diabetics) started PD urgently at 36 facilities. 62.5% had received prior nephrology care. On average, PD was started in the outpatient facility 5.0 ± 3.2 days after PD catheter placement. 51 patients had a CVC placed and 50 had one or more HD treatments. 10 patients did not start PD within 14 days and were excluded from the analysis. With a mean follow-up of 6.8 months, 154 patients (90%) remain alive and on PD, 8 transferred to in-center HD (5 patient choice, 1 non-compliance, 1 bleeding during PD catheter insertion, 1 could not be trained for PD), 5 patients died (3 sudden cardiac deaths, 1 sepsis, and 1 liver cancer). 3 patients transferred to outside facilities while on PD, and 1 patient withdrew from dialysis.

Conclusions: This multi-center study demonstrates urgent-start PD can be broadly and successfully used in patients with advanced CKD in urgent need of dialysis in a structured, protocol-driven program. This management strategy allows patients the opportunity to choose PD as a modality. A major benefit is the avoidance of CVC use in many patients.

Funding: Pharmaceutical Company Support - DaVita HealthCare Partners, Inc
SA-PO491
Peritoneal Dialysis First Policy of Thailand Brought About Much Higher Penetration Rate and Good Outcomes Dhaves Sirivongs,1 Piyatida Chungsangaman,2 Siribha Changsirikulchai,3 Adisorn Lumpsapong.4 1Renal Service Center, Siriraj Hospital, Khon Kaen Uniy, Khon Kaen, Thailand; 2CAPD Service and Training Center, Banphaoe Hospital (Public Organization), Bangkok, Thailand; 3Dept of Medicine, Sirirakhinwarin Univ, Nakhon-Nayok, Thailand; 4Phramongkutklao Hospital, Bangkok, Thailand.

Background: Since October 2007, Thai government has provided PD first policy for non-hemodialysis dialysis population covering about 48 million people. This policy provides free of charge continuous ambulatory peritoneal dialysis (CAPD) for ESRD patients, so it had brought about rapidly increasing number of CAPD patients.

Methods: To analyze outcomes of CAPD treatment under the policy, we reviewed a first 60-month data from the 137 hospitals, 114 of them were new to CAPD, that recruited the patients during October 2007-September 2012.

Results: Total number of the registered patients was 19,464 cases, but only 15,211 cases actually received the treatment. Female to male ratio was 1:1.04, average age was 55.36 ± 14.3 years. Diabetes (46.1%) was the found in 51.3%: Mean eGFR at the registered step was 8.01 ± 5.0 mI/min. Drop-out rate was 3.47%; death in 30.10%, shift to HD 74.5% and kidney transplantation 0.91%. Regarding causes of death, cardiovascular disease was the most common cause, only 10.96% of total death from PD related peritonitis. The 1-year, 2-year, 3-year and 5-year patient survival rates were 82.1%, 66.3% 53.1% and 38.6% respectively. PD penetration was increased from 4% to 25% by 5 years of the policy. DM had significant negative impact to the survival (p<0.05).

Conclusions: PD first policy has markedly influence on patterns of treatment in Thailand. Increase of ESRD patients number is a result of decreased hospitalizations for non-participating hospitals were new to CAPD, the outcomes of treatment are quite successful. The success of Thai PD-first policy is due to combination of strong policy, systematic manipulation, and good attitude of medical personnel to the treatment.

Funding: Government Support - Non-U.S.

SA-PO492
Decreasing ESRD Patients’ Hospital Length of Stay and Readmissions through Patient Centered Care Redesign Using Quality and Design Methods Amy W. Williams, Kathryn Zavaleta, John J. Dillon, Mary Tibor, Susan Dornack, Mary Ann Ryan, Mark Nagle, Jerilynn Wilson, Bradley D. Wick, Aaron Eckblad, Stephen F. Gudgell, Robert C. Albright. Mayo Clinic, Rochester, MN.

Background: In 2011 we began a quality and design methods approach to improve ESRD patient outcomes by creating high value patient-centered care across all settings.

Methods: One aim was to decrease chronic dialysis patients’ hospitalizations.

Methods: The multi-disciplinary team completed process mapping of current & future ideal state followed by small scale pilots and spread for in-center & home (PD & HD) dialysis patients (pts). Interventions included standardization of hospital care & hospital care team communication, roles & EMR tools, handoffs and transitions between care settings enhanced by consistent integrated flow of information, expansion of multidisciplinary care teams to include pharmacists and palliative care specialists, improved pt preference-focused care, and EMR tools, handoffs and transitions between care settings.

Results: The multi-disciplinary team completed process mapping of current and future ideal state followed by small scale pilots and spread for in-center & home (PD & HD) dialysis patients (pts). Interventions included standardization of hospital care & hospital care team communication, roles & EMR tools, handoffs and transitions between care settings enhanced by consistent integrated flow of information, expansion of multidisciplinary care teams to include pharmacists and palliative care specialists, improved pt preference-focused care, and EMR tools, handoffs and transitions between care settings.

Conclusions: Patient interactions within groups were analyzed with social network methods, and a novel mortality prediction model was developed based on the discovered social links. Experiments validated the discovered social links and confirmed the contribution of the social network information to the accuracy of mortality prediction. This study extends the body of the eight social networks based on serum phosphorus were statistically significant with the highest network density (0.24) found in the Monday, Wednesday, Friday afternoon shift (t-value 5.97, Confidence 99.9%). Comparing the accuracy of our model to five alternative models showed that incorporating the social network data yielded the greatest predictive accuracy with an Area Under the Curve of 0.67 ± 0.02.

Conclusions: To the best of our knowledge ours is the only study to have modeled patient social networks within a hemodialysis clinic. We use phosphoryl correlations to demonstrate the existence of social links among hemodialysis patients and improve the accuracy of a mortality prediction model based on survey and medical record data.

Funding: Government Support - Non-U.S.

SA-PO493
Higher Ultrafiltration Rates Are Associated with Greater Mortality at Higher BMI Levels Len A. Usuva,1 Peter Kotanko,2 Franklin W. Maddux,2 Eduardo K. Laczon,1 1FMHCNA, Waltham, MA; 2RRI, NY, NY.

Background: Higher ultrafiltration rate (UFR) during HD may be associated with poor survival. With this observation negative correlation vs UFR and BMI observed by our group, we evaluated whether differences in survival persist if UFR is calculated in mL/hr within strata of BMI.

Methods: We studied incident HD patients in FMHCNA who initiated dialysis b/t Jan 1, 2010 and Jan 1, 2013, tracking mortality until May 1, 2013. Only patients who survived first 90 days and with Kru<0.1 mL/min at initiation were included. The average UFR (in mL/hr) was computed in first 90 days. Patients were stratified into 4 groups of baseline UFR: <400, 400 to 600, 600 to 800, and >800 mL/hr and into 6 groups of BMI: <21, 21 to 25, 25 to 30, 30 to 35, and >35 kg/m2. Stratified Cox models adjusted for age, gender, DM status, race, ethnicity, and albumin levels were constructed to assess survival after the first 90 days in these 4 groups of UFR, in each analysis, UFR>800 was ref group.

Conclusions: The greatest predictive accuracy with an Area Under the Curve of 0.67 ± 0.02.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author/disclosure.
Obesogenic Associations among End-Stage Renal Disease Patients Not Listed for Kidney Transplantation

John C. Sieverdes,1 David J. Taber,2 Kenneth Chavin,1 John McGillicuddy,3 Titte Srinivas,2 Frank Treiber,1,2 Prabhakar Baliga,1 College of Nursing, Medical Univ of South Carolina, Charleston, SC; College of Medicine, Medical Univ of South Carolina, Charleston, SC.

Background: Rising obesity rates may be causing kidney transplant centers to shift their allowable BMI thresholds, which is a potential concern for successful outcomes. The purpose of this study is to examine the reported reasons end-stage renal disease (ESRD) referrals are not being listed for transplantation and to describe the rates of obesity at a large academic transplant program in the southeastern United States.

Methods: Between January 2006 and December 2010, there were 4,494 referrals who underwent evaluation for potential transplantation; 34% of which met eligibility and were placed on the waiting list, leaving 2,961 included in this cross-sectional analysis.

Results: The four predominant etiologies cited for not being initially listed over the 5-year period included missed education classes (39.5%), incomplete testing (17.3%), age (11.8%), and obesity (8.8%) (Figure 1). Overall, the analysis demonstrated that even though a higher percentage of patients were presenting with class II obesity or above (BMI ≥ 35) in 2010 compared to 2006 (X²=0.03), fewer patients were being rejected due to their BMI (p for trend <0.001) (Figure 2).

Conclusions: These results imply that the transplant community is extended the boundaries of weight-suitability in response to the obesity epidemic. Future studies are warranted to determine how this is impacting perioperative outcomes, quality of life, and graft and patient survival rates after transplant. Interventions promoting active lifestyle changes and weight management for ESRD patients should be used to manage these modifiable risk factors.

SA-PO498

Active Vitamin D and Nutrition Are Predictors of Infectious Diseases in Secondary Hyperparathyroidism of Uremia (SHPT) on Maintenance Hemodialysis Patients: Results from the MBD-5D Study

Yusao Inamishi,1 Ikue Kobayashi,1 Masaaki Inaba,1 Masafumi Fukagawa,2 Shunichi Fukuhara,3 Osaka City Univ, Japan; Tokai Univ, Japan; Kyoto Univ, Japan; Showa Univ, Japan.

Background: Although nutrition is a significant predictor of mortality in dialysis patients, little is known about the role of nutrition in infectious diseases. This study examined the combination effects of nutritional status and intravenous (iv) vitamin D receptor activator (VDRA) administration on infectious diseases.

Methods: The Mineral and Bone Disorder Outcomes Study for Japanese CKD Stage 5D Patients (MBD-5D) is a multicenter, prospective observational study of hemodialysis patients with SHPT in Japan. This study is a subcohort of MBD-5D, and 2,022 prevalent patients, who were receiving hemodialysis for more than 3 months and met at least one of the following conditions: having intact PTH levels >180 pg/ml, or receiving iv vitamin D receptor activators (VDRAs) or oral VDRA analog, were employed. Nutritional status was assessed by Geriatric Nutritional Risk Index (GNRI) which was calculated using serum albumin, dry weight and ideal body weight. Patients were categorized into quartiles by GNRI and assessed the association between GNRI and infection related mortality or hospitalization.

Results: At follow-up time of 36 months, highest risks for both infection-related mortality and hospitalization were observed in the 1st GNRI quartile (poorest nutritional status). Time dependent Cox regression model revealed hazard ratio (HR) for the 1st GNRI quartile was 6.22 in mortality (95% confidence interval, 1.58-24.45), and 1.85 in hospitalization (1.13-3.02) in the iv VDRAs non-receiving group compared to the 4th GNRI quartile. In the iv VDRAs receiving group, these associations were not observed in mortality (HR, 1.67, 0.83-3.36) or in hospitalization (HR, 1.07, 0.68-1.67).

Conclusions: These results demonstrated that GNRI is a significant predictor for mortality in CKD-5D patients with SHPT. Administration of iv VDRA may have a preventive effect on the incidence of both infection related mortality and hospitalization in the patients with poor nutritional status.

Funding: Pharmaceutical Company Support - The MBD-5D study is supported by research grants from Kyowa Hakko Kirin co.,Ltd. without restrictions on publications.

SA-PO497

Associations of Race, Obesity and Diabetes on Risk of Attrition from the Kidney Transplant Waiting List

John C. Sieverdes,1 David J. Taber,2 Kenneth Chavin,1 John McGillicuddy,2 Titte Srinivas,2 Frank Treiber,1,2 Prabhakar Baliga,2 College of Medicine, Medical Univ of South Carolina, Charleston, SC; College of Medicine, Medical Univ of South Carolina, Charleston, SC.

Background: This study examined the associated variables related to why patients become inactive on the kidney transplantation waiting list.

Methods: Between January 2006 and December 2010, 4,494 referrals to the center for evaluation for transplantation wait-list suitability were cross-sectionally examined.

Results: Thirty-four percent (n=1,531) who met eligibility requirements were placed on the waiting list. Follow-up analyses revealed that 489 (32%) patients subsequently had their status changed from active to inactive. Multiple medical comorbidities was the predominant factor for removal from the wait list (26%), followed by socioeconomic status (18%), and cardiovascular events (16%) (Figure 1). Binary logistic regression demonstrated that age at referral (p<0.05), diabetes status (p=0.04), marital status (p=0.02), and education (18%), and cardiovascular events (16%) were risk factors for having diabetes. Patients with diabetes had a 41% increased risk of becoming inactive (odds ratio [OR]: 1.34 [CI: 1.08-1.66]) and obesity (BMI ≥ 30 kg/m²) (OR 1.60 [CI: 1.27-2.03]) were risk factors for the development of diabetes, may indirectly increase the risk of being inactive (OR: 1.41 [95% CI: 1.31-1.77]).

Conclusions: Overall, HRQOL did not change from 2010-2012 in this cohort, but in the sub-sample of patients (45%) who had Hb declines ≥1 g/dL, HRQOL decrements were observed in several anaemia-related items.

Funding: Pharmaceutical Company Support - Amgen, Inc.

SA-PO496

Figure 1. Proportions for becoming inactive on the transplant list (n=459).

Figure 1. Proportions for becoming inactive on the transplant list (n=459).

Conclusions: All associations were risk factors for development of diabetes, and may indirectly increase the risk of being inactive. Future research should be focused on developing interventions to modify obesity rates in multiple socioeconomic and age-related areas.

Figure 1. Proportions for becoming inactive on the transplant list (n=459).

Conclusions: These results demonstrate that obesity and race, which are well known risk factors for the development of diabetes, may indirectly increase the risk of being listed inactive or dying before receiving a kidney transplant. Future research should be focused on developing interventions to modify obesity rates in multiple socioeconomic and age-related areas.
SA-PO499

Improvements in Survival and Major Amputations Observed with the Implementation of a Foot Check Program in Diabetic Hemodialysis Patients

Andrea Jarn-mern-pernt1, Vanja Pesci,1 Len A. Usvyat,2 John Rogus,2 Franklin W. Maddux,1 Eduardo K. Lacson,2 Peter Kotanko,2 1Univ Medical Center Ljubljana, Slovenia; 2RRI, NY, NY; 3FMCNA, Waltham, MA.

Background: Diabetic HD patients (pts) are at high risk of lower limb amputations. In order to improve foot care in diabetic HD pts, monthly intra-dialytic foot checks [FC] were implemented as part of a standard clinic operating procedure in FMCNA clinics in January 2008 [foot check program implementation date]. We aim to understand whether regular FCs are associated with reductions in major lower limb amputations and survival.

Methods: We compared incident diabetic HD pts before [pre-period: between 1/2004 and 12/2007] and after [post-period: between 1/2008 and 12/2011] FC program implementation. In post-period, we divided patients into those who were in clinics performing FC on >1/15 [high FC rate] or ≤1/20 [low FC rate] HD tx in diabetic pts. We performed Kaplan-Meier analysis to evaluate time to death. Poisson regression was constructed with # of major amputations.

Results: We studied 37624 pts in pre-period and 40651 pts in post-period. In latter cohort, 29335 were in ‘high FC rate’ group and 11316 were in ‘low FC rate’ group. Compared to pre-period, all-cause mortality decreased by 25% in ‘high FC rate’ group and 3% in ‘low FC rate’ group (overall log-rank test P<0.001). In ‘high FC rate’ group, the major lower limb amputation rate was reduced by 18% in ‘high FC rate’ group (p=0.001) and 16% in ‘low FC rate’ group (p=0.001).

Conclusions: Frequent FCs are associated with reduction of all-cause mortality and major amputations in diabetic HD pts (less frequent FC are associated with notably smaller reduction in mortality). Implementation of intra-dialytic FCs has a potential of saving lives and preventing major lower limb amputations. Further analyses should also check for overall reductions in mortality and amputation rates.

SA-PO500

Candidate Gene Analysis of Mortality in Dialysis Patients

Garbev Oekak,1 Jeffrey J.W. Verschuren,1 Carolien Rothuizen,1,2 Friedo W. Dekker,1 Ton J. Rabellink,3,4 J.wouter Jukema,1,2 Joris I. Rottmans,1,4 1Clinical Epidemiology, Leiden Univ Medical Center, Netherlands; 2Cardiology, Leiden Univ Medical Center, Netherlands; 3Nephrology, Leiden Univ Medical Center, Netherlands; 4Einhoven Laboratory for Experimental Vascular Medicine, Leiden Univ Medical Center, Netherlands.

Background: Dialysis patients have high mortality risks with cardiovascular mortality as an important cause of death. The aim of this study was to investigate the association between SNPs involved in vascular processes and mortality in a large population of incident dialysis patients.

Methods: We followed 1330 incident dialysis patients in which 42 SNPs in 25 genes involved in vascular processes (endothelial function and vascular remodeling, growth factors, inflammation, coagulation, and calcium/phosphate metabolism) were genotyped. Cox regression analysis was used to investigate the effect of these SNPs on five-years mortality.

Results: The mortality rate was 114 per 1000 person-years for the 1330 dialysis patients. We showed that vascular endothelial growth factor rs999947 (hazard ratio [HR] 1.48, 95% CI 1.14-1.92), vitamin D receptor rs2238135 (HR 0.98, 95% CI 0.35-0.94), interleukin 6 rs1800795 (HR 1.32, 95% CI 1.00-1.74), lymphoplasmin alpha rs1799964 (HR 0.60, 95% CI 0.37-0.98) and CD180 rs7544478 (HR 2.27, 95% CI 1.07-4.79) were associated with an increased mortality risk.

Conclusions: In this large cohort of dialysis patient, we found that three SNPs related to inflammatory processes, one SNP involved in endothelial function, and one SNP related to vitamin D metabolism were associated with an increased mortality risk. This study provides further evidence for an important role of these processes in the comorbid conditions of dialysis patients. Future studies are warranted to unravel the underlying mechanisms responsible for the increased mortality in these patients.
Asymmetric Dimethyl-Arginine (ADMA), Race, and Mortality in Hemodialysis Patients

Background: Asymmetric dimethylarginine (ADMA) levels are elevated in kidney disease and associated with mortality in studies evaluating predominantly Caucasian and European hemodialysis (HD) populations. No studies have explored whether this association extends to African American (AA) hemodialysis patients.

Methods: ADMA levels were measured at baseline in 258 maintenance HD patients. Multivariable Cox proportional hazards models were used to evaluate the association of ADMA to all-cause mortality. An interaction between race and ADMA level was evaluated and subgroup analyses were performed.

Results: The mean (SD) age was 63 (17) years, 54% were women and 22% were African American, with the remaining participants predominantly Caucasian. Mean (SD) ADMA level in non-AA patients was 0.79 μmol/L (0.16) vs 0.70 μmol/L (0.11) in AAs (p <0.001). 132 deaths occurred over median follow up of 2.5 years, with death rates of 23.4 and 7.0 per 100 person years among non-AA and AA, respectively. Higher ADMA levels were associated with an increased risk of all-cause mortality (adjusted HR [95%CI] =1.24 per SD increase [1.03, 1.49]). An interaction was found between AA race and ADMA level (p value = 0.01), such that, when analyzed by race, higher ADMA levels were associated with increased mortality in non-AAs (adjusted HR =1.34 [1.10, 1.63]) but trended towards protective in AAs (adjusted HR =0.51 [0.25, 1.04]).

Conclusions: African Americans have lower ADMA levels in comparison with non African Americans. High ADMA was a risk factor for mortality only in non African Americans. Given historically better survival among AA dialysis patients, these results need to be explored in larger, racially diverse studies, which will be able to investigate potential etiologies for this relationship.

Funding: NIDDK Support, Private Foundation Support

Health Related Quality of Life in the Saudi Arabia Dialysis Outcomes and Practice Patterns Study (DOPPS)

Background: Health related quality of life was similar in SA pts versus pts in 12 other DOPPS countries, despite notable differences in pt characteristics and HD practices across countries.

Methods: DOPPS is supported by research grants from Amgen (founding sponsor, since 1996), Kyowa Hakko Kirin (since 1999, in Japan), AbbVie (since 2009), Sanofi Renal (since 2009), Baxter Healthcare (since 2011), and Vifor Fresenius Medical Care Renal Pharma (since 2012), with additional country-specific support provided in Canada by Amgen-Canada, Janssen, BHC Medical, Takeda and Kidney Foundation of Canada, and in Germany by Hexal and WiNe Institute. Support from the DOPPS sponsors is provided without restrictions on publications.

Conclusions: Health related quality of life was similar in SA pts versus pts in 12 other DOPPS countries, despite notable differences in pt characteristics and HD practices across countries.

Funding: Pharmaceutical Company Support - The DOPPS is supported by research grants from Amgen (founding sponsor, since 1996), Kyowa Hakko Kirin (since 1999, in Japan), AbbVie (since 2009), Sanofi Renal (since 2009), Baxter Healthcare (since 2011), and Vifor Fresenius Medical Care Renal Pharma (since 2012), with additional country-specific support provided in Canada by Amgen-Canada, Janssen, BHC Medical, Takeda and Kidney Foundation of Canada, and in Germany by Hexal and WiNe Institute. Support from the DOPPS sponsors is provided without restrictions on publications.

Survival among Elderly versus Younger Maintenance HD Patients – Results from the International MONDO Consortium Database

Background: The largest growing segment of hemodialysis (HD) patients is the elderly population. Previously the DOPPS III study described survival of elderly vs. younger HD patients (N=8,161) in 12 countries using age stratification of >45, 45-75 and >75-yr-old. In this study we evaluate the hazard ratio of elderly HD patients (≥75) vs. 65-75 vs. <65 in the MONDO international database (N=86,169).

Methods: The MONDO research initiative consists of HD databases from the US, Europe, Asia & Latin America [Usryat, Blood Purif 2013]. We extracted data for all incident patients from RRI, FMC Europe, Latin America, and Asia Pacific between 2000 and 2012. Patients were stratified by age ≤65, 65-75, ≥75. Cox proportional hazards models were constructed for each database to assess the hazard ratio of death adjusted for gender, initial access type, race (for RRI only), and comorbidities (diabetes, cancer, cardiovascular and hepatitis).

Results: We studied 86,169 HD patients from 4 continents (Table):

<table>
<thead>
<tr>
<th>Continent</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>South America</td>
<td>85,309</td>
</tr>
<tr>
<td>Europe</td>
<td>6,090</td>
</tr>
<tr>
<td>Asia</td>
<td>1,869</td>
</tr>
<tr>
<td>North America</td>
<td>968</td>
</tr>
</tbody>
</table>

In general, risk of death increased with age. In Asia, older patients had the highest hazard ratio of death vs. younger patients, compared to their counterparts in other continents. In the US, older patients had the lowest hazard ratio vs. younger patients (Figure):

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

Underline represents presenting author/disclosure.

742A
Conclusions: The mortality hazard ratio of elderly vs. younger HD patients, within the same geographical region, varies across continents; it is highest in Asia and lowest in the US.

SA-PO506

Higher Mortality for Women Beginning Dialysis Treatment in the United States

Austin G. Stack,1,2 Hoang Thanh Nguyen,3 Ahad Abdalla,1,3 Liam F. Casserly,2,3 1Nephrology and Internal Medicine, Univ Hospital Limerick, Ireland; 2Graduate Entry Medical School, Univ of Limerick, Ireland.

Background: Studies to date have yielded conflicting results on the survival of men and women who begin dialysis therapy in the US and may reflect differences in baseline comorbidity, differences in access to pre-dialysis care or differences in treatments following dialysis initiation. The overall goal of this study was to explore mortality differences between men and women who initiated dialysis from 1995-2008.

Methods: We identified 662,985 men and 557,015 women who commenced dialysis from 1995-2008 in the US Renal Data System. Baseline clinical health of patients was assessed at dialysis initiation and patients were followed from date of first dialysis to death or survival at the end of the study period. Mortality comparisons between men and women were stratified by race: White, Black, Asian and Native American. Adjustments were made for baseline clinical and laboratory health indicators, measures of pre-dialysis care and the timing of dialysis initiation. Ethical approval was received from the University Hospital Ethics Committee.

Results: Adjusted hazard ratios were significantly higher for White and Black women compared to White men and Black men respectively at follow-up. In contrast the hazard ratios of Asian and Native American women were similar to their male counterparts. White women experienced the highest overall risks.

Conclusions: Women experience higher mortality risks than men starting dialysis treatment in the US, with the greatest risks for White women. Differences in the severity of underlying disease or access to therapeutic interventions prior to or following dialysis onset may account for some of these differences and require further exploration.

SA-PO507

Factors Predicting Survival during the First 90 Days of Hemodialysis (HD): A Global Perspective

Adrian Marcos Guinsburg,1 Cristina Marelli,1 Daniele Marcelli,2 Len A. Usvyat,3 Michael Etter,4 Peter Kotanko,3 Mondo Consortium.3,4
1Fresenius Medical Care, Buenos Aires, Argentina; 2Fresenius Medical Care, Bad Homburg, Germany; 3Renal Research Institute, New York, NY; 4Fresenius Medical Care North America, Waltham, MA; 5Fresenius Medical Care, Hong Kong, Hong Kong.

Background: Mortality during first 90 days on HD may account for predialysis care (preDC) and patient status at HD initiation. We aimed to analyze factors predicting survival in the first 3 months on HD in a large international sample of incident HD patients.

Methods: The MONitoring Dialysis Outcomes (MONDO) consortium was described previously [Usvyat, Blood Purif, 2013]. Incident HD patients between 01/2000 and 12/2010 were followed until day 90 or death. Cox reg models were constructed to identify factors associated with survival in the first 90 days.

Results: We studied 14,829 patients (Asia 4,277; Europe 3,083; LA 2,506; USA 4,969). HR (p value) of factors are summarized in table 1.

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.03 (1.01 - 1.05)</td>
</tr>
<tr>
<td>Male (yes)</td>
<td>0.97 (0.95 - 1.00)</td>
</tr>
<tr>
<td>Diabetic (yes)</td>
<td>1.07 (1.00 - 1.12)</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>0.95 (0.91 - 1.00)</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>0.97 (0.93 - 1.01)</td>
</tr>
<tr>
<td>Pre-SBP (mmHg)</td>
<td>0.98 (0.96 - 1.00)</td>
</tr>
</tbody>
</table>

*p<0.05

Age predicts mortality in all regions while gender (male) only in LA and DFT only in Asia.

Conclusion: Albumin was positively associated with survival in all regions and pre-SBP in all regions except Asia. Ca and PO4 showed no effect (exception of Ca in USA). The association of Hgb mortality was heterogeneous: no association in LA and USA, positive association in Asia and negative in Europe.

Conclusions: Age, albumin and preSBP showed a similar pattern across regions suggesting an underlying biology independent of practice patterns and health policies. Ca, PO4 and Hgb showed variable effects possibly indicating differences in preDC and policies.

SA-PO508

Uninsured Unemployed and Insured Employed ESRD Patients Have Similar Mortality Outcomes

Paul L. Kimmel,1 Chyng-Wen Fwu,2 Jonathan Ranner,1 Kevin C. Abbott,1 Paul W. Eggers,3 1Div of Kidney, Urologic and Hematologic Diseases, NIDDK, NIH, Bethesda, MD; 2Social & Scientific Systems, Inc., Silver Spring, MD; 3Wesant, Inc., Rockville, MD; 4Walter Reed National Military Medical Center, Bethesda, MD.

Background: Uninsured US adults in the general population have less health-care access and utilization, but analogous evidence on mortality is sparse and contradictory. Nearly all US ESRD patients have Medicare available. Whether health insurance status before Medicare entitlement due to ESRD varies with probability of death is unknown.

Methods: We included ESRD adult patients less than 65 years from 2000-2008 US Renal Data System. To account for competing risks (transplantation and transfer to peritoneal dialysis [PD]), we used Fine-Gray sub-distribution proportional-hazards regression models, estimating cumulative incidence of death, controlling for known risk factors including residential income and income inequality parameters. Separate models by employment status were analyzed, because of a significant interaction between insurance and employment status.

Results: 274,921 patients were included: 23% were employed and 86% were insured (including private insurance, Medicare, and Medicaid) at ESRD onset. After follow-up (median 26.8 months), 110,373 (40.2%) patients died, 37,741 (13.7%) patients received renal transplant, and 14,079 (5.1%) started PD. Uninsured patients were younger, poorer, and healthier than the insured. Among the employed, the uninsured had higher mortality than the insured (sub-hazard ratio: 1.12, 95% confidence interval: 1.06-1.19). Among unemployed patients, the uninsured survived longer than the insured (0.84, 0.82-0.86).

Conclusions: As expected, in ESRD patients, mortality increases with unemployment. In the employed at ESRD onset, mortality increases with lack of insurance. Counterintuitively, in unemployed ESRD HD patients, lack of insurance is associated with improved survival. Selection bias - people with better perceived health opting to not buy insurance - may explain these surprising findings. In addition, entry into the ESRD program may differentially benefit the previously uninsured.

Funding: NIDDK Support, Other U.S. Government Support

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

743A
**SA-PO509**

**Age, Race and Ethnicity, and Risk of Hospitalization among Patients Undergoing Hemodialysis**

Guofen Yan,1 Keith C. Norris,2 Tom Greene,2 Wei Yu,1 Jennie Z. Ma,1 Alfred K. Cheung,3 1Univ of Virginia; 2Charles R. Drew Univ; 3Univ of Utah.

**Background:** Recent literature suggests overall hemodialysis (HD) mortality is lowest in Hispanics, intermediate in non-Hispanic blacks (blacks), and highest in non-Hispanic whites (whites), except for those under 30 years. Whether a similar pattern exists for hospitalization is unclear. We compared overall and age-stratified (18-30, 31-40, 41-50, 51-60, 61-70, 71-80, >80 yrs) hospitalization rates among the racial/ethnic groups.

**Methods:** We identified 563,281 (55% white, 33% black and 12% Hispanic) patients in the USRDS aged ≥18 yrs who initiated maintenance HD between 1995 and 2009, and survived the first 90 days, received in-center HD at day 91 for >60 days, with Medicare as primary payer. Hospital admissions and hospital days for all causes (AC), cardiovascular (CV), any infection, and dialysis-related infection (DRI) over one year were examined with Poisson regression.

**Results:** For both AC hospital days and admissions, unadjusted rates were highest in whites, intermediate in blacks, and lowest in Hispanics. After adjusting for various covariates, this pattern was evident only in the middle 2 age groups (51-60, 61-70 yrs), whereas among patients under 40 or above 70 years old, blacks had much higher rates than whites. Thus, the adjusted rate ratios (RRs) of blacks vs. whites exhibited a U-shaped relationship with age: RR of 1.29 (p<0.001) for 18-30 yrs, 1.02 (p=0.3) for 41-50 yrs, 0.91 (p<0.001) for 51-60 yrs, 0.97 (p=0.008), 1.08 (p<0.001) and 1.22 (p<0.001) for the hospital days from younger to older groups. Hispanics consistently exhibited the lowest adjusted AC rates for all ages under 70 yrs (RR ranging from 0.84 to 0.94 for the hospital days). However, hospitalization rates for DRI were consistently much higher in blacks than whites across all age groups, and higher in Hispanics than whites in age groups >60 yrs.

**Conclusions:** Our findings suggest that age modified the association of racial/ethnic factors with the overall and cause-specific hospitalizations. The delineation of the factors responsible for excess hospitalization rates among select subgroups may lead to reduced costs and improved quality of care for all dialysis patients.

**Funding:** NIDDK Support

**SA-PO510**

Association of Number of Comorbidities with Number of Readmissions

Eduardo K. Lacson, Welling Wang, Franklin W. Maddux. Fresenius Medical Care, North America, Waltham, MA.

**Background:** Comorbidity influences hospital readmission rates in the general population. We evaluated the association between comorbidity diagnoses and 30-day readmission rates in hemodialysis (HD) patients.

**Methods:** All adult HD patients, treated 3x/wk on 1/1/11 in Fresenius Medical Care, North America facilities with ≥1 hospital discharge in 2011 were included and readmissions tracked until 12/31/11. Case-mix (age, gender, race, diabetes, vintage, access type) and lab variables as well as 23 comorbidity categories from the Medicare Dialysis Facility Reports were recorded as of 1/1/11. The frequency of comorbidities was counted per patient among 16 categories identified by univariate logistic models to associate with readmission rate and assigned into groups: 0, 1, 2, 3, >3 (Table). Poisson regression was used to assess the association between number of comorbidities & readmissions.

**Results:** In 2011, 64,128 HD patients were hospitalized: mean age of 62.8±14.5 years, 52.5% male, 55.6% white, 39.3% black and 28.8% HD catheters. Dialysis vintage was 3.8±3.7 years and the mean number of comorbidities was 1.9±1.5 (IQR: 1-3, median: 2). 50,380 readmissions occurred with mean of 0.79±0.81 (median: 0) per patient. Readmission rate increased by 8% for each additional comorbid diagnosis (p<0.0001). Compared to no comorbidity, the rate of readmission with 2 comorbidities increased by 23% and by 45% for >3 (all p<0.0001). Results were similar after case-mix & lab adjustment.

**Conclusions:** Comorbidity is a significant risk factor for 30-day readmission. Further study is needed to determine potentially actionable attributes of specific comorbidity diagnoses that range from both specific and all causes of readmissions. Patients with multiple comorbidities will need to be considered in performance measure development to avoid unintended consequences such as selection bias that may limit subsequent access to care.

**SA-PO511**

Impact of Target Parathyroid Hormone (PTH) Range and Risk of Fractures in End-Stage Renal Disease (ESRD)

Chi-yan Hsu,1 David V. Glidden,2 Jeffrey R. Curtis,2 Barbara A. Grimes,1 Linda McCann,1 Brigitte Schiller,1 Kirsten L. Johansen,1 1Univ of California, San Francisco; 2Univ of Alabama, Birmingham; 3Satellite Healthcare.

**Background:** The optimal target range for PTH levels in hemodialysis (HD) patients is unclear. In the absence of randomized controlled trial data, “natural experiments” such as changes in protocol PTH target range implemented across a dialysis organization (in response to expert guidelines) regardless of individual patient characteristics may provide estimates of treatment effect that are relatively un-confounded.

**Methods:** We studied fracture risk among in-center maintenance HD patients treated at Satellite Healthcare, a non-for-profit dialysis organization, which has a uniform mineral metabolism protocol across all its dialysis facilities. The target PTH range was 150-300 pg/ml from April 2003-Jan 2005 and 150-400 after Feb 2005. We followed patients who had Medicare as their primary insurance starting Jan 2003. Using US Renal Data System data and time varying Cox regression analysis, we assessed the impact of changes in PTH target on rates of fracture. Fractures were identified using ICD-9 codes 820.x and 733.14 for hip, 813.x, 733.12, 812.x, and 733.11 for radius/ulna, 805.x, 806.x and 733.13 for spine and 814.x for wrist/carpal after 6-month lag. Outcomes were ascertained through Dec 2009 or 3 months after transfer out of a Satellite dialysis unit (for transplant or otherwise).

**Results:** 818 patients were observed 3x over 1760 person-years of follow-up (2.0 per 100 person-years) when the target PTH was 150-300 pg/ml and 150 fractures over 6563 person-years of follow-up (2.3 per 100 person-yrs) when the target PTH was 150-400 pg/ml. The hazard ratio (HR) for 150-400 (vs. 150-300 pg/ml) was 1.04 (95% CI 0.71-1.53; p=0.83). Similar results were seen after controlling for demographics and comorbidity conditions known to be fracture risk factors (adjusted HR 1.17; 95% CI 0.78-1.74; p=0.45).

**Conclusions:** Raising the upper limit of target PTH range from 300 to 400 pg/ml did not appear to be associated with significantly higher risk of fractures in maintenance HD patients, although confidence intervals were relatively wide.

**Funding:** NIDDK Support

**SA-PO512**

Relative Impact of Selected Indicators on Mortality: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS) Francesca Tontori,1 Lindsay Zepel,1 Angelo Karayabas,1 David C. Mendelsohn,2 T. Alp Ikizler,3 Brenda W. Gillespie,1 Werner Kleophas,3 Brian Bieber,4 Ronald L. Pisoni,4 Bruce M. Robinson.1 1Arbor Research; 2Humber River Regional Hosp.; 3Vanderbilt U.; 4U. of Michigan; 5Dialysezentrum Karlstrasse.

**Background:** The proportion of facility patients meeting a clinical target is often used as an indicator of quality of care (“quality indicator”). Achievement of targets varies for different markers. The impact of quality indicators on outcomes is likely greater for indicators that are highly prevalent and have a strong association with mortality. We aim here to assess the proportion of deaths that could have been prevented by achievement of selected quality indicators.

**Methods:** We analyzed 15,118 hemodialysis patients from 539 facilities in DOPPS 3 (2005-08) and 4 (2009-11) in North America, Europe, Australia and New Zealand. Quality indicators were based on guidelines during the study period. In prior work, the 4 quality indicators included had the strongest association with mortality. The proposed goal was chosen based on observed distribution and clinical judgment about feasibility. Using an adjusted attributable fraction, we calculated the attributable fractures as the proportion reduction in number of deaths if facilities below the goal were set counterfactually to the target goal.

**Results:** Achievement of the quality indicators varied widely, with higher % of facilities not meeting the albumin and fistula guidelines. The AF ranged from 5.2% (for albumin) to 9.5% (for fistula use), with a cumulative AF of 23.4% (Table 1).

**Conclusions:** Though these results cannot establish causality, they indicate that ~23% of deaths could have been prevented by meeting the quality thresholds. Increasing the facility % of patients with KiV ≥ 1.2 or fistula may yield the greatest improvement in mortality.

**Funding:** NIDDK Support, Pharmaceutical Company Support - The DOPPS is supported by research grants from Amgen (founding sponsor, since 1996), Kyowa Hakko Kirin (since 1999, in Japan), AbbVie (since 2009), Sanofi (since 2009), Baxter Healthcare (since 2011), and Vifor Fresenius Medical Care Renal Pharma (since 2012), with additional country-specific support provided in Canada by Amgen-Canada, Japan: JHMC Medical, Taiwan: National Kidney Foundation of Canada, and in Germany by Hexal and WiNe Institute. Support from the DOPPS sponsors is provided without restrictions on publications.

**SA-PO513**

End Stage Renal Disease due to HIVAN in the United States 2000-2010

Donal J. Sexton,1,2 Scott Reule,1,2 Craig Solid,1 Shu-cheng Chen,1 Allan J. Collins,1,2 Robert N. Foley,3 1USRDS Coordinating Center, MMRF, Minneapolis, MN; 2Medicine, Univ of Minnesota, Minneapolis, MN.

**Background:** The management of HIV has changed considerably in the last decade, and the effect of contemporary treatment on the standardized incidence of end stage renal disease (ESRD) due to HIV has not been characterized.

**Methods:** We combined US census data with data from the USRDS patients to determine whether incidence rates and outcomes of ESRD due to HIV associated nephropathy (HIVAN) have improved simultaneously with improvements in the management of HIV.

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

744A
Results: 8389 of 1,144,036 (0.8%) patients initiated dialysis due to HIV between 2000 and 2010. Using incidence rates for 2000 to calculate expected rates for subsequent years (based on age, sex and race/ethnicity), standardized incidence ratios remained unchanged between 2000 and 2003 and then declined to 0.66 in 2010. Characteristics of HIV patients included residence in the South (59.5% vs. 41.5% in non-HIV), age < 45 yrs (55.7% vs. 13.1%), male sex (66.9% vs. 55.3%), African American race (87.6% vs. 28.3%), catheters for hemodialysis (90.9% vs. 82.5%), nephrology care < 1 year (90.9% vs. 76.4%), and body mass index < 18.5 kg/m² (12.2% vs. 4.4%). HIV was associated with a greater likelihood of failure to be listed for transplant (adjusted hazard ratio [AHR] 4.55), failure to receive a transplant (AHR 6.67) and death (AHR 2.53). Among patients with HIV, while mortality (AHR for 2005-2010 0.94 vs. 2000-2004) and non-listing (AHR 1.22) increased (AHR 1.36), transplantation actually decreased (AHR 0.9). Regional variation in outcomes was apparent, with HIV patients in the South having higher risks of non-listing (AHR 1.52 vs. the Northeast), non-transplantation (AHR 1.96) and death (AHR 1.17).

Conclusions: While ESRD due to HIV has declined in the United States in the last decade, associated outcomes remain poor and exhibit substantial regional heterogeneity.

Funding: NIDDK Support

SA-PO514

End Stage Renal Disease due to Lupus Nephritis in the United States 2000-2010
Donal J. Sexton, 1 Scott Reule, 2 Scotty Reid, 2 Allan J. Collins, 1 Robert N. Foley, 2
1 USRDS Coordinating Center, MMRE, Minneapolis, MN; 2 Medicine, Univ of Minnesota, Minneapolis, MN.

Background: Despite advances in the treatment of lupus nephritis (LN), the impact of these developments on the standardized incidence of ESRD due to LN in recent years has not been defined.

Methods: We combined US census data with data from the USRDS patients to determine whether incidence rates and survival of ESRD due to LN have improved in parallel with developments in treatment.

Results: 1,161,218 of 1,127,050 (1.0%) patients initiated dialysis due to LN between 2000 and 2010. Using incidence rates for 2000 to calculate expected rates for subsequent years (based on age, sex and race/ethnicity), standardized incidence ratios peaked in 2007 at 1.01 declining subsequently to 0.85 by 2010. Characteristics of ESRD due to LN included age < 40 yrs (53.7% vs. 8.4% in non-LN), female sex (81.5% vs. 44.3%), African American race (50.2% vs. 28.6%), catheters for hemodialysis (89.4% vs. 82.5%), and nephrology care > 1 year (30.5% vs. 23.4%). LN was associated with a lower likelihood of death (adjusted hazard ratio [AHR] 0.99) and a higher likelihood of listing for (AHR 1.58) and receiving a renal transplant (AHR 1.32). Among patients with LN, mortality did not change over time (AHR for 2005-2010 0.99 vs. 2000-2004), and although the likelihood of listing increased (AHR 1.36), transplantation actually decreased (AHR 0.9). Regional variation in outcomes was substantial, with LN patients in the South having lower survival (AHR 0.82 vs. the Northeast) coupled with a higher likelihood of non-listing (AHR 1.39) and non-transplantation (AHR 1.32).

Conclusions: ESRD due to LN in the United States has declined in the last decade, however significant regional variation exists in terms of LN patient outcomes.

Funding: NIDDK Support

SA-PO515

International Mortality Trends among Hemodialysis Patients in the DOPPS
Keith McCullough, 1 Hugh C. Rayner, 2 David A. Goodkin, 1 Hal Morgensen, 1 Friedrich K. Port, 1 Michel Y. Jadoul, 5 Akira Saito, 4 Ronald L. Pisoni, 1 Bruce M. Robinson, 2
11,612 of 1,127,050 (1.0%) patients initiated dialysis due to LN between 2000 and 2010. Using incidence rates for 2000 to calculate expected rates for subsequent years (based on age, sex and race/ethnicity), standardized incidence ratios remained unchanged between 2000 and 2003 and then declined to 0.66 in 2010. Characteristics of LN patients included residence in the South (59.5% vs. 41.5% in non-LN), age < 45 yrs (55.7% vs. 13.1%), male sex (66.9% vs. 55.3%), African American race (87.6% vs. 28.3%), catheters for hemodialysis (90.9% vs. 82.5%), nephrology care < 1 year (90.9% vs. 76.4%), and body mass index < 18.5 kg/m² (12.2% vs. 4.4%). LN was associated with a greater likelihood of failure to be listed for transplant (adjusted hazard ratio [AHR] 4.55), failure to receive a transplant (AHR 6.67) and death (AHR 2.53). Among patients with LN, while mortality (AHR for 2005-2010 0.94 vs. 2000-2004) and non-listing (AHR 1.22) increased (AHR 1.36), transplantation actually decreased (AHR 0.9). Regional variation in outcomes was apparent, with LN patients in the South having higher risks of non-listing (AHR 1.52 vs. the Northeast), non-transplantation (AHR 1.96) and death (AHR 1.17).

Conclusions: While ESRD due to HIV has declined in the United States in the last decade, associated outcomes remain poor and exhibit substantial regional heterogeneity.

Funding: NIDDK Support

SA-PO516

Estimated GFR at Dialysis Initiation: Associations with Clinical and Non-Clinical Factors
Yun Li, 1,2 Alissa Kapke, 1 Yan Jin, 1 Jeffrey Pearson, 1,2 Friedrich K. Port, 1 Bruce M. Robinson, 2
1 Univ of Michigan; 2 Arbor Research Collaborative for Health.

Background: The average estimated glomerular filtration rate (eGFR) at dialysis start has continued to increase in the US. Our objectives are to examine the predictors of eGFR at dialysis start and its change over time.

Methods: The US Renal Data System ESRD database was used to identify 242,957 patients who initiated dialysis between 2006 and 2009, treated by 8,470 physicians and had complete information on variables of interest. Separate random effect models are used to model eGFR and its change over time (2006-2009).

Results: The eGFR at dialysis initiation averaged 10.9 (SD=4.6), rising by 0.5 from 2006 to 2009. On average, patients who were younger, female, uninsured, had fewer comorbidities, initiated dialysis in larger or free standing facilities, and/or in counties with higher poverty rates or lower education levels (Table 1) started dialysis at lower eGFR. The increase in eGFR at dialysis start was significantly steeper among patients who were non-Hispanic whites, received no prior nephrology care, and treated in hospital-based facilities or counties with less poverty (Table 1). The mean eGFR and its change over time also varied significantly by geography (ESRD Network). Between-physician variation accounted for 10% of the total variation in eGFR at initiation. The total variation was reduced by 14% after adjusting for measured patient characteristics and by an additional 4% after further adjustment of facility/county contextual factors.

Conclusions: Analysis of national US data indicates that the majority of variation in eGFR at dialysis initiation occurs at the patient level, though most is unexplained by measured variables in this dataset. Later initiation is correlated with some variables indicative of barriers to access in dialysis.

Table 1: Characteristics Associated with eGFR at Dialysis Start (2006-2009) and eGFR Change over time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (based on age, sex and race/ethnicity)</td>
<td>0.17</td>
<td>0.03</td>
</tr>
<tr>
<td>Sex</td>
<td>0.14</td>
<td>0.11</td>
</tr>
<tr>
<td>Race (Ethnicity)</td>
<td>0.19</td>
<td>0.17</td>
</tr>
<tr>
<td>Employment status</td>
<td>0.76</td>
<td>0.01</td>
</tr>
<tr>
<td>Education</td>
<td>0.81</td>
<td>0.04</td>
</tr>
<tr>
<td>Insurance (yes, no)</td>
<td>0.73</td>
<td>0.17</td>
</tr>
<tr>
<td>Prior nephrology care (yes, no)</td>
<td>0.28</td>
<td>0.14</td>
</tr>
<tr>
<td>Facility type (free standing, hospital based)</td>
<td>0.12</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
SA-PO517

Time Trends in the Association of Influenza Vaccination (IV) with Mortality and Hospitalization in U.S. Medicare Dialysis Patients (2006-2011)

E.L. Cope,1 K.A. Wisniewski,2 M. Curran,1 Bruce M. Robinson,1 Ronald L. Pisoni,1
1Arbor Research Collaborative for Health, Ann Arbor, MI; 2KECC, Univ of Michigan, Ann Arbor, MI.

Background: To assess the association between IV and improved health outcomes, we examined the association between facility-level IV and all-cause mortality and hospitalization over 5 seasons.

Methods: We examined 5 seasons (2006-2007 thru 2010-2011). Each season included Medicare ESRD patients on dialysis Oct 1-Dec 31. Vaccinations were counted using Medicare claims from any setting between Aug 1-Dec 31. Poisson regression was used to assess the relationship of facility IV rate with outcomes in the following year via each facility’s standardized mortality ratio (SMR) and hospitalization (SHR) ratios. Models were adjusted for facility and patient characteristics.

Results: Median facility IV rates fluctuated from 67.6%-71.1%. Facility IV rate was inversely associated with relative risk of mortality and hospitalization for all 5 seasons (Table 1). For mortality, the association was strongest during the 2006-2007 season (2.3% lower SMR per 10% higher facility IV rate, p<0.01), and weakest during the 2010-2011 season (0.8% lower SMR per 10% higher facility IV rate, p<0.01). The association between facility IV rate and hospitalization was relatively stable over time (1.6-2.2% lower SHR per 10% higher facility IV rate, all p<0.01).

Table 1. Mean facility SMR and SHR by percent of facility patients vaccinated against influenza.

<table>
<thead>
<tr>
<th>Facility % Vaccinated</th>
<th>Mean SMR</th>
<th>Mean SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-47.0</td>
<td>1.07*</td>
<td>1.07*</td>
</tr>
<tr>
<td>48-60.0</td>
<td>1.05*</td>
<td>1.05*</td>
</tr>
<tr>
<td>61-70.0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>71-80.0</td>
<td>0.96*</td>
<td>0.96*</td>
</tr>
<tr>
<td>≥80</td>
<td>0.91*</td>
<td>0.91*</td>
</tr>
</tbody>
</table>

Conclusions: An IV performance gap remains with 29% of patients appearing not to be vaccinated in 2010. However, this may be an overestimate due to underreporting of IV in the claims. Associations between facility IV rate and lower hospitalization appeared robust across seasons, whereas those with mortality were less stable and suggest a more modest effect than previously published. Variation in vaccine efficacy and seasonal severity may contribute to fluctuations in the associations over time.

Funding: Other U.S. Government Support

SA-PO518

Recent Risk Factors Associating with Development of Dialysis-Related Amyloidosis: A Nationwide Analysis from Japanese Dialysis Patient Registry

Junichi Hoshino,1 Kunihiro Yamagata,2 Ikuto Masakane,3 Shinichi Nishi,1 Kunimoto Iseki,1 Yoshinobu Tsukibhara,1 1Nephrology Center, Toranomon Hospital, Tokyo, Japan; 2Univ of Tsukuba, Ibaraki, Japan; 3Yabuki Hospital, Yamagata, Japan; 4Kobe Univ Graduate School of Medicine, Hyogo, Japan; 5Univ Hospital of Ryukyu, Okinawa, Japan; 6Osaka General Medical Center, Osaka, Japan.

Background: The aim of this study was to clarify recent risk factors associated with development of dialysis-related amyloidosis, with risk of cardiac tunnel syndrome operation (CTS) as a proxy.

Methods: The cohort consisted of 166,237 patients on dialysis (mean age, 66±12 years) who could be followed for a year between 2010 and 2011. Of these, 2,275 (1.3%) needed a new CTS. Logistic regression was used to calculate adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for new CTS, after adjusting patient’s backgrounds and dialysis factors.

Results: Adjusted OR (aOR) for dialysis vintage (vintage) 10-15, 15-20, 20-25, 25-30, and over 30 years were, respectively, 0.89 (0.81-0.98), 0.75 (0.68-0.83), 0.63 (0.57-0.70), and 0.51 (0.44-0.59), respectively. In addition, female, low serum albumin, and diabetic nephropathy were factors inversely associated with relative risk of mortality and hospitalization for all 5 seasons, we examined the association between facility-level IV and all-cause mortality and hospitalization over 5 seasons.

Methods: We examined 5 seasons (2006-2007 thru 2010-2011). Each season included Medicare ESRD patients on dialysis Oct 1-Dec 31. Vaccinations were counted using Medicare claims from any setting between Aug 1-Dec 31. Poisson regression was used to assess the relationship of facility IV rate with outcomes in the following year via each facility’s standardized mortality ratio (SMR) and hospitalization (SHR) ratios. Models were adjusted for facility and patient characteristics.

Results: Median facility IV rates fluctuated from 67.6%-71.1%. Facility IV rate was inversely associated with relative risk of mortality and hospitalization for all 5 seasons (Table 1). For mortality, the association was strongest during the 2006-2007 season (2.3% lower SMR per 10% higher facility IV rate, p<0.01), and weakest during the 2010-2011 season (0.8% lower SMR per 10% higher facility IV rate, p<0.01). The association between facility IV rate and hospitalization was relatively stable over time (1.6-2.2% lower SHR per 10% higher facility IV rate, all p<0.01).

Table 1. Mean facility SMR and SHR by percent of facility patients vaccinated against influenza.

<table>
<thead>
<tr>
<th>Facility % Vaccinated</th>
<th>Mean SMR</th>
<th>Mean SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-47.0</td>
<td>1.07*</td>
<td>1.07*</td>
</tr>
<tr>
<td>48-60.0</td>
<td>1.05*</td>
<td>1.05*</td>
</tr>
<tr>
<td>61-70.0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>71-80.0</td>
<td>0.96*</td>
<td>0.96*</td>
</tr>
<tr>
<td>≥80</td>
<td>0.91*</td>
<td>0.91*</td>
</tr>
</tbody>
</table>

Conclusions: An IV performance gap remains with 29% of patients appearing not to be vaccinated in 2010. However, this may be an overestimate due to underreporting of IV in the claims. Associations between facility IV rate and lower hospitalization appeared robust across seasons, whereas those with mortality were less stable and suggest a more modest effect than previously published. Variation in vaccine efficacy and seasonal severity may contribute to fluctuations in the associations over time.

Funding: Other U.S. Government Support

SA-PO519

End-Stage Renal Disease from Autosomal Dominant Polycystic Kidney Disease in the United States, 2000-2010

Scott Reule,1 Donal J. Sexton,2,3 Shu-cheng Chen,1 Craig Solod,1 Allan J. Collins,2 Robert N. Foley,1,2 USRDS Coordinating Center, MMRF, Minneapolis, MN; 3Medicine, Univ of MN, Minneapolis, MN.

Background: As early detection and treatment are usually feasible and kidney disease is typically not a consequence of other organ dysfunction, autosomal dominant polycystic kidney disease (ADPKD) can provide a useful perspective on the overall quality of nephrology care. Hence, we determined whether incidence rates and survival of dialysis-requiring ESRD from autosomal dominant kidney disease (ADPKD, N=22,262, 2% of all ESRD in the US) changed between 2000 and 2010.

Methods: Using incidence rates for 2000 to calculate expected rates for subsequent years (based on age, sex and race/ethnicity), standardized incidence ratios, stable with until 2008, declined to 0.89 in 2010.

Results: Characteristics of ADPKD at dialysis initiation included age 40-65 (65.5% vs. 40.8%), white race (80.9% vs. 65.0%), fistula (35.8% vs. 13.4%), and ≥1 year nephropathy care (45.3% Vs. 23.1%). On dialysis, ADPKD was associated with a lower likelihood of death (demography-adjusted hazards ratio [AHR] 0.41) and a higher likelihood of listing for (AHR 2.22) and receipt (AHR 2.83) of a renal transplant. Amongst patients with ADPKD, white race was associated with higher AHR for listing (AHR 1.34 Vs. African American) and transplantation (AHR 2.31).

Conclusions: While ESRD due to ADPKD may have declined and outcomes on dialysis are better than in many other conditions, disparities are present and seamless transition into renal replacement therapy appears to be the exception and not the rule.

Funding: NIDDK Support

SA-PO520

A Retrospective Study on Outcome of MPO-ANCA Associated Vasculitis in Renal Replacement Therapy

Midori Hasegawa, Kyoko Hattori, Kazuo Takahashi, Hiroki Hayashi, Shigeisha Koide, Yukio Yuzawa. Nephrology, Fujita Health Univ School of Medicine, Toyoake, Aichi.

Background: There are few reports on the clinical course of myeloperoxidase - antineutrophil cytoplasm autoantibody (MPO-ANCA) associated vasculitis in renal replacement therapy (RRT). The aim of this study was to conduct a retrospective review of patients with MPO-ANCA associated vasculitis in RRT.

Methods: Birmingham Vasculitis Activity Score (BV AS), patient survival, relapse, and relationships with treatment were examined in our institution, 2 related hospitals, and 5 outpatient clinics in the past 21 years.

Results: Of 90 patients (67±13 years, M/F 51/39) recruited, 69 had microscopic polyangiitis, 20 had renal limited vasculitis, and 1 had granulomatosis with polyangiitis. BV AS at the start of RRT was 12.7±3.4. Of 90 patients (67±13 years, M/F 51/39) recruited, 69 had microscopic polyangiitis, 20 had renal limited vasculitis, and 1 had granulomatosis with polyangiitis. BV AS at the start of RRT was 12.7±3.4. Of 90 patients (67±13 years, M/F 51/39) recruited, 69 had microscopic polyangiitis, 20 had renal limited vasculitis, and 1 had granulomatosis with polyangiitis. BV AS at the start of RRT was 12.7±3.4. Of 90 patients (67±13 years, M/F 51/39) recruited, 69 had microscopic polyangiitis, 20 had renal limited vasculitis, and 1 had granulomatosis with polyangiitis. BV AS at the start of RRT was 12.7±3.4.
SA-PO521
Outcomes in Infants Initiating Chronic Dialysis Less Than 24 Months of Age
Kera E. Luckritz, Rachel Galimberti, Kathryn S. Plommaritis. Pediatric Dialysis, Univ of Michigan, Ann Arbor, MI.

Background: Infants < 2 yrs of age make up less than 15% of the pediatric dialysis population. Survival is also the lowest of all the pediatric dialysis age groups. While peritoneal dialysis (PD) remains the preferred modality in this age group, hemodialysis (HD) is often necessary. Whether outcomes differ for either modality remains unclear.

Methods: Electronic health records were extracted for all patients who started chronic dialysis at <24months of age at our center between 1997 and 2012. Gender, cause of end stage renal disease (ESRD), age at dialysis start, dialysis modality, any modality changes, diagnosis, prescription status, age at transplant, and 6 month, 12 month, 18 month and 24 month survival were queried. Data was entered into a RedCap© database and analyzed with SAS® 9.2 (Cary, NC).

Results: Thirty three patients were identified with a mean age at dialysis initiation of 6.0 months (0.2-22). Most common diagnosis was dysplasia (48.4%). Seventy percent (70.6%) received chronic dialysis (42.1%) and 29.4% received therapy before reaching transplant. Only two of the patients who died were on HD at the time of death. Average age at time of death was 504 days. Causes of death included heart failure (1), infection (1), sepsis (1), pulmonary involvement was related with mortality. It is important to clarify the optimal duration of maintenance therapy after RRT.

Conclusions: The North American Pediatric Renal Transplant Collaborative Studies 2011 report cites a 75% survival in pediatric patients starting dialysis at less than one year of age. Our center demonstrates an overall survival rate >90% with no statistical difference between gender or dialysis modality.

SA-PO522
Changes in Incidence and Prevalence of Diabetic Kidney Disease (DKD) Patients on Renal Replacement Therapy (RRT) in Austria
Friedrich C. Prischl, Martin Auinger, Marcus Saemann, Gert J. Mayer, Antonio Alberto Lopes. 1Universidade Federal da Bahia; 2Universidade Federal do Ceará; 3Universidade Federal do Rio de Janeiro; 4Universidade Federal do Rio Grande do Sul.

Background: DKD is the leading cause of end stage renal disease (ESRD) in Austria.

Methods: We analyzed the Austrian Dialysis- and Transplant Registry for DKD-related ESRD for changes from 1965-2010.

Results: For all HRQOL scales there was a trend to reduction in scores toward higher CI quartiles. CI represents how many patients decreases since 2007. 5-year survival probability has improved significantly between female and male dialysis patients. Measures to idealize unfavorable parameters in each group may improve ultimate outcome.

Funding: Pharmaceutical Company Support - Fresenius Medical Care - Turkey

SA-PO523
Dialyzing Ladies or Gentlemen: Does It Matter? Mehmet S. Seyler, Serra Artan, Fathi Kircelli, Murvet Yilmaz, Gulay Asci, Cengiz Dogan, Kutay Gunestepce, Ali Basci, Erkan Ok. 1Istanbul Medical Fac., Turkey; 2Fresenius Medical Care, Turkey; 3Bakıyok EH, Turkey; 4Ege Medical Fac., Izmir; Turkey; 5CEND Consulting, Turkey.

Background: Application and consequences of hemodialysis treatment may differ between genders. This observational study analyzes hemodialysis practice in a large cohort of male and female patients.

Methods: Data on 1,599,694 hemodialysis sessions performed in 1976 prevalent patients, who were treated in 55 centers between May 2009 - May 2012 were retrieved from the European Clinical Database (EuCID)-Turkey, and submitted for analysis.

Results: Results on various demographic, clinical, laboratory and outcome features of the patients are provided in table-1.

Conclusions: The results suggest that MHD patients with high abdominal fat relative to peripheral fat have, in general, poorer HRQOL. CI index is a simple indicator of abdominal fat deposition that may help identify MHD patient with poorer HRQOL.

SA-PO524
Associations of the Conicity Index, an Indication of Abdominal Fat Deposition, with Health-Related Quality of Life in Maintenance Hemodialysis Patients

Background: A high percentage of abdominal fat relative to peripheral fat represented by the conicity index (CI) is associated with higher death risk in maintenance hemodialysis (MHD) patients (Nephrol Dial Transplant 2010; 25: 562–68) but there is a lack of studies to investigate associations of CI with health-related quality of life (HRQOL). We investigated associations of the CI with HRQOL in MHD patients.

Methods: Cross-sectional analysis of data of 627 patients in the Prospective Study of the Prognosis of Chronic Hemodialysis Patients (PROHEMO) developed in 4 clinics in Brazil. SF-36 was used to generate HRQOL scores of 8 primary scales and two composite indexes. CI was calculated by the following equation(J Clin Epidemiol 1991; 44:955-56): waist circumference (WC) in meters/2 * hip circumference (HC) in meters. CI = WC/HC. CI was divided into 4 equal quartiles. HRQOL was compared between CI quartiles using ANOVA and Pearson’s correlation coefficient (p < 0.05 was considered to be significant).

Results: For all HRQOL scales there was a trend to reduction in scores toward higher CI. CI was also associated with higher death risk in maintenance hemodialysis patients (Nephrol Dial Transplant 2010; 25: 562–68) but there is a lack of studies to investigate associations of CI with health-related quality of life (HRQOL). We investigated associations of the CI with HRQOL in MHD patients.

Conclusions: The results suggest that MHD patients with high abdominal fat relative to peripheral fat have, in general, poorer HRQOL, mainly for physical dimensions. CI index is a simple indicator of abdominal fat deposition that may help identify MHD patient with poorer HRQOL.

SA-PO525
Changes in Rate of Staphylococcus aureus Bacteremia in Hemodialysis Population
Emily A. Christie, Neesh I. Pannu. Nephrology, Univ of Alberta, Edmonton, Canada.

Background: Despite advances in antimicrobial therapies and preventative measures to decrease the rates of catheter-related bloodstream infection (CRBSI) in hemodialysis patients, these infections remain an overwhelming cause of morbidity and mortality. Serious complications from CRBSI occur in approximately 30% to 40% of hemodialysis patients. A landmark study published in 2003 demonstrated a significant mortality benefit of topical antibacterial ointment to central line sites. We evaluated the effects of Northern Alberta Renal Program (NARP) topical antibiotic protocol changes and to study any associated impact on the spectrum of pathogens.

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

747A
Methods: The population studied were adult patients on hemodialysis within NARP, using temporary or tunneled catheters. All patients with documented bacteremia between January 1, 2006 and December 31, 2009 within the Infection Control Database were included. Our analysis focused on the changes in the spectrum of pathogens over time.

Results: Our results revealed a decrease in the overall infection rate from 1.29 to an average of 0.69 bacteremias per 1000 HD runs, a 46.4% decrease. The analysis of the bacterial spectrum causing CRBSI showed a decrease in the proportion of infection caused by common pathogens and a corresponding rise in the rate of Staphylococcus aureus (SA). MRSA rates have shown a gradual increase over time.

Conclusions: The rate of hemodialysis catheter related infections in the NARP population has decreased over the past ten years. The spectrum of pathogens responsible for line-related bacteremias has shifted toward a greater proportion of SA infections. The rate of SA bacteremia in the NARP population is high compared to current published rates. The rate of SA bacteremia in the NARP population has decreased over the past ten years. The spectrum of pathogens responsible for line-related bacteremias has shifted toward a greater proportion of SA infections. The rate of SA bacteremia in the NARP population is high compared to current published rates.

SA-PO526

Overview of Regular Hemodialysis Treatment in China (as of 31 December 2012): Data from Chinese National Renal Data System

Xiang-Mei Chen, Dong Zhang, Qiang Qiu, Xuefeng Sun. Dept of Nephrology, State Key Laboratory of Kidney Disease, General Hospital of Chinese People's Liberation Army, Beijing, China.

Background: This report provides a summary of the 2012 Chinese Renal Replacement Therapy Registry Annual Report.

Methods: The data was recorded on the nationwide, web-based, and prospective registry system, the Chinese National Renal Data System (CNRDS). The patient data including age, gender, laboratory data and clinical and pathology diagnoses was recorded on the web page of the CNRDS. We analyzed the characteristics and trends of chronic hemodialysis in 2012.

Results: There were 3,540 hemodialysis centers in China having been registered in CNRDS. The total number of patients undergoing hemodialysis at the end of 2012 was 221,628. The mean age of all patients was 52.4±14.4 years and the proportion of male was 58.7%. The mean duration of hemodialysis was 2.9±2.8 years. Primary diseases of all patients were respectively primary glomerular diseases (58.1%), diabetic nephropathy (16.5%), hypertensive nephropathy (10.1%), polycystic kidney disease (3.3%), renal calculus (2.0%) and others (10.0%). The standard-achieving rate of blood pressure (110/74 mmHg) was 36.8%. The average dose of erythropoietin was 4,879 RLS cases by ICD-9 RLS code (333.94) and 4 age-sex-race matched non-RLS controls. A total of 2,133,440 individuals with ESRD diagnosed between 1963 and 2009 were identified, and 13,560,760 hospital records from 1977 through 2008 were available for analysis. There were 459 (0.02%) patients who met the criteria for CPX. For this group: age was 50.4±15.7 years with 20.5% ≥ 65 years, 71.0% female, 59.0% white, and 31.3% African American. Treatment modality at the time of CPX diagnosis: center-based hemodialysis (HD) (361; 78.7%), peritoneal dialysis (PD) (68; 14.8%) and transplant (11; 2.4%). The median survival time for individuals with CPX was 1.1 years and 50% of the deaths were within 87 days of their CPX diagnosis. Co-morbidities associated with CPX included: obesity (79.1%), diabetes mellitus (65.8%), coronary artery disease (47.7%), bacteremia (43.1%), and history of parathyroidectomy (28.1%).

Conclusions: Although rare, CPX is associated with a very high mortality. It is more commonly seen in diabetics, obese individuals, females, and patients on in-center HD. Cardiovascular disease and severe mineral bone disorders may also be present. Bacteremia is a common complication and may contribute to the rapid demise associated with the diagnosis.

SA-PO528

Risks for Mortality in Hemodialysis Patients with Bacteremia

Stephanie L. Baer, Rhonda E. Colombo, Jay Desai, Lu Y. Huber, Puja Chebrolu, Mufaddal F. Kheda, Stanley Nahman, Kristina W. Kintziger. A VAMC, Augusta, GA; Georgia Regents Univ, Augusta, GA.

Background: Bacteremia (BAC) occurs in over 20% of incident hemodialysis (HD) patients (Chebrolu, IDS 2012). BAC is clinically associated with significant morbidity and mortality. We queried the USRDS to assess risk factors associated with 30-day mortality after a diagnosis of BAC.

Methods: All incident adult HD cases from the USRDS for 2005-2008 were queried for a diagnosis of BAC, mortality, and comorbidities, using ICD-9 codes and data from form 2728. Bivariant and multivariable analyses were performed.

Results: There were 359,882 adult incident HD patients available for analysis, of which 78,425 (21.8%) had BAC during the study period. Of these, 15,576 (19.9%) died within 30 days of BAC. Those with a significantly greater risk of 30-day mortality were 65+ years [relative risk (RR) 2.19, 95% confidence interval (CI) 2.12-2.27], and: Candida colonization [RR 1.73, 95% CI 1.61-1.22], cirrhosis [RR 1.73, 95% CI 1.64-1.83], peripheral vascular disease [RR 1.20, 95% CI 1.16-1.24], meningitis [RR 1.62, 95% CI 1.28-2.0], pneumonia [RR 1.23, 95% CI 1.18-1.27], endocarditis [RR 1.30, 95% CI 1.21-1.40], pancytopenia [RR 1.17, 95% CI 1.02-1.35], diabetic ulcer [RR 1.53, 95% CI 1.48-1.59], C. difficile colitis [RR 1.18, 95% CI 1.12-1.24], TPN [RR 1.73, 95% CI 1.62-1.85], or critical care [RR 1.42, 95% CI 1.38-1.46]. The following factors significantly reduced the risk of 30-day mortality: being black [RR 0.79, 95% CI 0.77-0.82], Hispanic [RR 0.76, 95% CI 0.72-0.80], diabetes [RR 0.87, 95% CI 0.84-0.89], kidney transplant [RR 0.56, 95% CI 0.45-0.70], lupus [RR 0.79, 95% CI 0.68-0.93], glomerulonephritis [RR 0.81, 95% CI 0.72-0.92], osteomyelitis [RR 0.80, 95% CI 0.74-0.87], and MRSA infection [RR 0.72, 95% CI 0.67-0.77].

Conclusions: Of HD patients, over 20% will acquire BAC and 20% of those will die within 30 days. Risk factors for mortality include age, Candida colonization, cirrhosis, peripheral vascular disease, meningitis, pneumonia, endocarditis, pancytopenia, decubiti, C. difficile, TPN, or critical care.

SA-PO529

Restless Legs Syndrome and Drug Therapy among Dialysis Patients: USRDS Part D and Special Study Data

Nancy G. Kutner, Rebecca H. Zhang, Donald L. Bliwise. USRDS Rehabilitation/Quol Special Studies Ctr, Emory Univ, Atlanta, GA; ‘Neurology, Emory Univ, Atlanta, GA.

Background: Restless legs syndrome (RLS) is reported by 15%-30% of dialysis patients, but RLS contributors are not well specified. Use of medications with central nervous system (CNS) effects, shown to be associated with symptoms of RLS in the general population, merits study.

Methods: In USRDS Part D data for incident patients 10/1-12/31/10 we identified 4,879 RLS cases by ICD-9 RLS code (333.94) and 4 age-sex-race matched non-RLS controls (n=1,616). Patients identified as having Restless Leg Syndrome (RLS) per the International Restless Legs Syndrome Study Group criteria, with symptom frequency of 5 times/month or more and severity rated at least moderate or more severe over the last month, and patients’ current home medication lists were reviewed. Use of dopamine agonists prescribed for RLS was also examined. In addition, among 377 prevalent patients undergoing hemodialysis 2009-11 in the Atlanta USRDS ACTIVE-AIDPOSE study cohort, patient-reported RLS was identified by the International Restless Legs Syndrome Study Group criteria, with symptom frequency of 5 times/month or more and severity rated at least moderate or more severe over the last month, and patients’ current home medication lists were reviewed.

Results: RLS Dx was clearly associated with use of Requip, Mirapex, and Sinemet, drugs commonly prescribed to treat RLS. However, the odds of patients with RLS Dx having CNS drugs prescribed were significantly greater for every comparison except antipsychotics prior to RLS Dxs.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-POS30

Maternal and Long Term Offspring’s Outcomes Derived from Pregnancies in Women Suffering from End Stage Renal Disease under Renal Replacement Therapy

Amelia Rita Bernascconi,1 Ricardo M. Heguilen,1 'Medicine, Hospital J.A. Fernandez, Calba, Bs As, Argentina; 'Medicine, Hospital J.A. Fernandez.

Background: Despite fertility is compromised in women with end stage renal disease (ESRD), pregnancy occurs even in those receiving renal replacement therapy (RRT). In this retrospective study we report a 13-year experience of a nephro-obstetric group. The main aim was to analyze the outcome of a large cohort of pregnant women under RRT. Long-term maternal follow up with emphasis in perinatal and childhood outcomes are described. Methods: Transversal study which including non-DBT RRT-requiring ESRD women and their offspring’s. Results: 40 consecutive P (3 twin, and 1 triple) in 38 non-DBT ESRD pts (30.6 ± 1.2 y/o), assisted from January 1, 2000 until June 1, 2013 were analyzed. 27/38 pts were already under RRT at pregnancy, 11 started HD during pregnancy. Hypertension worsened in 8 so dose had to be increased or an additional drug had to be added. Polyhydramnios and/or metoclopramide therapy prescribed. In the Atlanta prevalent cohort (median age 3 years), RLS was reported by 17.8%, and 40% of these participants had one or more antidepressant, anti-histamine, anti-psychotic, and/or metoclopamid therapy prescribed. Conclusions: These data suggest the value of carefully reviewing prescription of CNS drugs known to increase the risk for RLS symptoms. Funding: NIDDK Support

SA-POS31

Procalcitonin (PCT) as Bacterial Infection Marker in Patients with Renal Disease

Alba Santos, Nayara Panizo, David Arroyo, Javier Reque, Borja Quiroga, Isabel Galán Carrillo, Mariano Goicoechea, Jose Luno. Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

Background: PCT is a well-known marker to identify bacterial infections in general population. However, the usefulness of this biological marker has not been proved in patients with renal disease. The aim of this study was to evaluate the accuracy of PCT as bacterial infection marker in patients with renal dysfunction. Methods: 62 patients (mean age: 60.1 ±15.1 years, 33 M, 29 W) with renal disease (34 on dialysis, 34 transplant recipients and 4 with AKI) who were admitted to the emergency department with fever (> 38ºC) were included in the study. Baseline characteristics, analytical and microbiological data were collected. Results: Positive microbiological cultures was found in 33 patients. PCT levels were higher in patients with positive cultures than in negative-cultured patients (17.7±33.4 vs 2.1±4.9 μg/L, p=0.012). No differences in CRP, leukocytes and fibrinogen levels were found between patients with positive or negative cultures. Positive cultures included 27 bacterial (17 gram-negative and 10 gram-positive ), 2 fungi and 4 viral infections. PCT levels were higher in bacterial vs viral infection (20.06±35.02 μg/L vs 0.47±33.33 μg/L, P=0.018). PCT levels were correlated to CRP (r=0.689, p=0.001), fibrinogen (r=0.413, p=0.003) and neutrophil count (r=-0.243, p=0.05). PCT concentration was negatively correlated with systolic (r=-0.412, p=0.01) and diastolic blood pressure (r=-0.287, p=0.029). Positive microbiological cultures and CRP levels determined PCT concentration in multivariate lineal regression analysis (β=0.258 y 0.484, p=0.045 y p=0.001, respectively). The ROC curve for PCT was 0.640 with pooled specificity 97% and sensitivity 31%, LR positive: 10.33 and LR negative: 0.71. Conclusions: PCT is a useful infection marker in patients with renal disease, as it helps to identify bacterial infection, with high specificity although low sensitivity. Other clinical and biological markers do not permit to identify bacterial infection in renal disease patients.

SA-POS32

Glycemic Control Is a Predictor of Infection in Hemodialysis Patients: Miyazaki Dialysis Cohort Study (MID Study)

Tatsunori Toida,1 Yuki Satō,1 Hiroyuki Komatsu,1 Masao Kikuchi,2 Shouichi Fujimoto.2 'Dept of 1st Internal Medicine, Faculty of Medicine, Univ of Miyazaki; ‘Dept of Hemovascular Medicine and Artificial Organs, Faculty of Medicine, Univ of Miyazaki, Japan.

Background: There are limited data on the association between infection and glycemic control in diabetic patients on hemodialysis (HD). We investigated the impact of glycemic control on infection risk among diabetic patients on HD. Methods: Patients with maintenance HD (n=1551) were enrolled in the MID Study in December 2009 and followed up for 3 years. The diagnosis of diabetes at baseline and information on clinical events of infection (1 hospitalization with infection, 2 hospitalization with pneumonia, 3 onset of pneumonia) during follow-up were extracted from the medical records. Cox regression analysis was used to examine the association between glycemic control and the events. Results: At baseline, there were 493 patients with diabetes and 1058 patients without it. Compared with those in the bottom criterion of HbA1c level (HbA1c<5.0%), the multivariable-adjusted hazard ratio for hospitalization with infection was not increased in the second and third criterion of HbA1c (HbA1c 5.1–6.0% to 6.1–7.0%), but was significantly increased to 8.43 (95% CI 2.62-27.11) in the group with poorest glycemic control (HbA1c>7%). Similarly for hospitalization with pneumonia or onset of pneumonia, the multivariable-adjusted hazard ratios in the group with poorest control were 6.30 (95% CI 1.15-34.55) and 3.88 (95% CI 1.06-14.17), respectively. Conclusions: Poor glycemic control (HbA1c≥7%) was associated with high infection risk among HD patients. The relationship between glycemic control and infection risk is not linear, so there might be a possibility of increasing the risk of infection depending on the glycemic control threshold.

SA-POS33

p-Cresyl Sulfate Directly Associates with FGF23 and Aortic Calcification in Chronic Kidney Disease Patients, Independent of Kidney Function

Liesbeth Viaene,1 Sam Heye,2 Kathleen Claes,1 Bjorn Meijers,1 Pieter Evenepoel.1 'Nephrology, Univ Hospitals, Belgium; ‘Radiology, Univ Hospitals, Belgium.

Background: Vascular calcification is common in patients with chronic kidney disease (CKD) and associates with increased cardiovascular morbidity and mortality. As opposed to coronary artery calcification, data on the prevalence and risk factors of aortic calcification (AC) in CKD are scarce. Recent studies suggested that uremia-related risk factors may be of great importance, as they may act synergistically with traditional risk factors. The present cross-sectional observational study aimed to clarify the role of p-cresyl sulfate (PCS), indoxyl sulfate (IndS) and mineral metabolism disturbances in the pathogenesis of AC in CKD.

Methods: Parameters of mineral metabolism, including FGF23, calcitriol, calcitriol and PTH, and PCS and IndS (HPLC) were assessed in 264 CKD patients (61% males; 58 ±14 years, CKD stage 1-5D). AC was assessed by lateral lumbar X-ray. Results: AC was present in 68% of patients. Age and diabetes were identified as major determinants of AC. The adjustment for traditional risk factors attenuated but did not erase the association between CKD and AC.

PCS and FGF23 levels showed an inverse relationship with renal function and a direct relationship with AC. PCS was identified as determinant of FGF23, independent of classical determinants. In multivariate regression analysis, age, diabetes mellitus and PCS were identified as independent determinants of AC. When FGF23 was included, it replaced PCS in the final model.

Conclusions: High PCS and FGF23 levels are associated with an increased risk of aortic calcifications, independent of traditional risk factors and renal function. The link between PCS, FGF23 and AC requires further research. Experimental data suggest that Klotho deficiency might be the common pathway.
SA-PO534
Correlation of Fibroblast Growth Factor-23 with Carotid Atherosclerosis in Patients with Chronic Kidney Disease
Anil Kumar Yadav, Alok Goel, Sunil Agarwal, Shuchi Bhattacharjee, Om Parkash Kalra. 
Univ College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India.

Background: FGFR-23 is increased early in CKD and is recognized as an important predictor of cardiovascular morbidity and mortality in these patients. Carotid Intima Media Thickness (CIMT) has been used as a surrogate marker of atherosclerosis and can be used to predict cardiovascular risk in these patients. Study the levels of FGFR-23 and intact parathyroid hormone (iPTH) and measure CIMT and then assess the correlation between these parameters in patients with various stages of CKD.

Methods: This cross-sectional study consisted of 75 subjects in the age group of 21 to 60 years, divided into 3 groups (25 in each). Group I: Healthy controls, Group II: CKD stage 2, 3, and 4 patients and Group III: CKD stage 5 patients on hemodialysis for ≥3 months. C-FGF-23 and iPTH estimation was done by ELISA method. CIMT was measured using Doppler ultrasound.

Results: All the 3 groups were age and sex matched. Mean C-FGF-23 was found to be significantly higher in Group III patients (622.17±42.45 rU/mL) when compared with group I (53.95±8.11 rU/mL), or Group II patients (213.59±107.21 rU/mL) (p<0.001 for all). Further, C-FGF-23 levels in stage 2 CKD patients were found to be significantly higher than healthy controls (p<0.001). Similarly mean iPTH was significantly higher in Group III patients (543.90±59.24 pg/mL) as compared to group I (42.99±8.84 pg/mL), and group II patients (150.39±126.48 pg/mL) (p<0.001 for all). Further, no significant difference in iPTH was found between healthy controls and stage 2 CKD patients (p=0.708). Mean CIMT was significantly higher in Group III (0.45±0.1 mm) when compared with Group I (0.45±0.1 mm) or Group II patients (0.50±0.1 mm) (p<0.001 for all). A significant positive correlation was found between C-FGF-23 and CIMT in all groups (r=0.716).

Conclusions: C-FGF-23 is the earliest marker of mineral bone disorder and is increased in CKD even in stage 2 patients and shows a positive correlation with carotid atherosclerosis. Funding: Government Support - Non-U.S.

SA-PO535
Urinary Soluble Klotho Significantly Predicts Renal Outcomes in Patients with Chronic Kidney Disease

Background: Low serum Klotho levels have been reported to be associated with adverse kidney disease outcomes, while the urinary Klotho levels have been suggested to be a more sensitive biomarker than the serum Klotho levels in patients with chronic kidney disease (CKD). The purpose of this study was to identify the relationship between the urinary Klotho levels and the renal function in patients with CKD and investigate whether the urinary Klotho levels can predict kidney disease outcomes in patients with CKD.

Methods: We analyzed the urinary soluble Klotho levels in a cohort of 161 patients with stage 1-5 CKD and assessed the relationships between the urinary Klotho-to-creatinine ratio (Klotho/ Cr) and proteinuria and the kidney function. The patients were prospectively followed for two years to monitor for doubling of the baseline serum creatinine concentration and the initiation of renal replacement therapy.

Results: The urinary Klotho/Cr level was positively correlated with eGFR and proteinuria and negatively correlated with changes in proteinuria during the follow-up period. The patients were categorized into two groups according to the baseline median urinary Klotho value. Renal survival was significantly lower in the patients with a Klotho/Cr ratio of ≤0.321 µg/gCr than in those with a urinary Klotho/Cr ratio of >0.321 µg/gCr (p=0.0398). A Cox regression analysis adjusted for age, gender, hypertension, diabetes, dyslipidemia, eGFR, proteinuria, hemoglobin, phosphate and fibroblast growth factor 23 showed that a urinary Klotho/Cr ratio of >0.321 was significantly associated with a reduced risk for the renal end point. The adjusted odds ratio for a urinary Klotho/Cr ratio of >0.321 was 0.62 (95% confidential interval: 0.37-0.99; p = 0.0471).

Conclusions: In this study, lower levels of urinary Klotho were significantly associated with renal outcomes, suggesting that a lower urinary Klotho level can serve as a novel biomarker for CKD progression.

SA-PO536
Klotho Deficiency Contributes to Uremic Cardiac Hypertrophy and Fibrosis in Mice
Jian Xie, Joonho Yoon, Makoto Kuroo, Chou-Long Huang. UT Southwestern Medical Center, Dallas, TX.

Background: Klotho (KL) is a membrane protein produced mostly in the kidney; its ectodomain is released as a soluble protein. We have reported that soluble Klotho (sKL) protects the heart against stress-induced cardiac hypertrophy and fibrosis, by inhibiting TRPC6 channel in the heart & independently of FGFR23. We examined whether reduced serum sKL contributes to cardiomyopathy in CKD.

Methods: Wild type (WT) and heterozygous (Het) KL-deﬁcient (kl) mice (129Sv) were rendered CKD by 5/6 nephrectomy (Nx) or sham surgery for 4 wk.

Results: Serum sKL levels (assayed by IP + western blot) were lower in Het vs WT mice, and both were further reduced by 5/6 Nx. CICl was reduced ~60% by 5/6 Nx, but not different between WT and Het. Heart weight/body weight ratio (HW/BW, mg/g) of WT mice was increased by 5/6 Nx (sham & CKD: 4.1±0.1 & 5.4±0.2, p<0.01); CKD-induced increase was enhanced in Het (sham & CKD: 4.0±0.1 & 6.2±0.2, p<0.01; also p<0.01.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Comparison of Cinacalcet plus Paricalcitol to Cinacalcet plus Calcitriol Therapy in Hemodialysis Patients with Severe Hyperparathyroidism

Siren Seger,1 Zeynep Bal,2 Emre Tutar,1 Özfur Kılınç,2 İbrahim Yıldırım,3 Burak Sayın,4 Ruya Ozelsonak,5 Sultan Ozturk,3 Nurhan Özdemir Acar,3 1Dept of Nephrology, Baskent Univ Faculty of Medicine, Turkey; 2Dept of Nephrology, Sakarya Univ Education and Research Hospital, Turkey; 3Dept of Nephrology, Bursa Ege Univ Faculty of Medicine, Turkey; 4Dept of Medicine, Hitt&ruml;i Univ Education and Research Hospital, Turkey.

Background: Clinical guidelines and literature reviews support the combination therapy with cinacalcet and vitamin D receptor (VDR) agonist (calcitriol) in dialysis patients with SHPT. However, there are no widely accepted consensus on the most effective type and dose of combination. The aim of this study is to evaluate and compare the effectiveness of cinacalcet and paricalcitol or calcitriol treatment in MHD patients with severe SHPT.

Methods: A total of 114 patients with severe SHPT on chronic hemodialysis three times a week for at least 3 months were enrolled into the study. Patients with serum calcium concentration <10.5 mg/dL, serum Ca × P<7.5 and PTH level ≥1000 pg/ml were divided into two groups either who received cinacalcet plus intravenous paricalcitol (Group CP) or cinacalcet plus intravenous calcitriol (Group CC). Patients were followed up during a 52-week safety assessment period (SAP). Adverse events were collected throughout the trial.

Results: 292 subjects were on FC. The 149 AC subjects included 78 on SC, and 41 on CA and 30 (CB). During the SAP, 49% of subjects in the AC group experienced a serious adverse event (SAE) while only 10% of subjects did so in the FC group (p ≤ 0.001). The percentages of AC subjects with SAE’s in the infection, gastrointestinal (GI), cardiac and vascular categories were greater than those in the FC group. The number of treatment emergent adverse events (including serious and non-serious adverse events) per subject was 5.6 in FC and 6.5 in AC.14.2% of FC subjects and 9.4% of AC subjects discontinued from the trials or stopped study drug and continued in the trial. Despite a greater percent of GI SAEs in the AC group, the most common reason for discontinuation of study drug or withdrawal from the trial in the FC group was a GI adverse event. The difference in GI adverse events was expected because of the entry criterion requiring tolerance to AC drugs, while all subjects were naïve to FC.

Conclusions: FC, an efficacious phosphate binder, had an excellent safety profile when compared to currently available phosphate binders.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

SA-PO544

A Prospective Study to Evaluate the Efficacy of Total Parathyroidectomy in Retarding Vascular/Valvular Calcification and Improving Bone Mineral Density in End-Stage Renal Disease Patients—PROCEED Study

Anjela Yee Moon Wang,1 Brian Lang,2 Yu Yau,1 Wai Kei Lo,3 1Medicine, Queen Mary Hospital, Univ of Hong Kong, Hong Kong, Hong Kong; 3Radiology, Queen Mary Hospital, Univ of Hong Kong, Hong Kong, Hong Kong; 2Imaging Center, Hong Kong, Hong Kong; 3Medicine, Tung Wah Hospital, Hong Kong, Hong Kong.

Background: Severe hyperparathyroidism (aSHPT) has been associated with increased risk of mortality & cardiovascular deaths in chronic kidney disease (CKD)-5D patients. We hypothesized that total parathyroidectomy (PTx) may retard vascular/valvular calcification & improve bone mineral density (BMD).

Methods: We conducted a prospective longitudinal study in 62 CKD-5D patients (mean age:55±11y;28% with previous fracture) with severe SHPT resistant to conventional medical therapy who underwent total PTx with forearm autograft. Primary endpoints were changes in vascular & valvular calcification assessed by plain coronary multislice computed tomography 1 year after PTx. Secondary endpoint was changes in BMD, Z-score & t-score by dual X-ray absorptiometry scan.

Results: Pre-operative median (interquartile range) total coronary artery calcium score (CACS) was 560 (190 - 1338) & significantly increased to 609 (228 - 1558)(P<0.014) at 1 year while mitral & aortic valve calcium score did not change significantly after 1 year. BMD at forearm [P=0.05], femur [P<0.001] & lumbar spine [P<0.001] showed significant increase 1 year after PTx & was associated with sig. improvement in t-score & z-score at corresponding sites. CACS was stabilized or reduced in 30 patients while progression in CACS (as defined by ≥15% increase from pre-op CACS) was observed in 20 patients (40%). iPTH [P<0.001], serum calcium [P<0.001], phosphorus [P<0.001] & alkaline phosphatase [P<0.001] showed sustained significant reduction 1 year after PTx.

Conclusions: Total PTx significantly improves biochemical parameters of CKD-mineral bone disease & BMD but did not necessarily retard vascular/valvular calcification in CKD-5D patients with severe SHPT, contrary to previous reports. The exact mechanisms whereby PTx improves clinical outcomes in PTx patients warrants further investigation.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author/disclosure.

751A
Impact of Ferric Citrate, an Oral Phosphate Binder, on Mineral and Bone Metabolism Markers in Dialysis Patients

**Background:**
We conducted a multicenter, international, randomized, open-label clinical trial of a novel phosphate binder.

**Methods:**
441 dialysis subjects were enrolled in a trial consisting of two weekly washout periods during which both binders were stopped and a 52-week Safety Assessment Period (SAP) in which patients were randomized to 2:1 ferric citrate (FC) or calcium carbonate (CC). Successful compliance was observed in both groups.

**Results:**
Results for mean serum phosphorus, calcium, iPTH and albumin post-washout and at the completion of the SAP are in the table. Throughout the study, between 51% and 61% of patients had phosphorus in the 3.5 to 5.5 mg/dL range, without significant differences between the two groups.

**Conclusions:**
Traditional markers of bone and mineral metabolism were similar in the AC and FC groups. The authors concluded that FC can achieve control of MBD parameters comparable to current usual care among both groups.

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

**Funding:**
Pharmaceutical Company Support - Keryx Biopharmaceuticals

SA-PO543

**Impact of Ferric Citrate, an Oral Phosphate Binder, on Mineral and Bone Metabolism Markers in Dialysis Patients**

**Methods:**
A Phase 3, multicenter, randomized, double-blind, placebo-controlled study of 610 patients randomized to FC and 149 to AC. The AC group consisted of 292 participants treated with sevelamer carbonate, 41 with calcium acetate, and 30 with a combination of these agents.

**Results:**
Results for mean serum phosphorus, calcium, iPTH and albumin post-washout and at the completion of the SAP are in the table. Throughout the study, between 51% and 61% of patients had phosphorus in the 3.5 to 5.5 mg/dL range, without significant differences between the two groups.

**Conclusions:**
Traditional markers of bone and mineral metabolism were similar in the AC and FC groups. The authors concluded that FC can achieve control of MBD parameters comparable to current usual care among both groups.

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

**Funding:**
Pharmaceutical Company Support - Keryx Biopharmaceuticals

SA-PO544

**The Effect of JTT-751 (Ferric Citrate Hydrate) on Phosphorus and FGF-23 in Chronic Kidney Disease**

**Background:**
JTT-751 is a novel iron-based phosphate binder (P) that is developed for hyperphosphatemia in patients with chronic kidney disease (CKD).

**Methods:**
A Phase 3, multicenter, randomized, double-blind, placebo-controlled trial conducted the efficacy and safety of JTT-751 in non-dialysis dependent patients with CKD. A total of 90 patients with a serum P level of 5.0 mg/dL or higher were randomized to a 52-week safety assessment period, with overall low aluminum levels in both groups despite the citrate component of FC and as expected given the use of calcium-containing binders.

**Results:**
The mean change in serum P level at EOT was -1.29 mg/dL in the JTT-751 group and 0.06 mg/dL in the placebo group (P<0.001). The percentage of patients achieving a target serum P level at EOT was 64.9% in the JTT-751 group and 6.9% in the placebo group (P<0.001). Treatment with JTT-751 significantly reduced intact FGF-23 levels (P<0.001).

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

**Funding:**
Pharmaceutical Company Support - Keryx Biopharmaceuticals

SA-PO545

**Calcium Supplementation Affects Calcium Balance but Not Bone Mineral Density in Older Women with Moderate Chronic Kidney Disease**

**Background:**
Serum calcium and intact parathyroid hormone (iPTH) were 9.3 ± 0.4 mg/dL and 66 ± 34 pg/mL, respectively. Fecal calcium excretion was assumed to be 1.000 mg/day. Participants were in negative calcium balance at baseline. During the course of the study the change in calcium balance was positive and significantly higher than baseline (m 0 to m 12: 1170.8 ± 1001.0 pg/mg/day; P=0.001). In linear regression models adjusted for age, height, weight, serum calcium, iPTH, 25-hydroxyvitamin D, eGFR, and intervention, a positive calcium balance was not associated with increased radial BMD at 12 (m 0.70) and 24 months (m 0.08).

**Conclusions:**
Calcium supplementation of 1,200 mg/day produced a positive calcium balance in older women with CKD, which was not related to improvements in radial BMD.

**Funding:**
NIDDK Support

SA-PO546

**Cinacalcet Improves Survival in Dialysis Patients – A European Cohort Study**

**Background:**
Dialysis patients are at excess risk of mortality. Observational studies have shown that high PTH, serum phosphorus and calcium are independent risk factors for cardiovascular and all-cause mortality in dialysis patients. Cinacalcet has proven to be data sufficient to improve these parameters. Aim of the present study was to test whether Cinacalcet treatment is associated with better survival in a cohort of Austrian dialysis patients.

**Methods:**
Data from all prevalent dialysis patients from 01.01.2004 to 31.12.2009 (n=8225) were retrospectively evaluated. Data were obtained from the Austrian Dialysis and Transplant Registry. Patients without information about prescription of cinacalcet (n=164), age <18 years as well as a survival time of <90 days were excluded. Survival analysis was performed using the Kaplan Meier model and the Royston-Parmar model. (n=8225) were retrospectively evaluated. Data were obtained from the Austrian Dialysis and Transplant Registry. Patients without information about prescription of cinacalcet (n=164), age <18 years as well as a survival time of <90 days were excluded. Survival analysis was performed using the Kaplan Meier model and the Royston-Parmar model. Survival analysis was performed using the Kaplan Meier model and the Royston-Parmar model.

**Results:**
The final study cohort included 7983 dialysis patients (n=7251 hemodialysis; n=752 peritoneal dialysis), where 1572 (19.7%) had a prescription of cinacalcet.

**Conclusions:**
Cinacalcet treatment is associated with better survival in a cohort of Austrian dialysis patients.

**Funding:**
Pharmaceutical Company Support - Keryx Biopharmaceuticals
SA-PO547

Meal-Induced Change in Bone Mineral Variables in End-Stage Renal Disease Hariprasad S. Trivedi, Aniko Szabo. Medical College of WI.

Background: Management of mineral and bone disorder is one of the important facets of care of end-stage renal disease (ESRD) subjects. As part of the same, bone mineral variables are regularly tested. However, these are randomly tested generally depending on when the patient presents for dialysis. Whether meals consumed by the patient affects those variables is not known.

Methods: As part of a study of circadian variation of bone mineral variables in ESRD we pre-planned evaluation of the effect of a mid-day meal on bone mineral variables in these subjects. Consenting subjects with ESRD and controls consumed a study diet containing 1200 mg calcium and 1000 mg of phosphorus per day for 5 days. In ESRD subjects phosphate binders, active vitamin products, and cinacalcet were discontinued prior to beginning the study diet. On the sixth day while the same diet was continued blood was drawn around 12 noon, followed by lunch and a second blood draw at 2:00 pm. In each sample phosphate, ionized calcium, intact parathyroid hormone (PTH), and 25-hydroxy vitamin D (25OHD) were tested. Within each group, mean difference of log-transformed values of each analyte, post-lunch versus pre-lunch, were analyzed using a paired t-test. Data are presented as ratios (post-lunch-pre-lunch). Two sample t-test was used to compare the values.

Results: 17 ESRD subjects (15 men, 2 women, mean age 45±12 years, 7 whites, 10 African-Americans) and 8 controls (6 men, 2 women, mean age 55±14 years, 4 whites, 4 African-Americans) participated in the study. In ESRD subjects post-lunch phosphate was significantly higher by about 12% (ratio 1.12, p=0.0039) while ionized calcium was lower (ratio 0.94, p=0.06). PTH tended to be higher post-lunch but did not reach statistical significance (ratio 1.12, p=0.06). In control subjects only 25OHD was significantly different after the meal (ratio 0.94, p=0.0365). The between-group comparison showed that post-lunch the change in phosphate tended to be greater in ESRD subjects versus controls (p=0.05).

Conclusions: In ESRD phosphate is higher while calcium is lower after a meal. These variations should be considered during clinical testing.

Funding: Other NIH Support - Supported in part by grant 1UL1RR031973 from the Clinical and Translational Science Award (CTSA) program of the National Center for Research Resources, National Institutes of Health, Pharmaceutical Company Support - Genzyme Corporation, Private Foundation Support, Clinical Revenue Support

SA-PO549

Biochemical and Clinical Results (Phase I) of the Multicentric Study on the Prevalence of Vascular Calcifications and Vertebral Fractures in Parathyroidectomised (PTX) Dialysis Patients (Cave PTX Study) Sandro Mazzafferro, Sapienza Univ, Rome, Italy.

Background: The CA VE PTX study aims to evaluate, in PTX dialysis pts, the control of divalent ions and medical therapies (phase I), and the prevalence of aortic calcifications and vertebral fractures (phase II).

Methods: Biochemistries (Ca, P, PTH) and therapies of PTX patients were collected from 149 Italian dialysis Units. A control group (C), comparable for age, sex and dialysis duration, was selected from the whole cohort. We report the data of biochemistries and therapies.

Results: Out of 12515 patients (HD = 87.7%; PD = 12.3%), 528 (4.22%) received PTX. PTX prevalence was higher in HD (4.5% vs 1.9% in PD). Cases and C (n=437) data are in tab 1.

SA-PO550

Success of Educational Interventions in the Management of CKD-MBD Nimish Mehta, Anne Le. Medscape, LLC, New York, NY.

Background: Mineral and bone disorders in patients with chronic kidney disease (CKD-MBD) are frequently underrecognized and inadequately treated. A study was conducted to determine if on-line educational interventions could improve competence and performance of nephrologists and cardiologists with respect to CKD-MBD management.

Methods: A cohort of US-practicing nephrologists and cardiologists who participated in 1 of 3 educational interventions designed to address gaps in care of patients with CKD-MBD was assessed. The outcomes survey method, previously validated to measure performance, included knowledge- and case-based, multiple-choice questions focused on current evidence-based recommendations for the assessment and management of patients with CKD-MBD. Responses from the clinical cases and questions aligned with individual interventions were collected from the participant cohort and compared with a matched control group of nonparticipants.

Results: For each educational intervention, 200 nephrologists and cardiologists were assessed, divided equally between participants in the education and a matched control group of nonparticipants. Significant improvements were found as a result of participation in the educational interventions. For example, participants were more likely than nonparticipants to determine:

- A greater calcium intake than output in a patient, resulting in a positive calcium balance (nephrologists 80% vs 60%, P<0.001; cardiologists 74% vs 40%, P<0.05)
- The role of the vitamin D-independent pathway for calcium absorption (nephrologists 56% vs 32%, P<0.02; cardiologists 36% vs 18%, P<0.04)
- Influence of diurnal fluctuation in serum phosphorus levels and dietary protein intake on a patient's serum phosphorus measurements
- Increased risk of cardiovascular calcification with calcium-containing phosphorus binders (cardiologists 52% vs 35%, P<0.05)

Conclusions: This study demonstrated the success of targeted educational interventions on improving the practice patterns of nephrologists and cardiologists in the assessment and management of patients with CKD-MBD.

Funding: Pharmaceutical Company Support - Amgen unrestricted grant

SA-PO551

Examination of Tissue Phosphorus Deposition in Patients Undergoing Hemodialysis Using Current Standard Techniques Tomu Hyodo,1 Noriko Mikami,1 Yasuhashi Kurata,1 Miho Hida,1 Daisuke Ishii,1 Kazunari Yoshida,1 Masatsugu Iwamura,2 Junko Kawakami.2 1 Dialysis Center, Eijin Clinic and Kurata Hospital, Sagamihara, Kanagawa, Japan; 2 Clinical Nutrition, Sagami Women's Univ, Sagamihara, Kanagawa, Japan; 1 Urology, Kitasato Univ, School of Medicine, Sagamihara, Kanagawa, Japan.

Background: With advances in dalcyclic techniques and the development of phosphorus (P) adsorbents, the tissue deposition of P may differ from that previously reported. In this study, we examined P loading in patients undergoing hemodialysis.

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

Underline represents presenting author/disclosure.
**Mineral Disease: CKD-MBD - II**

**Poster/Saturday**

**Methods:** The subjects were 73 hemodialysis patients. They consisted of 53 males and 20 females. Thirty patients had diabetes, whereas it was absent in 43. The mean age was 65±6 years, duration period 8±2.33±3.74 months, blood flow volume 209.7±5.27 mL/min, dialyzer membrane area 2.11±0.2 mm, and dialytic fluid flow volume 400 mL/min. The frequency of dialysis was 3 times a week. The tissue deposition of P was calculated using the following formula: Protein catalytic rate (PCR) x 1.5 x 0.65 – (Removal on dialysis) – (Removal with P adsorbent) – (Urinary excretion). P intake (calculated by multiplying the protein intake by a coefficient of 1.5) was adopted from the guidelines established by the Japanese Society of Nephrology in 2007. P removal on dialysis was measured by reserving dialytic fluid drainage. The urinary excretion of P was measured by 24-hour urine. Lanthanum carbonate and sevelamer hydrochloride alone were administered to patients, and regarded as adsorbing 90 and 33.75 mg/g of P, respectively, for calculation.

**Results:** The dialytic fluid excretion of P was 298.6±164.9 mg/day. The urinary excretion of P was 89±53.3 mg/day (n=21). The volume of adsorption achieved by P adsorbents was 221.0±108.3 mg/day. The mean tissue deposition of P was -32.1±125.4 mg/day. The following correlation formula was obtained: [Dialytic fluid P Removal per dialysis session] (= 157.6 x [P](mg/dL) + 37, r²=0.691; 96% (151/157) were within TPINP range (15-90ng/mL). Relation between TPINP and eGFR tended to be linear.

**Conclusions:** The IDS-iSYS Ostase BAP assay performed well and showed suitable characteristics to achieve acceptable precision and accuracy. The patient comparison between the IDS-iSYS and the Immunoenzymetric showed an excellent relationship. The IDS-iSYS Ostase BAP is a suitable tool in clinical laboratories for the follow-up of osteoporosis therapy or for the differential diagnoses of other metabolic bone diseases such as Paget’s disease and renal osteodystrophy.

**SA-PO554**

**Performance of a Novel Fully Automated Method for the Detection of Diphospho-Un carboxylated Matrix Gla Protein (dp-ucMGP)**

**Etienne Cavalier, 1 Pierre Delanaye, 2**

1 Clinical Chemistry, Univ of Liege, CHU Sart-Tilman, Belgium; 2Nephrology Dialysis Hypertension, Univ of Liège, CHU Sart-Tilman, Belgium.

**Background:** Matrix Gla-protein (MGP) is one of the strongest inhibitors of vascular calcification, produced by vascular smooth muscle cells and chondrocytes. MGP can undergo gamma-glutamyl carboxylation (vitamin K dependent step) and serine phosphorylation. Circulating dp-ucMGP reflects the amount of uncarboxylated MGP produced in the arterial vessel wall and is a direct marker for the vascular vitamin K status. Different studies, using cumbersome elisa methods have shown conflicting results regarding association of dp-ucMGP and abdominal aortic calcification score. We assessed the analytical performance of the fully automated IDS-iSYS InaKtif MGP assay (IDS, UK) and compared the results vs. an ELISA method in a cohort of haemodialysis patients.

**Methods:** Precision profile was determined with 4 plasma samples (264-2703pM) measured twice a day for 10 days. Linearity was assessed with 2 sets of high/low samples. dp-ucMGP concentrations were determined with both and ELISA kit from IDS and ELISA from 118 plasma sample of patients without Vitamin K supplementation and under three-weekly hemodialysis for at least 3 months, (mean age 68.7±14.4 years; median dialysis vintage: 21 months, range: 3-396), 78(65.0%) had history of cardiovascular diseases.

**Results:** On IDS, intra-assay coefficient of variation (CV) was 2.9-8.9%; Inter-assay CV was 4.1-13.4%. Linearity equation from 18 dilutions was obtained 0.95xExpected+209, R²=0.99. The Passing-Bablok regression was IDSYS=1.26ELISA+241. Bland Allmam plot showed that IDSYS gave higher results than ELISA, especially in the higher range.

**Conclusions:** The IDS-iSYS InaKtif MGP is the first fully automated dp-ucMGP kit which will be soon available commercially for the measuring of the diphospho-uncarboxylated MGP levels. Different observations in the studies that used the ELISA method might be explained by the its poor linearity in the higher range. The dp-ucMGP blood test could be included as part of routine monitoring biomarkers for hemodialysis patients after further proven its clinical validity.

**SA-PO555**

**Seasonal Vitamin D Levels in Untreated Incident Dialysis Patients**

**Gero D. von Gersdorff, 1 Philipp B. Marquardt, 2 Mathias Schaller, 1 Thomas Bengzing, 1 Claudia Barth, 2**

1 Nephrology - QiN Group, Univ Hospital Cologne, Cologne, Germany; 2Curatorium for Dialysis and Kidney Transplantation, Neu-Isenburg, Germany.

**Background:** Studies on the association between VitD and mortality are often not adjusted for season of sample collection. We report on seasonal VitD levels in a current large cohort of chronic ambulatory dialysis patients without VitD Supplementation.

**Methods:** The database of a large dialysis organization in Germany was queried for all patients >18 years in the period 2006–2012 who had a first VitD drawn in 1 year after starting hemodialysis (HD) or peritoneal (PD) dialysis, respectively. VitD levels were grouped by month of draw and by patient’s state of VitD supplementation. VitD sufficiency was defined as a level >30 ng/ml and severe deficiency as <12.5 ng/ml. Results are expressed as mean (SD) or %, and as odds ratio (OR) of mortality for VitD <12.5ng/ml vs. VitD >20ng/ml. Results: 19,474 patients (p) were available for analysis. In 3568 VitD naïve p (age 71.9(14) years, 61.6% male, 44.1% diabetic (DM)), VitD levels were 17.2 (10.9) ng/ml in winter and 20.4 (12.7) ng/ml in summer. Levels in PD were substantially lower than in HD (Fig 1). VitD levels were also low in women and DM (Fig 1). Of 3135 incident HD patients without supplementation, 17.5% were VitD sufficient and 36.3% were severely deficient. In corresponding PD patients (N=253), only 7.1% were sufficient and 58.5% were severely deficient. Mortality risk was 1.44 for HD and 1.35 for PD patients with a first VitD level <12.5 ng/ml.

**Conclusions:** The IDS-iSYS Ostase BAP assay performed well and showed suitable characteristics to achieve acceptable precision and accuracy. The patient comparison between the IDS-iSYS and the Immunoenzymetric showed an excellent relationship. The IDS-iSYS Ostase BAP is a suitable tool in clinical laboratories for the follow-up of osteoporosis therapy or for the differential diagnoses of other metabolic bone diseases such as Paget’s disease and renal osteodystrophy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO556

Seven Years of Experience with the German Calciphylaxis Registry
Vincent Brandenburg,1 Thilo Krueger,2 Jürgen Floege,1 Markus Ketteler,3 Cardiology, University Hospital RWTH Aachen; 2Nephrology, University Hospital RWTH Aachen; 3Nephrology, Klinikum Coburg.

Background: Calciphylaxis is a rare disease (ORPHA280062) and devastating condition associated with high morbidity and mortality. Calciphylaxis is characterised by painful, ischemic, partly necrotic skin ulcerations. Pathomorphologically, media calcification of cutaneous arterioles and extracellular matrix remodelling are the hallmarks of the disease.

Methods: We established an international internet-based registry in 11/2006 to allow online notification for all cases of established or suspected CUA. A comprehensive data base including various parameters concerning patient characteristics, laboratory data, clinical background and presentation as well as therapeutic strategies was established. The diagnosis of CUA is made on clinical and/or histological grounds by the referring physician.

Results: Altogether 184 patients with CUA have been documented in 6.5 years: 61% females; 88% dialysis (HD and PD) patients, median age 67 (21-88) years. Stored serum samples were used for central laboratory analysis in core facility in n=92 dialysis patients: PTH levels varied broadly within unpredictably low and > 1100 pg/mL, mean 191 +/-176 pg/mL; fetuin-A: 0.21 +/-0.01 g/L. Fetuin-A levels in control HD pts without CUA were significantly higher (n=65; 0.46 +/-0.1 g/L, p < 0.01). Oral anticoagulation with Vit K antagonists was common in ESRD CUA pts (47%). Cutaneous lesions were localized in 79% of patients in the lower extremities or gluteal region. Among the most frequently recorded therapeutic procedures were: surgical necrosectomy, intensifying dialysis modality, i.v. sodiumthiosulfat application. The median survival time was 516 days after online notification.

Conclusions: CUA is a rare disease among ESRD pts with increased mortality. PTH levels vary substantially but do not exceed current KDIGO target levels in most cases. Decisions on therapeutic strategies also vary significantly among centers. The present internet based ICRN registry is a valuable tool to collect data upon CUA cases and may become a basis for prospective systematic evaluations of treatment modalities in the near future.

Funding: Pharmaceutical Company Support - Amgen and Sanofi

SA-PO557

A 10-Year Retrospective Analysis of Parathyroidectomy (PTX) for Renal Hyperparathyroidism
Alasdair Dupuid,1 Chen Beverly B. Lin, Samina Hussain, Zorica Vujovic, David Monro Smith. Ninewells’ Hospital, Dundee, United Kingdom.

Background: Patients with advanced kidney disease are known to be at risk of developing renal bone disease (CKD-MBD) due to the development of secondary hyperparathyroidism. When this cannot be controlled with medical treatment alone surgical intervention may be indicated. Our aim was to assess the clinical and biochemical outcomes of patients who underwent PTX for renal hyperparathyroidism.

Methods: Retrospective review of all renal patients who had PTX from April 2003 to March 2013 at one institution. Relevant patients were identified from electronic medical records and theatre logs.

Results: 97 patients underwent PTX for renal hyperparathyroidism. There were 45 women and 49 men with a median age of 55 years (range 25-80 years) plus 3 who were excluded due to incomplete data. At the time of PTX, 20 patients had functioning renal transplants, 66 were on renal replacement therapy, 49 were on haemodialysis, 17 were on peritoneal dialysis and 8 patients were at a peri-dialysis stage. Of these patients, 30 had four parathyroid glands removed, 28 had three and a half removed, 11 had three removed, 9 had two removed and 16 had one removed. Histopathology showed 80 cases had hyperplastic changes, 12 had parathyroid adenomas and 2 were normal. 2 patients experienced recurrent laryngeal nerve injury and 1 patient died secondary to pneumonia.

Recurrent hyperparathyroidism led to re-operation in 5 patients and 4 patients were on calcium. Post PTX 66 patients were on alfacalcidol (median 0.5 micrograms, range 0-14 micrograms). When comparing pre and post-operative biochemical, parathyroid hormone (PTH) levels were found to be significantly different using Wilcoxon matched-pairs test (W=4183, P<0.001) with a median reduction of 75.2pmol/L (interquartile range 26.3-75.2). Corrected calcium levels were also significantly reduced (W=3829, P<0.001) with a median reduction of 0.23mmol/L (interquartile range 0.09-0.39).

Conclusions: Most patients undergoing PTX were receiving haemodialysis. The majority of patients had a subtotal rather than total PTX with hyperplasia being the prevailing pathology. PTX has been shown in these patients to significantly reduce both PTH and corrected calcium.

Funding: none

SA-PO558

Analysis of CKD-MBD Markers in a Phase 3 Study of PA21 and Sevelamer in Patients with Hyperphosphatemia
Stuart M. Sprague,1 Adrian Covic,2 Markus Ketteler,3 Anjay Rastogi,4 Bruce S. Spinowitz,5 Jürgen Floege,6 1Thomson Reuter, 2Jürgen Floege, 3NorthShore Univ Health System, Evanston, IL; 4Gr T. Popa Univ of Medicine and Pharmacy, Iasi, Romania; 5Coburg Clinic and KfH-Dialysis Center, Coburg, Germany; 6Univ of California; 7New York Hospital Queens; 8RWTH Univ Hospital Aachen, Aachen, Germany.

Background: Effects of PA21 – a novel polynuclear iron(III)-oxo/hydroxide phosphate binder (PB) – and sevelamer carbonate (SEV) on CKD-MBD markers were assessed.

Methods: Dialysis patients received PA21 1.0-3.0 g/day (n=710) or SEV 2.4-14.4 g/day (n=139) for 12 weeks’ dose titration then a 12-week maintenance period. Eligible patients entered a 28-week extension study. Markers of CKD-MBD were measured.

Results: In both treatment groups (Table): serum intact parathyroid hormone (iPTH) decreased initially, then increased to Week 52; fibroblast growth factor 23 (FGF-23) decreased and serum Ca2+ levels remained relatively stable over 52 weeks; tartrate-resistant acid phosphatase 5b (TRAP5b) decreased over 52 weeks; carboxyterminal cross-linking telopeptide (CTX) increased initially, then returned to near baseline values at Week 52; bone-specific alkaline phosphatase (BAP) increased initially, then returned to near baseline values at Week 21; osteocalcin (OST) increased over 52 weeks. No significant differences between treatment groups were noted.

Table: Mean (S.D) change from baseline in CKD-MBD markers

Funding: Pharmaceutical Company Support - Vifor Pharma Ltd

SA-PO559

Administration of Activated Vitamin D for Patients with Predialysis Chronic Kidney Disease May Reduce Cardiovascular Disease Events after Dialysis Initiation
Daijo Inaguma. Nephrology, Japan Red Cross Nagoya Daini Hospital, Nagoya, Aichi, Japan.

Background: Only a few studies have focused on whether or not administration of activated vitamin D (VD) during the predialysis stage can reduce CVD events in patients after dialysis initiation. We therefore examined whether activated VD therapy improves short-term survival after the initiation of dialysis.

Methods: We conducted a multicenter prospective cohort study of 487 patients with CKD who began dialysis during the period from October 2011 to January 2012. The last data collection was done at the end of September 2012. Incidences of CVD events and all-cause mortality were compared between patients in the treatment group (138 patients) who received administration of dialysis to whom activated vitamin D was orally administered for at least 12 weeks, and patients in the non-treatment group (357 patients).

Results: The data at the time of dialysis initiation are presented.

CVD events occurred in 111 patients during the follow-up period. Comparing the two groups revealed a significantly lower CVD-event occurrence in the treatment group.

Funding: none

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

Underline represents presenting author/disclosure.

755A
**SA-PO560**

Comparative Study between the Impact of Calcium Acetate versus Sevelamer Carbonate on Progression of Vascular Calcification in Pre-End Stage Renal Disease (CKD Stage 4 and 5) Patients

**Methods:** 150 pre-ESRD (CKD stage 4 & 5) patients were screened for abdominal aortic calcification (AC) using digital X-ray lumbar spine and multi-slice abdominal CT scan. 50 hyperparathyroidemic CKD 4-5 patients having AC were selected & randomized to receive calcium acetate or sevelamer carbonate (25 in each group). The patients were serially studied for impact of phosphate binders on the progression of VC by measuring aortic calcium (CA) using digital X-ray and calcium acetate (CA) using digital X-ray lumbar spine and multi-slice abdominal CT scan. Calcium and other biochemical parameters were estimated. The patients were serially studied. The Cox regression survival analysis showed that age (1.056), Hb (0.674) and PTH (0.836) were significant predictors of mortality. The adjusted hazard ratio of age, Hb and PTH was 1.06, 0.66 and 0.84, respectively.

**Results:** Among 150 patients, 75% had AC with median CAI of 17.15%. CAI correlated positively with X-ray AAC score (r=0.8106; p<0.0001). Sevelamer and calcium provided equivalent control of sP (0.4-0.51 & 4.4-0.74, respectively; p<0.01). At baseline, the mean CAI in sevelamer group was significantly greater than the mean CAI in calcium group (23.45±1.8% vs 18.84±0.9%; p=0.035). In calcium treated patients, the mean CAI increased significantly at 6 months (20.8±1.06%) & 1 year (23.2±1.18%) (p<0.01); but the increase was insignificant in sevelamer group.

-- **Conclusions:** The prevalence of VC in pre-ESRD patients was 75%. Sevelamer carbonate was more effective in retarding the progression of VC than calcium acetate in pre-ESRD patients due to its pleiotropic properties.

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

-- **SA-PO562**

Serum Bicarbonate and Bone Mineral Density in United States Adults

**Methods:** Our analysis included 10,610 adults (≥20 years old) with estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m² who completed dual-energy X-ray absorptiometry (DXA) testing. We excluded participants who were pregnant, taking bisphosphonates or had a diagnosis of chronic obstructive pulmonary disease. Bone mineral density (BMD) was measured by DXA. Low BMD was defined as 1 standard deviation below the sex-specific mean. Linear and logistic regression models were created to examine associations of serum bicarbonate levels with lumbar and total BMD.

**Results:** Participants with lower serum bicarbonate were younger, more likely to be female, current smokers, had higher BMI, and were less likely to use diuretics. In the fully adjusted model, compared with participants with bicarbonate ≥24 mEq/L, those with <22 mEq/L had a 0.012 g/cm² higher lumbar BMD (95% CI 0.0002, 0.025). In sex-stratified analyses, compared with bicarbonate ≥24 mEq/L, only bicarbonate ≥22 mEq/L was associated with higher lumbar BMD among men; but among women, bicarbonate between 22-25, 25.1-25.9, and ≥27 mEq/L were all associated with higher lumbar BMD. For total BMD, no statistically significant association was observed with serum bicarbonate among all participants. However, in sex-stratified analyses, bicarbonate level was independently associated with total BMD among women but not men. The odds of having low total BMD were 1.48 times higher in women with bicarbonate level <24 mEq/L compared to ≥27 mEq/L (OR 1.48 (95% CI 1.03, 2.14)).

**Conclusions:** Higher serum bicarbonate levels were significantly associated with higher lumbar BMD and a difference in threshold effect among men and women. For total BMD, an association with serum bicarbonate was observed only among women. This suggests a gender difference in the association of acidosis and bone density.

**Funding:** Other NIH Support - Clinical and Translational Science Award (CTSA) grants UL1TR000086, TL1RR000087, and KL2TR000088. NIH, through CTSA grant numbers UL1TR000086, TL1RR000087, and KL2TR000088.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: Prospectively followed cohort of 371 type 1 diabetic patients (55% men; age [mean±SD] 53±9 years, 42±8 years of diabetes, and 35% with long duration of diabetic nephropathy (DN)). Femoral neck bone mass density (BMD) (g/cm2) was measured by dual energy x-ray. Measures of arterial stiffness were heart rate (HR) adjusted augmentation index (AI75), augmentation pressure (AP), and pulse wave velocity (PWV) (SphygmoCor, Atcor Medical). The calcification markers sclerostin, endostatin and osteoprotegerin (OPG) were measured in serum by immunoenzymometric assays (Biomedica Medizinprodukte).

Results: In total, 105 (28%), 197 (53%) and 69% had BMD (T-score) corresponding to normal, osteopenia and osteoporosis (-1.0 to -1.0 and < -2.5, respectively). Mean±SD AI75 18±10, 18±10, and 22±10; p=0.011 and PWV 10±2.3, 11±3.3,1 and 12±1.3±8; p=0.002 increased while AP tended to increase 10.4±7.7, 9.8±6.7, and 12±1.7±5; p=0.10 with deteriorating BMD group.

Following multivariate adjustment (ANCOVA: Sex, diabetes duration, HbA1c, height, HR, mean arterial pressure, eGFR, urinary albumin excretion, cholesterol, smoking, and antihypertensive treatment), AI75 and AP were elevated with decreasing BMD status (p=0.002 and 0.006, respectively).

Similarly, sclerostin and endostatin correlated with PWV (p=0.018) while OPG correlated with AI75 and AP and PWV (p<0.001). However, after the adjustment only OPG remained significantly related to all three measures of arterial stiffness (p<0.05).

Conclusions: These data suggest that in patients with longstanding type 1 diabetes, augmentation index and arterial pressure as measures of arterial stiffness correlates with bone mass and OPG independent of potential confounders.

SA-PO564

Relationship between Coronary Artery Calcification and Cardiac Valve Calcification at Hemodialysis Initiation in Patients with End Stage Renal Disease
Ken Kitamura, Hideki Fujii, Kentaro Nakai, Keiji Kono, Shinichi Nishi.

Background: Coronary artery calcification (CAC) and cardiac valvular calcification (VC) are associated with end-stage renal disease (ESRD) and may affect significant morbidity and mortality. The purpose of this study was to investigate CAC and VC at hemodialysis initiation in patients with ESRD.

Methods: This study included 63 patients with ESRD who were just planned to start hemodialysis therapy. Multi-detector computed tomography for quantification of CAC using the Agatston score and transthoracic echocardiography for assessment of VC were performed for all the study patients. We semi-quantitated the severity of VC as VC score by counting the number of calcified valve cusp of aortic valve (AV), mitral valve (MV) and the presence of mitral annular calcification (MAC).

Results: Among 63 patients at hemodialysis initiation, 51 (81.0%) had CAC and 35 (55.6%) had AV calcification. Twenty-five (49.0%) of 51 patients with CAC had severe CAC (CAC score ≥ 400). AV calcification, MV calcification and MAC were observed in 30 patients (47.5%), 17 patients (26.3%) and 8 patients (12.2%), respectively. CAC score is closely and significantly associated with VC score (r=0.39, p<0.005). Especially, significant associations of CAC score with AV calcification and MAC were detected. In addition, when the patients were divided into the following three groups on the basis of the degree of CAC and VC (group 1: severe CAC- and VC-; group 2: severe CAC+ or VC+; group 3: severe CAC+ and VC+), the number of patients with left ventricular hypertrophy was the highest in the group 3 and it was higher in the group 2 than in the group 1.

Conclusions: At hemodialysis initiation, most of the patients with ESRD had CAC and VC, and these were well correlated with each other. These findings suggested that we need to follow hemodialysis patients with CAC and/or VC carefully as high-risk patients for cardiovascular disease.

SA-PO565

Maxacalcitol Prevents the Progression of Cardiac Damage in Diabetes by Suppressing Oxidative Stress
Hideki Fujii,1 Kentaro Nakai,1 Keiji Kono,1 Shunsuke Goto,1 Riko Kitazawa,2 Masami Shinhara,3 Michinori Hirata,3 Shinichi Nishi,1 Masafumi Fukagawa,1,4 Division of Nephrology and Kidney Center, Kobe Univ Graduate School of Medicine, Kobe, Japan.

Background: Diabetes mellitus (DM) is an important risk factor for chronic kidney disease (CKD) and cardiovascular disease (CVD). Recent reports have shown the significant association between vitamin D and CVD. Recently, we have reported that maxacalcitol (OCT), which is a vitamin D receptor activator, reduces oxidative stress. In this study, we investigated the effect of OCT on oxidative stress and cardiac damage in DM.

Methods: In this study, we used SDT rats, which are non-obese type 2 diabetes model rats. Twenty-week-old male SDT rats were divided into three groups: vehicle-treated SDT rats (DM, N=6), insulin-treated SDT rats (INS, N=6), and maxacalcitol-treated SDT rats (OCT, N=6). At 30 weeks of age, urinary and blood biochemical analysis and cardiac histological analysis were performed in these groups.

Results: At 30 weeks of age, despite comparable blood pressure and renal function, urinary excretion of 8-hydroxydeoxyguanosine (8-OHdG) and serum NT-proBNP levels were significantly lower in the OCT group than in the DM group. In addition, heart volume was significantly lower in the OCT group compared to the DM group. The mRNA expressions of NADPH p22 and BNP in the heart were significantly decreased in the OCT groups compared to the DM group. Further immunohistological analysis revealed that the number of 8-OHdG positive cardiomyocyte was reduced and cardiac and perivascular fibrosis was ameliorated by OCT administration.

Conclusions: Oxidative stress may play a key role for the development of cardiac hypertrophy and cardiac fibrosis in DM. Furthermore, it is suggested that OCT suppresses oxidative stress and ameliorated the cardiac damage in DM.

Poster/Saturday

SA-PO566

Higher Serum Alkaline Phosphatase Is Associated Not Only with Mortality but also the Incidence of Hip Fracture among Patients Receiving Hemodialysis in Japan
Yukio Koyama,1 Kentarou Yokoyama,1 Takashi Shigematsu,2 Masatomo Taniguchi,3 Junichiro J. Kazama,4 Tatsuho Horoya,1 Takashi Yoko.1 Div of Kidney and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan; Division of Nephrology and Blood Purification Medicine, Wakayama Medical Univ, Wakayama, Japan; Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyusyu Univ, Fukuoka, Japan; Div of Blood Purification Therapy, Niigata Univ Medical and Dental Hospital, Niigata, Japan.

Background: The monitoring of serum alkaline phosphatase (ALP) is widely recommended in the management of chronic kidney disease-mineral and bone disorder (CKD-MBD). However, unlike calcium, phosphate, or parathyroid hormone, relationship between serum ALP and outcome of the patients receiving hemodialysis (HD) in Japan is unknown.

Methods: We collected the baseline data of 187,792 patients receiving HD three weeks (66 ± 12 years, males 61.9%, and median HD vintage of 7.9 years) extracted from a nationwide dialysis registry at the end of 2009 in Japan. Then we evaluated the patient survival and development of complication using the registry at the end of 2010.

Results: During one-year follow-up, 14,419 (7.9%) died of all causes. Univariate logistic regression analysis, patients of the highest quartile of ALP had higher all-cause and cardiovascular mortality and incidence of hip fracture compared with those of the lowest quartile (OR, 1.45; 95% CI, 1.34 to 1.57, and OR, 1.26; 95% CI, 1.13 to 1.40, and OR, 1.69; 95% CI, 1.37 to 1.99, respectively).

Conclusions: In this large observational cohort study, higher levels of serum ALP were independently associated not only with mortality but also the incidence of hip fracture among Japanese HD patients. Close monitoring of serum ALP is thought to be useful for the management of CKD-MBD.

SA-PO567

Aluminum Intoxication: The Problem Has Not Disappeared
Clarissa Jacob Barros Carvalho,1 Camila Barbosa L. Oliveira,2 Carla Queiroz Neves,3 Alline S.A. Oliveira,3 Vanda Jorgetti,1 Jose Edevanilson Guerino,1 Ana Paula Guerios.1 Nephrology, UFPE, Recife, Pernambuco, Brazil; Nephrology, UNP, Sao Paulo, Brazil.

Background: Aluminum intoxication (AI) is associated with low bone formation rates and increased risk for fractures. The aim of this study was to assess the prevalence of AI in hemodialysis patients who underwent bone biopsy in a Brazilian center.

Methods: We performed a retrospective analysis of 158 patients underwent bone biopsy from March 2003 to March 2013. Patients were divided into 2 groups: AI group (patients with AI) and NA group (patients free of AI). Clinical data were evaluated: age, sex, time on dialysis, occurrence of vascular calcification and fractures. Laboratory tests: total calcium, phosphorus, intact parathyroid hormone (iPTH pg/mL), alkaline phosphatase (ALP U/L). Bone biopsy was performed after double tetracycline labeling and specimens were classified as osteitis fibrosa (OF), mixed disease (MD), adynamic bone disease (ABD), osteoporosis (OS) or osteomalacia (OM). AI or iron intoxication were defined when more than 20% of the trabecular bone surface were covered by metal. We performed a comparative analysis between the groups to assess factors associated with AI. The frequency of IA was evaluated in two periods of 5 years (2003-2007 and 2008-2013).

Results: The prevalence of AI was 51.3% and did not decreased with the time. There were no differences between the groups regarding clinical parameters. ALP (median 155 vs 430; p<0.001) and iPTH (median 814 vs 1732; p<0.001) levels were lower in the AI group (p=0.021) and iron intoxication (p<0.001) were closely associated with AI. Patients with MD had lower frequency of AI (p=0.003). A cox regression multivariate analysis showed that variables associated with AI were: time on dialysis (p=0.024), ALP (p=0.006) and iPTH (p=0.008).

Conclusions: Although the prevalence of aluminum-related bone diseases has declined in the world, AI still persists at a high prevalence in Brazil. Furthermore, IA had a close association with ABD and with iron intoxication.
SA-PO568

Post-Hoc Analysis of Pharmacodynamic Interaction of PA21 with Statins in a Phase 3 Study of PA21 in Dialysis Patients with Hyperphosphatemia

Victoria Levesque,1 Edward M.F. Chong,2 Patrick Monseue,1 Vifor Pharma, Canada; 3Vifor Pharma, Glattbrugg, Switzerland.

Background: Dialysis patients often require phosphate binders (PBBs) for hyperphosphatemia, and concomitant statins for hyperlipidemia. In vitro studies showed interactions between PA21 and atorvastatin, especially in an absence of phosphate. Clinical data showed sevelamer (SEV) lowered total cholesterol (Total-C) and low-density lipoprotein cholesterol (LDL-C), but not triglycerides (TG), but not triglycerides (TG). Therefore, an analysis of data from a Phase 3 study investigating PA21, a novel polynuclear iron(III)-oxyhydroxide PB, and SEV assessed whether these PBBs altered the lipid-lowering effects of statins.

Methods: Dialysis patients received PA21 1.0-3.0 g/day (n=707) or SEV carbonate 2.4-14.4 g/day (n=348) for up to 52 weeks. A post-hoc analysis investigated lipid parameters to assess potential interactions between PA21 or SEV and atorvastatin, simvastatin, or other statins or no statins (Table). Decreases in LDL-C and SEV, respectively. PA21 had minimal effect on lipid parameters in patients taking stable dose of atorvastatin, simvastatin, or other statins or no statins (Table). Decreases in LDL-C and HDL-C and with mortality in non-dialysis dependent (NDD) CKD has not been studied extensively.

Results: The post-hoc analysis included 677 and 333 patients treated with PA21 or SEV, respectively. PA21 had minimal effect on lipid parameters in patients taking stable dose of atorvastatin, simvastatin, other statins or no statins (Table). Decreases in LDL-C and HDL-C and with mortality in non-dialysis dependent (NDD) CKD has not been studied extensively.

Table: Mean (%) change (mmol/L) in lipid parameters: baseline to Week 52 endpoint.*

<table>
<thead>
<tr>
<th>medication</th>
<th>PA21 (n=677)</th>
<th>SEV (n=333)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-C</td>
<td>0.0 (0.82)</td>
<td>-0.1 (0.05)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.1 (0.27)</td>
<td>-0.7 (0.72)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-0.7 (0.84)</td>
<td>-0.7 (0.84)</td>
</tr>
<tr>
<td>TG</td>
<td>0.1 (0.70)</td>
<td>0.1 (0.70)</td>
</tr>
</tbody>
</table>

*Last available observation under stable dose of statin.

Conclusions: PA21 did not interfere with the lipid-lowering effects of statins, despite prior in vitro data showing an interaction. SEV lowered LDL-C and Total-C, consistent with its known effects on these parameters.

Funding: Pharmaceutical Company Support - Vifor Pharma

SA-PO569

Association of Serum Alkaline Phosphatase Levels with Kidney Function and with Mortality in a Nationally Representative Cohort of U.S. Veterans with Non-Dialysis Dependent CKD

Csaba P. Kovesdy,1,2 Miklos Zsolt Molnar,3 Jennie Z. Ma,1 Leigh Darrel Quaile,1 Kamary Kalantar-Zadeh,1 Memphis VA Medical Center, 2Univ of Tennessee Health Science Center, 3Univ of California, Irvine.

Background: Bone and mineral disorders are common and are associated with mortality in ESRD. The association of serum total alkaline phosphatase (ALP) with kidney function and with mortality in non-dialysis dependent (NDD) CKD has not been studied extensively.

Methods: We evaluated the association of ALP with estimated GFR (eGFR) and with mortality in a nationally representative cohort of U.S. Veterans with all stages of NDD-CKD. Associations were examined in regression models, and in time-dependent Cox hazard analyses. The adjusted odds ratio (95%CI) for one unit higher natural log-transformed ALP. Associations with mortality were similar in patients with all stages of NDD-CKD.

Results: The adjusted odds ratio (95%CI) for one unit higher natural log-transformed ALP was 1.25 (1.23-1.26, p<0.001). Over a median follow-up of 6.2 years 214,374 patients died (mortality rate: 70.0/1000 patient-years). The adjusted odds ratio (95%CI) of ALP>120 U/L was 0.74 (0.72-0.76, p<0.001) for patients with ALP=120 U/L and >=200 U/L were associated with adjusted mortality hazard ratios (95%CI) of 0.74 (0.72-0.76, p<0.001) for one unit higher natural log-transformed ALP. Associations with mortality were similar in patients with all stages of NDD-CKD.

Conclusions: Higher ALP levels are associated with decreased kidney function, and is associated with increased mortality in patients with NDD-CKD. The effect of therapeutic interventions lowering ALP level will need to be examined in clinical trials.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO570

Early Detection of Vascular Calcification in Retinal Vessels and Skin of Dialysis Patients

Ramya Bhargava,1 Faisal R. Ali,1 Katie A. Law,1 Jane Gray,1 John Lear,1 Nicholas D. Bryan,2 David B. Henson,2 Paul E. Brenchley,3 Alastair J. Hutchison,1 1MHI, UK, United Kingdom; 2Manchester Univ.

Background: Vascular calcification is common in dialysis(HD) patients but early detection is difficult. We hypothesised that 1) retinal imaging by fundus photography & OCT scan may detect early calcification in retinal vessels and 2) that skin biopsies from calcified dialysis patients may have higher phosphorus(P31) & calcium(Ca43) content than normal.

Methods: HD patients with Xray evidence of vascular calcification in hands & pelvis with Atragago score >4 were invited to take part in the study. 10 had fundus photography & OCT scans. 20 patients & 10 normal controls underwent skin biopsies. Biopsy samples were incinerated & acid digested; P31 & Ca43 were measured by spectroscopy. Skin content of P31 & Ca43 were compared in patients & controls. P31 was correlated with Serum PTH, Serum P & Ca43.

Results: 1. No retinal vascular calcification was evident in any HD patients with vascular calcification in hands/pelvis; 2. No significant difference was seen in P31 & Ca43 between calcified patients & normal controls; 3. Positive correlation seen between P31 & Ca43 in patients & controls; 4. No correlation between P31 & Serum PTH or serum P in patients & controls.

Conclusions: Retinal vascular calcification may be early signs of calcification that occurs elsewhere in HD patients; 2. Skin content of Phosphorus & Calcium is not a marker of vascular calcification.

SA-PO571

Clinical Significance of Breast Arterial Calcification in End-Stage Renal Disease

Ekamol Tantisattamo,1 Na'Da Abouhassan,2 Jane Gray,1 John Lear,1 Nicholas D. Bryan,1 David B. Henson,2 Paul E. Brenchley,3 Alastair J. Hutchison,1 1MHI, UK, United Kingdom; 2Manchester Univ.

Background: The clinical significance of medial arterial calcification in end-stage renal disease (ESRD) is unclear because it often coexists with atherosclerotic calcification. As opposed to other sites, breast arterial calcification (BAC) is exclusively medial and is a convenient marker to address this question.

Methods: Mammograms were identified in 162 women with ESRD and those closest to the date of ESRD were reviewed. Coronary artery disease (CAD) was defined as a history of myocardial infarction or coronary stenosis of >50% by angiography. Peripheral artery disease (PAD) was defined as a history of medial arterial calcification in hands/pelvis; 2. No signiﬁcant difference was seen in P31 & Ca43 between calcified patients & normal controls; 3. Positive correlation seen between P31 & Ca43 in patients & controls; 4. No correlation between P31 & Serum PTH or serum P in patients & controls.

Results: Age at baseline mammography was 60.0 +/- 1.0 (SEM) y, ESRD duration was 6.2 +/- 1.0 (SEM) y. The adjusted hazard ratio (95%CI) for one unit higher natural log-transformed ALP was 1.25 (1.23-1.26, p<0.001). Over a median follow-up of 6.2 years 214,374 patients died (mortality rate: 70.0/1000 patient-years). The adjusted odds ratio (95%CI) of ALP>120 U/L was 0.74 (0.72-0.76, p<0.001) for patients with ALP=120 U/L and >=200 U/L were associated with adjusted mortality hazard ratios (95%CI) of 0.74 (0.72-0.76, p<0.001) for one unit higher natural log-transformed ALP. Associations with mortality were similar in patients with all stages of NDD-CKD.

Conclusions: Retinal vascular calcification may be early signs of calcification that occurs elsewhere in HD patients; 2. Skin content of Phosphorus & Calcium is not a marker of vascular calcification.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO571

Clinical Significance of Breast Arterial Calcification in End-Stage Renal Disease

Ekamol Tantisattamo, Na'Da Abouhassan, W. Charles O’Neill. Renal Div, Emory Univ, Atlanta, GA.

Background: The clinical significance of medial arterial calcification in end-stage renal disease (ESRD) is unclear because it often coexists with atherosclerotic calcification. As opposed to other sites, breast arterial calcification (BAC) is exclusively medial and is a convenient marker to address this question.

Methods: Mammograms were identified in 162 women with ESRD and those closest to the date of ESRD were reviewed. Coronary artery disease (CAD) was defined as a history of myocardial infarction or coronary stenosis of >50% by angiography. Peripheral artery disease (PAD) was defined as a history of bypass or amputation.

Results: Age at baseline mammography was 60.0 +/- 1.0 (SEM) y, ESRD duration was 4.7 +/- 0.4 y, 55% had diabetes, and 61% had BAC; follow-up was 2.9 +/- 1.7 y. Patients with BAC were older (62.6 +/- 1.2 vs. 53.2 +/- 1.6, p<0.0001) and more likely to be diabetic (65% vs. 40%; p=0.002). Serum calcium, phosphorus, and parathyroid hormone did not differ significantly between patients with and without BAC of Ca-based and Ca-free phosphate binders, vitamin D compounds, and calcimimetics was similar. Patients with BAC had a higher prevalence of PAD (20% vs. 4.8%; p=0.006) but not CAD (27% vs. 22%) at follow-up. Follow-up duration was similar in the 2 groups. In a logistic regression
model, BAC (4.2:1.1-16) and diabetes (10;2.2-47) were independent determinants of PAD (odds ratios; 95% confidence intervals). After exclusion of patients with pre-existing disease at baseline, the incidence of PAD was greater in patients with BAC (10 vs. 3.2%) but was not significant due to small numbers. The incidence of CAD was not increased.

Conclusions: Breast arterial calcification is independently associated with peripheral arterial disease in ESRD, suggesting that medial arterial calcification contributes to the pathophysiology of this disorder. Coronary artery disease is not associated with BAC in ESRD. In addition to being a marker, BAC may also predict PAD. Mammmography may be a convenient and useful tool to identify patients at risk for peripheral arterial disease.

Funding: Pharmaceutical Company Support - Genzyme

SA-PO572

Prevalence and Determinants of Bone in Vascular Calcification

W. Charles O' Neill.1 Randolph A. Hennigar.2 Renal Div; Emory Univ, Atlanta, GA; 3Dept of Pathology, Emory Univ, Atlanta, GA.

Background: The occurrence of bone in calcified arteries has led to the hypothesis that vascular calcification is an osteogenic process. However, the prevalence and distribution of bone in calcified arteries and its relationship to the calcification and other factors are not known.

Methods: A total of 175 arteries in specimens of lower limb amputations from 60 patients were examined retrospectively by reviewing sections stained with hematoxylin and eosin. ESRD was present in 21 patients, CKD in 21, and no CKD (defined as a serum creatinine <1.0) in 18. Mean age was 65 ± 1.9 years and 58% had diabetes. Warfarin was prescribed in 15 patients.

Results: Calcification was present in 136 arteries from 52 patients, which was medial in 62, intimal in 63, and both in 61. Bone was observed in 16 arteries (medial in 14, intimal in 2) from 13 patients. There was no association with age, gender, diabetes, renal failure, or warfarin use, but bone was present in more than one artery in 3 patients, suggestive of patient-specific factors. Bone was present in 5% and 14% of arteries above and below the knee, with the highest prevalence in the posterior tibial artery (28%). The presence of bone did not correlate with the severity of calcification and was absent in over 80% of sections with severe calcification (>50% of arterial circumference). Medial cells staining for osteocalcin were noted in only 2 of 10 sections from heavily calcified arteries. Osteoclasts were noted in 9 sections from 7 patients and bone was present in all but one of these sections.

Conclusions: Bone formation is uncommon in arterial calcification, even when severe, indicating that not all calcification events in bone formation. Although larger numbers are needed, the data suggest that patient-specific factors and arterial distribution, rather than severity of calcification are determinants of bone formation. Bone appears to be required for recruitment of osteoclasts to calcified arteries. These results question the notion that bone formation is an integral component of vascular calcification.

Funding: Clinical Revenue Support

SA-PO573

Statins and Vitamin D in U.S. Veterans with Chronic Kidney Disease (CKD)

Marvam Sharif- Hassanabadi,1 Andy Cheng, Seyed-al ı Sadjadi, Navin Jaipaul, Nephrology, Jerry T, Pettis VA Medical Center, Loma Linda, CA.

Background: Low (insufficient or deficient) Vitamin D and hyperparathyroidism are common in CKD patients and associated with increased mortality. Prior studies have suggested variable effects of statins on 25-hydroxy Vitamin D [25(OH)D] levels. We conducted a single center retrospective cohort study of 632 patients with CKD stage 3 or 4 to determine whether vitamin D status is associated with statin use.

Methods: Computerized extraction was used to identify patients with at least one 25(OH)D level between January 2010 to October 2012. Data on patient demographics, laboratory variables, comorbidities, season of 25(OH)D level, and Statin use was collected by chart review. All statistical analyses were performed using SPSS version 20.

Results: Briefly, 592 (93%) patients were male with mean age of 71(+/-10.7). 477 (77%) had CKD stage 3 or 4 and 355 (56%) had Vitamin D insufficiency. Statin use was associated with Vitamin D insufficiency (p=0.05).

Conclusions: Statins may decrease vitamin D insufficiency in CKD patients. Further studies are needed to determine the mechanism of action of statins on vitamin D status.

Funding: Pharmaceutical Company Support - Amgen

SA-PO574

Results of a 12-Week Dose Titration Study Evaluating the Safety and Efficacy of Velcalcetide, a Novel Peptide Agonist of the Calcium-Sensing Receptor (CaSR), for the Treatment of Secondary Hyperparathyroidism (SHPT) in Hemodialysis (HD) Subjects

Geoffrey A. Block,1 Kevin J. Martin,2 David A. Bushinsky,3 Yan Sun,4 David M. Spiegel,5 Reshma Kewalramani,6 Christian Mix,7 Denver Nephih,8 St. Louis Univ; 1Univ of Rochester; 2Amgen.

Background: Velcalcetide (AMG 416; KAI-4169), a novel peptide agonist of the CaSR given intravenously thrice-weekly at the end of HD, is being evaluated as a treatment for SHPT.

Methods: A single arm, 12-week, dose titration study. Major inclusion criteria: serum iPTH <350 pg/mL (≤12 subjects with iPTH >700 pg/mL), corrected Ca (cCa) ≥8.5 mg/dL, and stable doses of vitamin D. Subjects receiving cinacalcet entered a ≥2-week washout period. Velcalcetide was initiated at 5 mg and titrated every 3 weeks (max dose 20 mg) to achieve iPTH <300 pg/mL. Serum iPTH, corrected Ca (cCa), and FGF23 were measured pre- and post-treatment weekly. The primary endpoint was % change from baseline in iPTH during the efficacy period (14 days before and 3 days after the last dose of velcalcetide).

Results: 37 subjects were enrolled and received at least one dose of velcalcetide. 32 subjects (87%) completed the 12-week treatment period; 5 subjects discontinued: adverse event (2), withdrawal of consent (1), “other” reasons (2); no subject discontinued for GI adverse event or symptomatic hypocalcemia. Mean(SD) baseline iPTH was 85(644) pg/mL. Mean reductions from baseline during the efficacy period included iPTH 53.6% (95% confidence interval: 46.4%-60.8%), cCa 15%(13%,17%), P 10%(4%,17%) and FGF23 52%(34%,70%); 89% had ≥30% reduction in iPTH and 56% had iPTH <300 pg/mL. The most common individual treatment-emergent adverse events (TEAEs) were blood calcium decreased (9 subjects,24%), diarrhea (5 subjects,14%), and symptomatic hypocalcemia (4 subjects,11%). Serious TEAEs were reported in 3(8%) subjects and none deemed related to drug. 2 subjects (5%) had cCa <7.5 mg/dL and 2(5%) experienced nausea; no vomiting events were recorded.

Conclusions: Velcalcetide was well-tolerated, resulted in substantial reductions in serum iPTH and FGF23 without discontinuation of therapy due to hypocalcemia or GI adverse events, may address some limitations of oral daily medications.

Funding: Pharmaceutical Company Support - Amgen

SA-PO575

Long Term Safety and Efficacy of Velcalcetide (AMG 416), a Calcium-Sensing Receptor (CaSR) Agonist, for the Treatment of Secondary Hyperparathyroidism (SHPT) in Hemodialysis (HD) Subjects

Geoffrey A. Block,1 Kevin J. Martin,2 David A. Bushinsky,3 Yan Sun,4 David M. Spiegel,5 Reshma Kewalramani,6 Christian Mix,7 Denver Nephih,8 St. Louis Univ; 1Univ of Rochester; 2Amgen.

Background: Velcalcetide (AMG 416; KAI-4169), a novel peptide agonist of the CaSR given intravenously (IV) thrice-weekly at the end of HD, is being evaluated as a treatment for SHPT.

Methods: Among subjects who completed a 12-week dose escalation study (parent study), data are reported from the subsequent 40 weeks of treatment in a single arm, open-label extension (OLE) study. The OLE study is currently ongoing. Major inclusion criteria for the parent study included iPTH ≤350 pg/mL, corrected Ca (cCa) ≥8.5 mg/dL and stable doses of active vitamin D. Following entry into the OLE study, doses of velcalcetide were adjusted to achieve and maintain iPTH ≤300 pg/mL. The primary objective for this observation period was assessment of long-term safety and tolerability. Change over time in iPTH, cCa and P from baseline in the parent study was also assessed.

Results: 30 subjects from the parent study enrolled in the OLE study. During the 40-week follow-up, 4(13%) subjects reported the adverse event of symptomatic hypocalcemia and 3 additional subjects(10%) developed at least 1 episode of asymptomatic serum cCa <7.5 mg/dL. No subjects experienced 2 consecutive cCa <7.5 mg/dL. The adverse events of nausea and vomiting were each reported by 2 subjects(7%). Mean(SD) baseline iPTH on entry to the parent study was 862(672) pg/mL. Velcalcetide decreased iPTH at week 13 of the OLE study start) to 444(676) pg/mL, at week 26 to 305(550) pg/mL (n=25), and at week 52 to 252(131) pg/mL (n=20). At week 52, 17(85%) achieved at least a 30% reduction in iPTH, 16(80%) achieved a iPTH ≤300 pg/mL, and mean(SD) serum cCa and P were 8.9(1.6) mg/dL and 5.1(5.5) mg/dL, respectively (similar to week 13 values of 8.6(0.7) and 5.1(1.6) mg/dL, respectively).

Conclusions: This is the first report of long-term use of velcalcetide, an IV CaSR agonist, given with thrice-weekly HD. Velcalcetide was well-tolerated with no subjects withdrawing from study drug due to hypocalcemia, nausea or vomiting. reductions in serum iPTH during this time were maintained.

Funding: Pharmaceutical Company Support - Amgen
The Long Acting Calcimimetic R-641 Does Not Induce Adynamic Bone Disease in Chronic Kidney Disease

Thilo Krueger,1 Peter Boor,1 Vincent Brandenburg,2 Georg Schlieper,3 Willi Jahnen-dechant,3 Markus Ketteler,2 Xiaodong Li,2 William G. Richards,6 Jürgen Floege,3,1

Nephrology, RWTH Univ Clinic Aachen, Aachen, Germany; 2Cardiology, RWTH Univ Clinic Aachen, Aachen, Germany; 3Cardiology, RWTH Univ Clinic Aachen, Aachen, Germany; 4Biomedical Engineering, RWTH Univ Aachen, Aachen, Germany; 5Nephrology, Hospital Coburg, Coburg, Germany; 6Amgen Inc., Thousand Oaks, CA.

**Background:** Secondary hyperparathyroidism contributes to vascular calcification in chronic kidney disease (CKD). Calcimimetics lower parathyroid hormone (PTH) secretion by activating the calcium sensing receptor in the parathyroid gland. Here we investigated whether administration of a calcimimetic and PTH injection influences vascular calcification and serum levels of FGF23 in a rat CKD model.

**Methods:** CKD was induced in rats by adenine diet for 4 weeks. Four treatment protocols then continued for further 4 weeks: vehicle, PTH-(1-34), R-641+vehicle, R-641+PTH-(1-34). R-641 or vehicle were administered every third day. In the R-641+PTH group each R-641 dose was followed 48 hrs later by 80 μg/kg PTH s.c. Blood samples were collected; vascular calcification was assessed by measurement of calcium content in aortic walls. PTH-(1-84) and FGF23 serum levels were measured by ELISA.

**Results:** Compared to healthy controls, adenine significantly increased aortic calcium content. R-641 administration significantly reduced aortic calcium content (65 vs. 9 μg/g). Serum PTH was significantly lower in R-641 treatment groups compared to CKD rats (939 vs. 3212 pg/ml). Adenine diet induced a significant increase in FGF23 serum levels (1.4 vs. 198.4 ng/ml). R-641 treatment resulted in significantly lower values (71.4 ng/ml). PTH administration did neither change vascular calcium content in CKD nor FGF23 serum levels in CKD alone or with R-641 co-administration.

**Conclusions:** After 4 weeks treatment, administration of R-641 significantly reduced vascular calcification and lowered serum FGF23 levels in experimental CKD. PTH injection had no influence on vascular calcification or FGF23 content. R-641 administration signifi cantly reduced aortic calcium content (65 vs. 9 μg/g, p<0.05).

**Funding:** Pharmaceutical Company Support - AMGEN Inc.

****

Use of Sevelamer Carbonate to Examine the Role of Intraluminal Phosphate in Secondary Hyperparathyroidism

Kenneth R. Phelps,1 Darius Mason,2 Stratton VAMC, Albany, NY; 2Albany College of Pharmacy, Albany, NY.

**Background:** In CKD, [PTH] rises with influx of phosphate (P), and filtrate [P] ([P]f) rises in the cortical distal nephron (CDN). We surmised that increased [P], promotes sequestration of Ca in complexes and thus creates a need for high [PTH] to maintain Ca reabsorption (IRTCa/Ccr) in the CDN. Because [Ca]i is usually normal in PHPT, we hypothesized that [PTH] would correlate with E P/Ccr in CKD, and would fall with E P/Ccr as sevelamer (SC) reduces filtrate P.

**Methods:** Patients with CKD (mean eGFR 28 ± 1.7) were randomized in double-blind fashion to SC (2.4 g with meals) or placebo (PL) for 4 wks. E P/Ccr was calculated as [P]f/[cr]i, [PTH]-1.84 was measured by IRMA (Sandwiches), [1,25(OH)2D) by RIA (Labcorp), and intact [FGF23] by ELISA (Immutopics). Data are post-treatment means (SEM). A is change with treatment. Differences were analyzed by unpaired t-test, and regressions by least squares.

**Results:** In SC, E P/Ccr was lower and decrements in E P/Ccr were greater than in PL. [PTH] was unrelated to E P/Ccr in SC (R2 = 0.56; P = 0.002) and PL (R2 = 0.36; P = 0.02). Δ[PTH] correlated with A E P/Ccr in SC (R2 = 0.56; P = 0.002) and PL (R2 = 0.36; P = 0.02). [PTH] was unrelated to [P]f and [1,25(OH)2D]. In SC, [PTH] varied directly (not inversely) with [FGF23] (R2 = 0.37; P = 0.02).

**Conclusions:** SC reduced E P/Ccr, and decrements in [PTH] were greater in SC. In both groups, [PTH] correlated with E P/Ccr for [P] in the CDN, and Δ[PTH] correlated with A E P/Ccr. Coplandies did not explain the correlations. The results support the hypothesis that in CKD, high [P] creates an impediment to Ca reabsorption in the CDN.

**Funding:** Veterans Affairs Support, Pharmaceutical Company Support - Genzyme Corporation

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

**Poster/Saturday**

**Poster**

**SA-PO576**

**The Long Acting Calcimimetic R-641 Significantly Lowers Serum FGF23 in Experimental Chronic Kidney Disease**

Thilo Krueger,1 Chun Ouyang,2 Peter Boor,1 Vincent Brandenburg,2 Georg Schlieper,3 Willi Jahnen-dechant,3 Markus Ketteler,2 Xiaodong Li,2 William G. Richards,6 Jürgen Floege,3

Nephrology, RWTH Univ Clinic Aachen, Aachen, Germany; 2Cardiology, RWTH Univ Clinic Aachen, Aachen, Germany; 3Cardiology, RWTH Univ Clinic Aachen, Aachen, Germany; 4Biomedical Engineering, RWTH Univ Aachen, Aachen, Germany; 5Nephrology, Hospital Coburg, Coburg, Germany; 6Amgen Inc., Thousand Oaks, CA.

**Background:** Secondary hyperparathyroidism contributes to vascular calcification in chronic kidney disease (CKD). Calcimimetics lower parathyroid hormone (PTH) secretion by activating the calcium sensing receptor in the parathyroid gland. Here we investigated whether administration of a calcimimetic and PTH injection influences vascular calcification and serum levels of FGF23 in a rat CKD model.

**Methods:** CKD was induced in rats by adenine diet for 4 weeks. Four treatment protocols then continued for further 4 weeks: vehicle, PTH-(1-34), R-641+vehicle, R-641+PTH-(1-34). R-641 or vehicle were administered every third day. In the R-641+PTH group each R-641 dose was followed 48 hrs later by 80 μg/kg PTH s.c. Blood samples were collected; vascular calcification was assessed by measurement of calcium content in aortic walls. PTH-(1-84) and FGF23 serum levels were measured by ELISA.

**Results:** Compared to healthy controls, adenine significantly increased aortic calcium content. R-641 administration significantly reduced aortic calcium content (65 vs. 9 μg/g). Serum PTH was significantly lower in R-641 treatment groups compared to CKD rats (939 vs. 3212 pg/ml). Adenine diet induced a significant increase in FGF23 serum levels (1.4 vs. 198.4 ng/ml). R-641 treatment resulted in significantly lower values (71.4 ng/ml). PTH administration did neither change vascular calcium content in CKD nor FGF23 serum levels in CKD alone or with R-641 co-administration.

**Conclusions:** After 4 weeks treatment, administration of R-641 significantly reduced vascular calcification and lowered serum FGF23 levels in experimental CKD. PTH injection had no influence on vascular calcification or FGF23 content. R-641 administration significantly reduced aortic calcium content (65 vs. 9 μg/g, p<0.05).

**Funding:** Pharmaceutical Company Support - AMGEN Inc.

**SA-PO577**

**Does Decrease of Plasma Fibroblast Growth Factor 23 Concentration During Cinacalcet Treatment Depends on the Decrease of Serum Phosphate Concentration?**

Marcin Adamczak, Piotr Kuczera, Andrzej Wiecek.

4Biomedical Engineering, RWTH Univ Aachen, Aachen, Germany; 5Nephrology, Hospital Coburg, Coburg, Germany; 6Amgen Inc., Thousand Oaks, CA.

**Background:** During Cinacalcet Treatment Depends on the Decrease of Serum Phosphate Concentration.

5Amgen Inc., Thousand Oaks, CA.

**Results:** Serum PTH concentration decreased significantly from 3 and 6 months of treatment. The results are shown as means and 95% confidence index. Plasma PTH concentration decreased after 3 and 6 months of treatment from 593 (457-730) pg/ml to 513 (380-645) pg/ml (p=0.099 and to 433 (304-561) pg/ml (p=0.015, respectively. FGF23 concentration decreased in 52% of patients. In patients with FGF23 decrease a significant (p=0.05) decrease in serum phosphate concentration after 3 and 6 months of treatment (1.92 (1.69-2.14), 1.74 (1.53-1.95) and 1.68 (1.47-1.85)mmol/l, respectively) but not in patients with stable plasma FGF23 concentration (2.13 (1.91-1.35); 2.21 (1.97-2.44); 2.13 (1.92-2.33))mmol/l were observed. There was a significant positive correlation between changes of plasma FGF23 and serum phosphate concentration (0-3 month of treatment) (R=0.30, p=0.03). In the multivariate analysis changes of plasma FGF23 concentration (0-6 month of treatment) was explained by the serum phosphate concentration changes (β=0.29, p=0.04), but not by the serum PTH and calcium concentration changes, nor by the dose of cinacalcet.

**Conclusions:** Decrease of plasma FGF23 concentration in HD treated with cinacalcet seems to be related mostly to the decrease of serum phosphate concentration.

**Funding:** Government Support - Non-U.S.
The response of parathyroid glands to withdrawal of a calcimimetic compound was studied in 74 hemodialysis patients and 60 healthy controls. Relative quantity (RQ) of total leukocyte VDR mRNA expression (qRT-PCR, normalized on beta-actin) and frequency of monocytic subsets (flow cytometry, MACS Quant, Miltenyi) were determined. Monocytes were subdivided into CD14++CD16-(Mo1), CD14++CD16+(Mo2) and CD14++CD16+(Mo3) cells. Vitamin D medication was classified by use of cholecalciferol, active vitamin D or none of them.

**Results:** RQ of VDR was significantly higher in HD patients than in healthy controls (19.0±1.89 vs. 8.9±6.6, p<0.01). Likewise, Mo2 were higher in HD patients than in controls (8.5±0.3 vs. 3.2±0.2%, p<0.0001). Mo2 frequencies and VDR RQ were dependent on vitamin D status and supplementation. We therefore examined the correlation between frequency of parathyroid monocyte subsets and total leukocyte Vitamin D receptor (VDR) expression and their dependency on different vitamin D medications.

**Methods:** In 74 hemodialysis patients and 66 healthy controls, relative quantity (RQ) of total leukocyte VDR mRNA expression (qRT-PCR, normalized on beta-actin) and frequency of monocyte subsets (flow cytometry, MACS Quant, Miltenyi) were determined. Monocytes were subdivided into CD14++CD16-(Mo1), CD14++CD16+(Mo2) and CD14++CD16+(Mo3) cells. Vitamin D medication was classified by use of cholecalciferol, active vitamin D or none of them.

**Results:** RQ of VDR was significantly higher in HD patients than in healthy controls (19.0±1.89 vs. 8.9±6.6, p<0.01). Likewise, Mo2 were higher in HD patients than in controls (8.5±0.3 vs. 3.2±0.2%, p<0.0001). Mo2 frequencies and VDR RQ were dependent on vitamin D status and supplementation. We therefore examined the correlation between frequency of parathyroid monocyte subsets and total leukocyte Vitamin D receptor (VDR) expression and their dependency on different vitamin D medications.

**Background:** Parathyroid monocyte subsets are associated with cardiovascular morbidity in HD patients. It is known that mortality of dialysis patients is associated with vitamin D status and supplementation. We therefore examined the correlation between frequency of parathyroid monocyte subsets and total leukocyte Vitamin D receptor (VDR) expression and their dependency on different vitamin D medications.

**Methods:** In 74 hemodialysis patients and 66 healthy controls, relative quantity (RQ) of total leukocyte VDR mRNA expression (qRT-PCR, normalized on beta-actin) and frequency of monocyte subsets (flow cytometry, MACS Quant, Miltenyi) were determined. Monocytes were subdivided into CD14++CD16-(Mo1), CD14++CD16+(Mo2) and CD14++CD16+(Mo3) cells. Vitamin D medication was classified by use of cholecalciferol, active vitamin D or none of them.

**Results:** RQ of VDR was significantly higher in HD patients than in healthy controls (19.0±1.89 vs. 8.9±6.6, p<0.01). Likewise, Mo2 were higher in HD patients than in controls (8.5±0.3 vs. 3.2±0.2%, p<0.0001). Mo2 frequencies and VDR RQ were dependent on vitamin D medication, being highest in patients without vitamin D and lowest in healthy controls. Use of active vitamin D compounds in addition to cholecalciferol was beneficial (fig.1). Frequencies of Mo2 were significantly correlated with VDR RQ (R=0.11, p=0.001).

**Conclusions:** There are promising agents that ameliorate LVH. Both maxacalcitol (22-oxacalcitrol) and paricalcitol are clinically available less calcemic analogue of aVDR, however, their actions differ from each other in some points. Therefore, we examined (1) the potential of OCT as a therapeutic agent for LVH and (2) the underlying mechanisms especially focusing on the difference between OCT and paricalcitol.

**Methods:** Six-week-old male Wistar rats were subjected to hemipnephrectomy and then divided into four groups; normal saline + vehicle (N+V), normal saline + OCT (N+O), angiotensin II (Ang II) + vehicle (A+V), or Ang II + OCT (A+O). Vehicle or OCT at a dose of 0.15 μg/kg BW was administered subcutaneously twice a day. Using neonatal rat ventricular myocytes (NRVM), we examined the difference between OCT and paricalcitol in view of the calcineurin-NFAT pathway, which plays a pivotal role in the pathogenesis of LVH.

**Results:** Compared with group A+V, heart weight, wall thickness, and mRNA expression levels of the hypertrophic markers were decreased in group A+O. We found that OCT inhibited Ang II-induced activation of calcineurin A, and that OCT recovered mRNA levels for atrigoin-1 in AngII infused rats. In vitro analyses also demonstrated that OCT inhibited Ang II-induced hypertrophy by inhibiting the calcineurin-NFAT pathway. In comparison with the same concentrations of paricalcitol, OCT more effectively inhibited the hypertrophy by inducing atrigoin-1-dependent ubiquitination of calcineurin A in cardiac overexpressed NRVM.
Conclusions: Frequencies of proinflammatory monocyte subsets are correlated with VDR expression. Additionally, VDR expression and Mo2 frequencies vary between groups with different vitamin D compound medication. This may constitute a mechanistic link between beneficial effects of vitamin D supplementation and the prognostic value of proinflammatory monocyte subsets.

Funding: Clinical Revenue Support

SA-PO585

Local Synthesis of Calcitriol by 1α-hydroxylase Is Involved in Vascular Calcification Induced by Uremia

Noelia Torremade,1 M. Vittoria Arcidiacono,1 Petra Valcheva,1 Milica Bozic,1 Sara Panizo,2 Elvira Fernandez,1 Jose M. Valdiviezo.1 1IRBLleida; 2Hospital Universitario Central de Asturias.

Background: Vascular calcification is a complication of chronic kidney disease. We have previously demonstrated that uremia increases the expression of 1α-hydroxylase in vascular smooth muscle cells (VSMC). The objective of this study is to determine the role of the local synthesis of calcitriol on uremia-induced vascular calcification.

Methods: Wild type and alpha hydroxylase KO mice (1αOHase KO) underwent 75% of renal mass reduction, and were treated with calcitriol (400 ng/kg/day) for two weeks. In vitro WT and 1αOHase KO VSMC were treated with healthy and uremic rat serum to evaluate its effect on calcification.

Results: WT mice (n=7) showed increased mortality when treated with calcitriol. However, 1αOHase KO mice (n=10) did not. Serum calcium levels (WT: 16.38 ± 0.48; KO: 15.18 ± 0.46 mg/dl), phosphorus (WT: 8.15 ± 0.42; KO: 8.43 ± 0.46 mg/dl), BUN (WT: 44.99 ± 2.19; KO: 46.13 ± 4.02 mg/dl), and 1,25D levels (WT: 150.21 ± 0.89; KO: 185.74 ± 1.17 pg/ml) increased and were similar in both calcitriol-treated groups. PTH levels decreased in both groups (WT: 29,25±0.84, KO: 30,48±0.70 pg/ml). Vascular calcium (WT: 44.99±2.19, KO: 46.13±4.02 mg/dl), and 1,25D levels (WT: 150,21±0,89; KO: 185,74±1,17 pg/ml) and FEPO4 (p<0.03), low eGFR (P=0.05) and high baseline PTH (p<0.01). The change in 25 (OH)D (p<0.03) was not higher in CKD (18.6 ± 8 ng/ml vs 12.2 ± 9, p=0.03) and in 24,25(OH)2D (1.14 ± 0.89 ng/ml vs 1.02 ± 0.74, p=0.03) in CKD and CKD, respectively. 24,25(OH)2D were not higher in CKD (p<0.0005), and renin higher (5.4±1.5 vs. 3.8±0.92 ng/ml/hour, p<0.02). 1,25D correlated with PTH (r=0.6, p<0.01) and hypocalcemia in mice fed a low calcium diet. T33 decreases the basal transcriptional activity of the promoters (TRs, TR1), and the retinoid X receptor α (RXRα) in OK-P cells. Interestingly, we identified an everted repeat negative thyroid hormone response element (1αt-NRE) overlapping the sterol response element (SRE) and the TATA-box in the human CYP27B1 gene. Finally, we established that CYP27B1 gene transcription is positively and negatively regulated by SRE-binding proteins (SREBP5s) and T3,1β-subbound TR1/RXRα via the 1αt-NRE.

Conclusions: These results suggest that transcriptional repression of the CYP27B1 gene by T3-bound TRs/RXRα, acting through the 1αt-NRE, results in decreased renal CYP27B1 expression and plasma 1,25(OH)2D levels.

Funding: Government Support - Non-U.S.

SA-PO587

Vitamin D Is Cardioprotective but Not Essential for Fibroblast Growth Factor-23 Production

Carlos Cuervo, Gaston E. Zilleruelo, Michael Freundlich. Pediatric Nephrology, Univ of Miami Miller School of Medicine, Miami, FL.

Background: The mechanisms regulating FGF23 are unclear. 1,25(OH)2D (D), and PTH both increase FGF23 levels. However, undetectable FGF23 levels in 1α-hydroxylase ablated mice and the regulatory transcription by a D response element in the FGF23 promoter, suggest D-indsensibility for bone FGF23 secretion challenging the notion that PTH in the absence of D is sufficient for FGF23 production. Absent D also results in remin-angiotensin system (RAS) upregulation and may cause hypertension and cardiac hypertrophy (CH), as in CKD. These relationships were studied in vitamin D dependent rickets type 1 (VDDR-I), where abolised 1-αOH activity results in non-undiectable circulating D and PTH levels.

Methods: After diagnosing VDDR-I at age 8 months, oral calcitriol and supplemental Ca were maintained for the subsequent 12 years, and measurements obtained while under Rx (on-Rx) or following periods of non-adherence (off-Rx).

Results: Hypocalcemia and rickets healed on-Rx but reappeared off-Rx. Final height and blood pressure were normal, the echocardiogram displayed normal ventricular dimensions and cardiac function. Comparing off-Rx vs on-Rx, 1,25D levels were lower (15.45 ± 4.0 vs 12.8 ± 12.8 pg/ml, p<0.01), AlkP higher (1.986 ± 0.986 vs. 1.5 ± 1.8 U/L, p<0.05), PTH higher (931 ± 228 vs. 43 ± 24 pg/ml, p<0.005), 25(OH)D lower (270 ± 3.5 vs. 270 ± 0.3 RU/ml, p<0.0005), and renin higher (5.41 ± 1.5 vs. 3.8 ± 0.92 ng/ml/hour, p<0.02). 1,25D correlated with renin (r = -0.61, p<0.05) and PTH (r = -0.87, p<0.005). Plasma aldosterone and Ang II, and urine tetradehydoroaldosterone were 10-fold Rx and normalized on-Rx. During off-Rx at nadir 1,25D levels <59 pg/ml, 24,25(OH)2D were normal levels (70 RU/ml) while 25(OH)D was 751 pg/ml and PEPO47 (65%).

Conclusions: VDDR-I replicates data in animals deficient in D biosynthesis with RAS stimulation, and shows D acting as a negative regulator of renin production. Long-term D therapy and VDDR-I effectively prevented hypertension and CH strengthening the notion that D displays cardioprotective properties. Furthermore, maintenance of normal FGF23 concentrations with prevailing undetectable 1,25D levels, suggests D-independent PTH-mediated FGF23 secretion by the bone.

SA-PO588

24,25(OH)2D Concentration During Treatment of Vitamin D Deficiency

Hala M. Alishaye1,2, Anil Shivakoti,3, Gerda G. Giamalani,2, 2Valentin David,2 Barry M. Wall.1,2 1Univ of Tennessee Health Science Center, Memphis, TN; 2VA Medical Center, Memphis, TN; 3Marshall Univ, Huntington, WV.

Background: Although FGF23 upregulates Cyp24a1 in CKD, 24,25(OH)2D levels have been shown to be directly related to eGFR in human subjects, possibly related to decreased total enzymatic activity in CKD (Kidney Int, 2012). Low 25(OH)D is a predictor of reduced 24,25(OH)D, suggesting that production may be substrate dependent. To further assess these interactions, 24,25(OH)2D levels were measured before and after treatment of vitamin D deficiency with cholecalciferol in patients with normal eGFR, CKD, and ESRD.

Methods: Patients with 250HD level < 20 ng/ml received 10,000 IU/week of cholecalciferol for 8 weeks: CKD patients(n=14) matched with non-CKD (n=14) for age, sex, race, and diabetes and unmatched ESRD hemodialysis patients (n=14).

Results: There were no significant differences between CKD and non-CKD groups in basal levels of 25(OH)D and 24,25(OH)2D. Baseline iPTH and FGF23 were higher in CKD patients. Cholecalciferol treated treatment resulted in increments in serum 25(OH)D (18.6 ± 8 ng/ml vs 12.2 ± 9, p<0.03) and in 24,25(OH)2D (1.14 ± 0.89 nmol/l vs 1.02 ± 0.74, p=0.03) in both non-CKD and CKD, respectively. 24,25(OH)2D were not higher in CKD (p>0.05) before or after cholecalciferol). Cholecalciferol resulted in an increase in FGF23 (44 ± 57 pg/ml, P=0.01) in non-CKD, but not in CKD or ESRD. In a multivariable analysis, low post-treatment serum 24,25(OH)2D level was predicted by low post-treatment 25(OH)D (p<0.03), low PTH(p=0.05) as well as PTH(p=0.01). The change in 25(OH)D level in ESRD cohort was 16.5 ± 0.7 ng/ml, while 24,25(OH)2D were extremely low and did not change with cholecalciferol.

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

Underline represents presenting author/disclosure.

762A
Conclusions: Vitamin D levels are related to all-cause mortality (ACM) and a composite of cardiac death or cardiac events. Methods: The HEMO Study was a randomized multicenter study evaluating the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)2D) levels were measured in stored serum samples obtained at baseline and annually in 1,340 patients in this cohort. Quartiles of serum 25(OH)D and 1,25(OH)2D concentrations were chosen as the primary predictor variable, with the lowest quartile serving as the reference category. Results: Twenty-one percent (n=282) of patients had ACM, whereas 514 (41%) had a cardiac event. Median (IQR) serum 25(OH)D and 1,25(OH)2D levels were 21.9 (14.2, 36.8) ng/ml and 6.3 (2.9, 14.5) pg/ml, respectively. Adjustment for potential confounders available in the database including inflammatory markers and usage of calcitriol, the highest quartile of 25(OH)D was associated with a decrease risk of ACM (HR=0.55, 95% CI 0.40-0.75) and cardiac events (HR=0.70, 95% CI 0.52-0.94), when compared to the lowest quartile. Similarly, when 25(OH)D was evaluated as a continuous variable, higher levels of 25(OH)D were associated with a decreased risk of ACM and cardiac outcomes (HR=0.97, 95% CI 0.66-0.90 and HR=0.79, 95% CI 0.68-0.92, respectively per doubling of 25(OH)D level). There was no association between 1,25(OH)2D levels and ACM or cardiac events. Conclusions: Low serum 25(OH)D level, but not 1,25(OH)2D level, is independently associated with ACM, cardiac hospitalizations and death in patients requiring hemodialysis.

SA-PO590
Human Cathelicidin and Vitamin D: Baseline Associates and Effects of Ergocalciferol Ishbir Bhan, Ravi I. Thadhani. Nephrology Div, Massachusetts General Hospital, Boston, MA.

Background: Cathelicidin is an antimicrobial peptide produced by the innate immune system that is regulated at a genetic level by vitamin D. Low plasma levels of cathelicidin have been to increased risk of infection in dialysis. We sought to determine baseline associates of plasma cathelicidin in a healthy population and to determine the effects of ergocalciferol (D2) treatment.

Methods: We enrolled 100 healthy subjects free of chronic kidney disease or active infection at a university clinical research center. Baseline levels of 25-OH vitamin D were measured in stored serum samples obtained at baseline and annually in 1,340 patients in this cohort. Quartiles of serum 25(OH)D and 1,25(OH)2D concentrations were chosen as the primary predictor variable, with the lowest quartile serving as the reference category. Time-dependent Cox proportional-hazards models were used to examine the association between vitamin D levels with ACM and a composite of first cardiac hospitalization or cardiac death.

Results: Participants had a mean age of 57±14 years, 55% were females and 46% were white. During a median follow-up of 3.0 years, 582 (43%) died from any cause, and 514 (41%) had a cardiac event. Median (IQR) serum 25(OH)D and 1,25(OH)2D levels were 21.9 (14.2, 36.8) ng/ml and 6.3 (2.9, 14.5) pg/ml, respectively. Adjustment for potential confounders available in the database including inflammatory markers and usage of calcitriol, the highest quartile of 25(OH)D was associated with a decrease risk of ACM (HR=0.55, 95% CI 0.40-0.75) and cardiac events (HR=0.70, 95% CI 0.52-0.94), when compared to the lowest quartile. Similarly, when 25(OH)D was evaluated as a continuous variable, higher levels of 25(OH)D were associated with a decreased risk of ACM and cardiac outcomes (HR=0.97, 95% CI 0.66-0.90 and HR=0.79, 95% CI 0.68-0.92, respectively per doubling of 25(OH)D level). There was no association between 1,25(OH)2D levels and ACM or cardiac events.

Conclusions: Low serum 25(OH)D level, but not 1,25(OH)2D level, is independently associated with ACM, cardiac hospitalizations and death in patients requiring hemodialysis.

Funding: NIDDK Support

SA-PO591
Loop Diuretics Are Associated with Higher PTH in Patients with Normal GFR Kristin M. Corapi,1 Gearoid M. McMahon,2 Julia Beth Wenger,1 Julian Bowlby,1 Luke H. Bickel,1 L. Seifter,2 Ishir Bhan.1 1Univ of Colorado; 2VASCCHS; 1Univ of Utah.

Background: Loop diuretics are associated with higher PTH levels in patients with normal renal function. We assessed whether loop diuretics are linked to higher PTH levels in patients with normal renal function.

Methods: We studied adult participants (≥18 years) from NHANES 2003-2004 and 2005-2006. Subjects with an eGFR <60 ml/min were excluded. The primary outcome, PTH, was log-transformed due to non-normality. Univariate analysis was done using a chi square test or simple linear regression to identify significant predictors of PTH. The association between the use of loop diuretics and PTH was tested using a multi-variable linear regression model adjusted for known covariates after application of appropriate weights.

Results: 8,875 participants were eligible for inclusion, of whom 19% were using loop diuretics. Loop users and non-users did not differ in season of exam, serum calcium, or serum phosphorus. Loop users were more likely to be older, African American, female, and have a higher BMI. Loop users also had a lower mean 25(OH) vitamin D and albumin, and higher 25-OH phosphatase and intact PTH. Median PTH was significantly higher in loop users than in non-users, 51.1 vs 37.3 pg/ml (p=0.001). In the multivariable-adjusted model, the use of loop diuretics was associated with significantly higher log PTH levels (p=0.002). After adjusting for other predictors, use of a loop diuretic was associated with a 12% higher median PTH value compared to non-loop users.

Conclusions: In patients with normal renal function, loop diuretics are independently associated with higher PTH levels. Given the known adverse consequences of elevated PTH, it is important that providers be aware of this relationship.

SA-PO592
Bone Mineral Metabolism Parameters and Microalbuminuria in the National Health and Nutrition Examination Surveys 1999-2010 Timotha J. Ellang, Sheila E. Francis, Timothy J. Chico. Dept of Cardiovascular Science, Univ of Sheffield, United Kingdom.

Background: Greater levels of serum phosphorus, parathyroid hormone (PTH) and alkaline phosphatase (ALP) are independent predictors of cardiovascular outcomes in the presence or absence of kidney disease. Endothelial dysfunction has been implicated as a causal mechanism. We hypothesized that these factors are associated with higher-normal albuminuria and the likelihood of microalbuminuria, a cardiovascular risk marker considered to reflect endothelial dysfunction.

Methods: We examined associations of the above bone metabolic parameters with urine albumin:creatinine ratio (ACR), urine albumin concentration and likelihood of microalbuminuria (ACR>15mg/m in men and >25mg/m in women). Linear and logistic regression analyses were performed in the NHANES 1999-2010 cohorts (N=11,287), NHANES 2005-2006 adults (N=11,243) with eGFR<60 and without microalbuminuria) with adjustment for covariates including age, gender, BMI, race, blood pressure, diabetes, poverty/income ratio, eGFR, serum lipids, hemoglobin, and CRP. Bone-specific ALP and PTH measurements were available in NHANES 1999-2004 (N=10,341) and 2001-2006 (N=6,923) respectively.

Results: Greater serum phosphorus or estimated dietary phosphorus intake (whether absolute, indexed to body weight, calorie intake or calcium intake) did not predict higher log ACR or likelihood of microalbuminuria. Serum total ALP, bone-specific ALP and PTH were independent predictors of higher log ACR and log urine albumin (p<0.001 for all), though increased likelihoods of microalbuminuria with increasing levels of these parameters were non-significant following full covariate adjustment.

Conclusions: Higher levels of ALP, Bone-ALP and PTH are independently associated with greater urinary albumin excretion in a representative sample of the general population. Whether targeting these parameters improves cardiovascular health remains to be determined.

SA-PO593
Parathyroid Hormone and Heart Rate Variability in Hemodialysis Patients Dimitrios J. Poulikakos,1,2 Debasish Banerjee,1,2 Marek Malik.1 Cardiovascular Sciences Research Centre, St. George’s Univ of London, London, United Kingdom; 2Renal and Transplantation, St. George’s Hospital NHS Trust, London, United Kingdom.

Background: Depressed Heart Rate Variability (HRV) reflects abnormal cardiac autonomic regulation and has been linked with increased cardiovascular risk and sudden cardiac death. High parathyroid hormone levels have been associated with sudden cardiac death. We aimed to investigate the association between HRV indices and parathyroid hormone (PTH) in hemodialysis (HD) patients.

Methods: Continuous Holter electrocardiograms were obtained during HD and repeated 5 times during the 3-h dialysis sessions in 80 stable HD patients. The high (HF) and low-frequency (LF) components of HRV in absolute values were calculated every 5 minutes and averaged during the first and last hour of the recordings denoted with (1) and (2) respectively. Logarithmic transformation was applied to normalize the distribution of data. Pre-HD intact PTH, corrected calcium (Ca) and phosphate (P) levels were measured before the first recording.

Results: Data were available for 75 subjects (Age 60±15.32 years, 37% diabetics, intact PTH=44±34 pmol/L, Ca=2.3±1.0mmol/l, P=1.6±0.4mmol/l). All HRV indices showed...
intrasubject stability. Diabetics had lower LF2 (-5.5±0.5 vs. -5.2±0.5 \(p<0.012\)). In non-diabetics PTH correlated negatively with all HRV indices (LF1 \(r=-0.348, p=0.016\), LF2 \(r=-0.038, p=0.739\)) but positively with LF4 \((r=-0.415, p=0.005)\), HF1 \((r=-0.437, p=0.003)\) and HF2 \(-0.319, p=0.033\). There was no association between PTH and HRV indices in diabetics. Scatterplots for PTH and HRV for non-diabetic patients are shown in Figure 1.

**Conclusions:** High PTH and phosphate were associated with depressed HRV in non-diabetic HD patients. Prospective studies are necessary to further evaluate the role of mineral abnormalities in autonomic imbalance in HD patients.

**SA-PO594**

**mTOR Is Central to Parathyroid Cell Proliferation in Experimental Secondary Hyperparathyroidism**  
Oded Volovelsky, Gil Cohen, Gilad Wasserman, Tomer Meir, Oded Meyuhas, Justin Silver, Tally Navel-Many, Hadassah Univ, Jerusalem, Israel.

**Background:** Parathyroid (PT) cell proliferation is central to secondary hyperparathyroidism (SHP). The signal transduction pathways for parathyroid cell proliferation are not well defined. We demonstrate the role of mTOR in parathyroid cell proliferation of SHP.

**Methods:** We induced SHP by a low calcium diet or adenine high PKD. PT cell proliferation was measured by BrdU and Ki67 staining of PT sections. Western blots of mTOR pathway activity were performed. The mTOR inhibitor rapamycin was injected ip or added to PT glands in culture. Knock-in mice, whose ribosomal protein S6 (rpS6) is unphosphorylatable due to substitution of all alanines (rpS6P-/-) and wild type (rpS6P+/+) mice were fed a calcium deficient diet.

**Results:** PT cell proliferation was increased in both models of SHP. Significantly, the mTOR pathway was activated in the PTs of the SHP rats, as measured by increased phosphorylation of components along this pathway. To examine the role of mTOR in SHP we injected the mTOR inhibitor rapamycin to the SHP rats. Rapamycin decreased mTOR activation and prevented PT cell proliferation in both models of SHP. Rapamycin decreased PT cell proliferation in CKD rats when injected at the start of the adenine diet (prophylactic effect) or later, to correct established PT cell proliferation. To verify whether the effect of mTOR inhibition is direct, PT glands from CKD rats were maintained in organ culture with and without rapamycin. Remarkably, proliferation continued in culture as measured by BrdU incorporation, and was inhibited by rapamycin, as observed in vivo, indicating a direct effect of the inhibitor on PT cell proliferation. rpS6 kinase is a downstream target of the mTOR pathway. Knock-in rpS6P-/- and wild type mice were fed a calcium deficient diet. Hypercalcemia led to the expected increase in serum PTH in rpS6P+/+ wild type mice but less so in the rpS6P-/- mice, emphasizing the role of mTOR in SHP.

**Conclusions:** This is the first demonstration that mTOR is a significant regulator of PT cell proliferation and it exerts this effect, at least partially, through rpS6 phosphorylation.

**SA-PO595**

**Elevated Sclerostin Levels Decrease Markedly after Successful Renal Transplantation and Correlate with Renal Function and Improvement of Persistent Hyperparathyroidism**  
Marco Bonani,1 Daniel Rodriguez Gutierrez,1 Nilufar Mohedebi,2 Thomas Fehr,2 Jens G. Brockmann,2 Rudolf P. Wuthrich,1 1Div of Nephrology, Univ Hospital Zurich, Zurich, Switzerland; 2Div of Visceral and Transplantation Surgery, Univ Hospital Zurich, Zurich, Switzerland.

**Background:** Sclerostin is a soluble inhibitor of Wnt signaling which inhibits bone formation. Secreted by osteocytes in response to mechanical unloading it acts as an important regulator of bone formation and localized bone remodeling. Sclerostin levels increase along CKD progression and are particularly elevated in patients on dialysis. The dynamic changes of sclerostin before and after renal transplantation have not been investigated.

**Methods:** We analyzed serum sclerostin levels in 42 patients (mean age 49±14 years, 64% male, BMI 25.7±6.0 kg/m²) before, and 0.5, 3, 6 and 12 months after kidney transplantation. We also explored the correlation of sclerostin with relevant parameters of CKD-MBD.

**Results:** Before transplantation (n=42) compared to control patients with normal renal function (n=96) (61.8±32.3 vs 28.4±10.9 pmol/l; p<0.001), within 14 days after transplantation and in parallel with the improvement of renal function, sclerostin values decreased markedly to levels slightly below the normal range (21.0±14.7). Sclerostin amounts lowered to 21.0±12.5 and 23.8±14.9 after 3 and 6 months, and increased to 28.0±16.8 pmol/l after 12 months. Sclerostin levels were similar in male and female, and in diabetic and non-diabetic patients at all timepoints. After transplantation, sclerostin correlated negatively with age (r=0.170, p=0.033) and positively with age (r=0.311, p=0.045), but there was no significant correlation between sclerostin and BMI, eGFR, serum calcium, phosphate, magnesium, 25OH- and 1,25(OH)-vitamin D. Furthermore, sclerostin levels did not correlate with pre- and post-transplant bone mineral density at the hip and lumbar spine.

**Conclusions:** The marked reduction of elevated serum sclerostin levels shortly after kidney transplantation reflects the improvement of renal function and may contribute to the normalization of bone health after renal transplantation.

**SA-PO596**

**Phosphaturic Hormones Predict the Progression of Anemia in Patients with CKD**  
Takahuki Hamano,1 Chikako Nakano,1 Naohiko Fujiji,1 Yoshitsugu Obi,1 Isao Matsui,1 Yoshitaka Isaka,1 Yoshiharu Tsubakihara.1 1Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 3Center for Clinical Epidemiology and Biostatistics, Univ of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

**Background:** It was reported that 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D (1,25D) levels are associated with severity of anemia in patients with CKD. However, it remains elucidated which MBD markers predict the progression of anemia in this population.

**Methods:** In the OVDIS-CKD study, we prospectively followed temporal change of hemoglobin (hgb) levels. At baseline, we measured 6 MBD markers including intact FGF23, 1-84 PTH, 25D, 1,25D, serum calcium, and phosphate. Outcome of interest is the slope of hgb. We followed the patients until the start of ESA therapy or the end of observation period. We employed a linear mixed effects model with hgb as a time-dependent outcome variable. The interaction term time*each MBD marker was entered into the model to examine if these markers modify the relationship between time and hgb (hgb slope). Since, we have already reported that FGF23 and 25D predict renal outcome (CJASN 2012), eGFR was adjusted as a time-dependent covariate in this model. Only for patients with hgb>10.5 and not receiving ESA at baseline, secondary outcome was defined as time to hgb<10.5 or the start of ESA therapy.

**Results:** We enrolled 738 Japanese predialysis outpatients. Cox models revealed that out of 6 makers only 25D and 25D levels predicted the time to the secondary outcome, in addition to prior CVD, proteinuria, baseline hgb, and eGFR. (adjusted HR per unit change of log FGF23 and 10 ng/mL of 25D: 1.65 [1.5-2.36] and 0.66 [0.46-0.96], respectively). However, this result was confounded by time-dependent eGFR. Mixed effects model adjusting for time-dependent eGFR revealed that FGF23 and PTH levels were associated with faster decline of hbg (+0.053 [-0.091—0.016]g/dL/year and -0.044 [-0.079—0.008] g/dL/year per SD increase, respectively.

**Conclusions:** Two phosphotitins predict the progression of anemia.

**SA-PO597**

**The Association between Handgrip Strength and Vitamin D Status in Maintenance Hemodialysis Patients**  
Keita Kimura,1 Akio Nakashima,2 Yasuo Ishida,1 Keitaro Yokoyama,2 Yoshiharu Tsubakihara.1 1Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

**Background:** Sarcopenia is highly prevalent in patient undergoing hemodialysis. Assessment and prevention of this disorder are important, because it relates to impairment of activity of daily life, falling, and even to poor prognosis. Hand grip strength (HGS) is simple and reliable method for evaluating muscle function. In hemodialysis patient, HGS correlates with lean body mass and nutritional status. Vitamin D is thought to play a role in sarcopenia. In elderly people, 25-hydroxy vitamin D (25(OH)D) positively associates with muscle strength. However, in hemodialysis patient, the association between muscle function and vitamin D is not fully explored.

**Methods:** HGS was measured in 139 patients on maintenance hemodialysis. Laboratory data including serum 25(OH)D, 1,25-dihydroxyvitamin D (1,25(OH)2D), calcium, phosphorus, alkaline phosphatase, intact-PTH, albumin, and hemoglobin were measured. Clinical characteristics of the patients were also obtained. The association of HGS with these factors was analyzed.

**Results:** Average serum 25(OH)D concentration was 19.4 ng/mL. Higher HGS was associated with younger age, male gender, higher hemoglobin, lower alkaline phosphatase and higher 25(OH)D. Neither 1,25(OH)2D nor use of vitamin D were not associated. After adjusting by the potential confounding factors, the association between HGS and 25(OH)D was still evident.

**Conclusions:** Our results clearly showed the association between 25(OH)D and HGS in hemodialysis patient. Considering high prevalence of Vitamin D deficiency and sarcopenia in this population, our results will provide the rationale for planning the controlled study using vitamin D for improving sarcopenia.
SA-PO598

25-Hydroxy Vitamin D Deficiency Is Common in Patients with Chronic Kidney Disease in a Scottish Community Cohort: Results from the Triple A Kidney Project
Shona Methven, 1 Alan G. Jardine, 2 Mark S. MacGregor 3
1 School of Clinical Sciences, Univ of Bristol, United Kingdom; 2 Institute of Cardiovascular and Medical Sciences, Univ of Glasgow, United Kingdom; 3 Renal Unit, Univ Hospital, Crosshouse, Kilmarnock, United Kingdom.

Background: There is increasing awareness of the importance of chronic kidney disease-mineral bone disorders (CKD-MBD), but little is known about primary vitamin D deficiency in patients with CKD. We describe the prevalence of 25-hydroxy vitamin D (25-OHvitD) deficiency in patients with CKD in a geographical area with low levels of sunshine.

Methods: Participants with a diagnosis of CKD stage 3 were recruited from 7 primary care facilities across Ayrshire, Scotland in the Triple A Kidney Project. Detailed baseline clinical and laboratory assessment was undertaken, including measurement of 25-OHvitD and parathyroid hormone (PTH) using an immunoassay in all participants (Abbott Architect).

Results: Four hundred and eleven participants were recruited, mean age 70.6±9.6 years, 59% female, 99.5% white, 20% diabetic and median eGFR 54 (IQR 44–61) ml/min/1.73m2. Serum adjusted calcium, phosphate and alkaline phosphatase levels were normal (2.2±0.1 mmol/L; 0.9±0.2 mmol/L and 78±24 µg/L respectively). Mean 25-OHvitD was 38 (±22)nmol/L, with 40.3% having insufficient 25-OHvitD levels (25-49nmol/L), 20.2% being deficient (14-24nmol/L) and 13.7% having undetectable 25-OHvitD (<14nmol/L). Mean PTH was 8.7 (±4.9)pmol/L (upper limit of normal [ULN] 7.5pmol/L) and 47.2% of the total cohort had elevated PTH, rising to 67.1% in those with CKD Stage 3B. Mild hyperparathyroidism was not related to severity of kidney disease (p=0.332), but PTH ≥500 pg/mL or cinacalcet prescription or therapy was associated with increased insulin requirement (p=0.02).

Conclusions: Primary 25-OHvitD deficiency and mild secondary hyperparathyroidism are very common in those with CKD stage 3 in Scotland, presumably related to low levels of sunshine and diet. The degree of 25-OHvitD deficiency did not vary with renal function, whereas secondary hyperparathyroidism was more severe with poorer renal function. Vitamin D deficiency may predispose to more severe CKD-MBD in the future. Intervention studies are required to assess vitamin D replacement in this group.

Funding: Pharmaceutical Company Support - Unrestricted educational grant from Bristol Myers Squibb

SA-PO600

RDW Is Associated with cFGF23 and Not with iFGF23
Carlo A. Gaillard 1, Fenna Breda, 1 Van, 1 Michele E. Emans, 2 Karien Van der Putten, 3 Branko Braam 4, 5 Frans J. van Itersum, 1 Marc G. Vervloet, 1
1 Nephrology, UMCG/FUMC, Netherlands; 2 Cardiology, UMCU, Netherlands; 3 Internal Medicine, TerGooiziekenhuis, Netherlands; 4 Medicine, Univ of Alberta, Canada.

Background: Fibroblast growth factor-23 (FGF23) and red cell distribution width (RDW) are associated with poor clinical outcomes. RDW is associated with iron deficiency. Recent studies suggest a mechanistic link between iron deficiency and FGF23. In this post-hoc analysis we hypothesized that in CKD patients with heart and renal failure, iron metabolism links FGF23 and RDW.

Methods: Associations between levels of iFGF23 (intact), cFGF23 (c-terminal) and RDW were analyzed in 54 participants of the EPOCARES study (PMD 20383871). Two assays detecting FGF23 were used: one detected only iFGF23, the other detected free c-terminal FGF23 fragments and iFGF23.

Results: cFGF23 and RDW (correlation coefficient (r) = 0.468, p = 0.003) were associated, and iFGF23 and RDW were not (r = -0.089, p = 0.627). Yet, iFGF23 and cFGF23 were both associated with cystatin C (r = -0.632, p < 0.001 and r = -0.414, p = 0.02). Multivariable linear regression analysis, that included PTH, phosphate, BMI, smoking and creatinine did not alter the strength of the association between cFGF23 and RDW (regression coefficient (R) = 0.163, [0.081-0.246]). After adjusting for markers of iron metabolism, this association was attenuated (R = 0.147, [0.061-0.232]). In the full adjusted model correcting for both markers of inflammation and iron metabolism the association remained statistically significant (R = 0.106, [0.0-0.201]).

Conclusions: cFGF23 and not iFGF23 levels were associated with RDW levels in CKD and CHF patients. This suggests a connection between c-terminal fragments and RDW, possibly independently of iron status and inflammation. Studies are needed that unravel what mechanisms are responsible for this association and whether this explains the link of RDW with outcome.

Funding: Other NIH Support - Netherlands Heart Foundation, Pharmaceutical Company Support - Roche

SA-PO601

Klotho, Proteinuria and Acidosis in CKD Patients
Solenne Pelletier 1, Laurence Dubourg, 2 Jocelyne Draï, 1 Sandrine Lemoine, 1 Aoumoue Hadj-assia, 2 Denis Fouque, 1
1 Nephrology, Centre Hospitalier Lyon Sud, Pierre-Benite, France; 2 Départements Fonctionnelles Renales, Hopital Edouard Herriot, Lyon, France; 3 Biology, Centre Hospitalier Lyon Sud, Pierre-Benite, France; 4 Nephrology, Hopital Edouard Herriot, Lyon, France.

Background: a-Klotho(Kl) is a recently discovered FGF23 cofactor involved in phosphorus metabolism. KI overexpression is associated with extended longevity, whereas Kl-KO animals die prematurely. We included 60 chronic kidney disease (CKD) stage 1-5 patients and studied relationships between renal function, proteinuria, bone biomarkers, acid status and serum a-Kl concentrations.

Methods: Blood was drawn after overnight fast for PTH, FGF-23, calcium, phosphorus, 25OH vitamin D, bone specific alkaline phosphatase (bSAP). Serum a-Kl was measured by ELISA (IBL, Japan, normal values 239-1266 pg/mL); proteinuria was obtained from 24hr urine. Renal function was assessed by urinary inulin clearance.

Results: We found positive relationships between a-Kl and FGF23 (p<0.005, r=0.36), serum bicarbonate (p=0.05, r=0.26), and an inverse relationship with proteinuria (p=0.03, r=−0.32). No relationship was found between a-Kl and renal function, serum PTH, vitamin D, bSAP, calcium and phosphorus. Multivariate analysis including proteinuria, FGF23 and bicarbonate showed that FGF23 and bicarbonate were significantly associated with serum a-Kl (p=0.001).

Conclusions: The present findings show for the first time a potential link between 2 important amenable conditions occurring during CKD: proteinuria and acidosis. We suggest including these parameters in future Klolo studies in CKD patients. Whether correcting acidosis may improve serum a-Kl deserves further research.

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

Poster/Saturday

765A
permissive to activity of a number of autoimmune diseases, and may be associated with poorer renal allograft survival. We asked whether PEX would induce vitamin D deficiency through reabsorption of vitamin D-binding protein (DBP).

Methods: We performed a prospective cohort study of patients receiving plasma exchange at Addenbrooke’s Hospital, Cambridge. Vitamin D metabolites, DBP and biochemical parameters were measured before and after the first and every plasma exchange treatment in 27 patients over 28 days after commencement of PEX.

Results: 11 Caucasian patients (7 males) aged 59 ± 13 years received 5.5 ± 0.9 PEX treatments, for ANCA-associated vasculitis (n=5), myasthenia gravis (n=3), paraneoplastic neuropathy (n=2) and voltage-gated potassium channel antibody-mediated encephalopathy (n=1). Baseline estimated glomerular filtration rate was 56.9 ± 39.5 ml/min/1.73 m² and 5 patients had chronic kidney disease stage 3 or worse. Baseline 25(OH)D levels were 50.6 ± 30.1 nmol/L. PEX significantly reduced 25(OH)D levels after 5 treatments to 22 ± 9 nmol/L (p = 0.001), and vitamin D remained low 7 days (26.4 ± 9.8 nmol/L, p=0.02) and 28 days (24.0 ± 8.5, p=0.048) after cessation of PEX. 1,25(OH)2D3 levels reduced from 103 ± 52 pmol/L to 42 ± 4 pmol/L (p = 0.003) with PEX, but had returned to baseline levels after 7 days. PEX also significantly reduced DBP levels from 206.5 ± 64.7 μg/mL to 98.5 ± 34 μg/mL (p < 0.001), but levels had returned to baseline after 7 days. PEX significantly reduced corrected Calcium from 2.73 ± 0.12 mmol/L to 1.98 ± 0.08 mmol/L (p = 0.007), but did not alter phosphate. Analysis of plasma effluent confirmed removal of DBP, vitamin D and PTH by PEX.

Conclusions: We identified sustained reduction in 25(OH)D and acute reversible reduction in 1,25(OH)2D by a typical course of PEX, likely through its removal with DBP in plasma effluent. PEX-treated patients should receive vitamin D supplementation.

SA-PO603
Serum Phosphorus and Fibroblast Growth Factor 23 Do Not Modify the Association of Angiotensin II Inhibition with Outcomes in Subjects with Advanced Chronic Kidney Disease

1 Kristen L. Jablonski, 1 Jessica B. Kendrick, 1 Alfred K. Cheung, 2, 3 Gerard John Smits, 1 Michel Chonchoel, 2 *Div. of Renal Diseases and Hypertension, Univ. of Colorado Denver, Aurora, CO; 3VA Salt Lake City Healthcare System, Salt Lake City, UT, 1 Univ. of Utah, Salt Lake City, UT.

Background: In chronic kidney disease (CKD), there is a fibroblast growth factor 23 (FGF23)-mediated increase in fractional excretion of phosphorus to compensate for decreased kidney function. Higher levels of phosphorus and FGF23 are associated with kidney disease progression and mortality in advanced chronic kidney disease. However, it is unknown whether these associations differ by degree of hyperphosphatemia or FGF23 level.

Methods: We studied the effects of ACE/ARB use in 1753 subjects with advanced CKD (1099 CKD, eGFR=18±6 ml/min/1.73m²; and 654 ESRD) who participated in the National Kidney Disease Surveillance Study. We studied patients in whom serum phosphorus and FGF23 levels were measured. We used the Association of Angiotensin II Inhibition with Outcomes in Subjects with Advanced Chronic Kidney Disease (AAKI) study to study the role of ACE/ARB in CKD.

Results: Average age was 66±12 years, 36% were black, and 870 (50%) were taking ACE/ARB. Over a mean follow-up of 3 years, there were 714 (41%) deaths and 615 patients (56%) initiated chronic dialysis. In adjusted analyses, all subjects treated with ACE/ARB had a significantly lower risk of death (HR 0.81 (95% CI, 0.70-0.95; P = <0.001)) and those with CKD had a significantly lower risk of dialysis initiation (HR 0.86 (95% CI, 0.73-0.97; P = 0.031)). Neither serum phosphorus nor FGF23 levels significantly modified the association of ACE/ARB use with each outcome (p interaction 0.4 for death and p interaction 0.7 for dialysis initiation).

Conclusions: ACE/ARB use is associated with a reduced risk of kidney disease progression and death even when simultaneously accompanied by higher serum phosphorus and FGF23.

Funding: NIDDK Support

SA-PO604
Signaling of FGF23-Klotho under Normal and Hyperglycemic Conditions

Sudha P. Chennasamudram, Ruchi Singh, Tetyana L. Vaalyeva. Pediatrics, Texas Tech Univ Health Sciences Center, Amarillo, TX.

Background: Fibroblast growth factor 23 (FGF23) is a protein produced by osteocytes and is involved in reabsorption of phosphorus in kidney. FGF23 binds to FGF receptors in the presence of a co-receptor called klotho to form a ternary complex in the distal tubule. This ternary complex acts on the proximal tubules to down-regulate tubular reabsorption of phosphate. In chronic kidney disease (CKD) patients, elevated levels of FGF23 have been observed leading to higher mortality rates. Diabetes is one of the leading causes of progression of CKD. The signaling pathways of FGF23-klotho under hyperglycemic conditions are poorly understood. Mechanisms involved in FGF23 pathways under hyperglycemic conditions could further provide information on the role played by FGF23 in the progression of CKD. The study objective is to investigate the effects of FGF23-klotho signaling under hyperglycemic conditions.

Methods: Human proximal epithelial cells (HK2) and glomerular endothelial cells (GEC) were cultured and maintained at 37 °C in a 5% CO2 incubator. Cells were treated with different concentrations (10, 25, 50 and 100 ng/mL) of FGF23 in the presence and absence of Klotho under normal (5mM) and hyperglycemic (25mM) conditions. Formation of reactive oxygen species (ROS) in HK2 cells was investigated by flow cytometry. Effects of FGF23 on apoptosis in glomerular endothelial cells were also studied.

Results: Treatment of HK2 cells with 100 ng/mL of FGF23 under hyperglycemic conditions resulted in significantly increased apoptosis when compared to normal glucose. When Klotho was added, there was a decrease in the percentage of ROS induced by FGF23 under hyperglycemic conditions. There was no change in the percentage of apoptotic cells before and after treatment of FGF23 under hyperglycemic conditions in HK2 cells. But the percentage of apoptotic cells in GEC after 24 hours of FGF23 treatment under hyperglycemic conditions was higher compared to the cells under normal glucose.

Conclusions: High concentrations of FGF23 under hyperglycemic conditions are toxic to glomerular endothelial cells. The stress induced by FGF23 under hyperglycemic conditions is ameliorated by klotho in HK2 cells.

Funding: Pharmaceutical Company Support - Sanofi

SA-PO605
Klotho and Human Coronary Heart Disease

Juan F. Navarro-Gonzalez, 1, 2 Javier Donato, 2 Mercedes Muros, 2 Horacio Perez Hernandez, 2, 3 Violeta Cazana, 2 Javier Garcia Perez, 1 Carmen Mora. 2 *Nephrology Service, Univ Hospital Ntra. Sra. de Candelaria, Tenerife, Spain; 2Research Unit, Univ Hospital Ntra. Sra. de Candelaria, Tenerife, Spain; 3Clinical Analysis Service, Univ Hospital Ntra. Sra. de Candelaria, Tenerife, Spain.

Background: Klotho is involved in maintenance of vascular health. We aimed to analyze the relationship between Klotho and human coronary artery disease (CAD).

Methods: Soluble Klotho were measured in 371 patients undergoing coronary angiography. Klotho gene expression was analyzed in thoracic aorta specimens from 70 patients underwent cardiac surgery.

Results: Soluble Klotho concentration was lower (P = 0.001) in patients with significant CAD (n = 233). The coronary stenosis severity index was significantly lower in patients with the higher soluble Klotho levels (P < 0.001). Multiple regression analysis showed that serum Klotho concentrations were inverse and significantly associated with CAD (adjusted R² = 0.67, P < 0.001). Multivariate logistic regression showed that risk factors for significant CAD included age, diabetes, smoking and inflammation, whereas serum Klotho levels were associated with a lower risk for CAD. Lower mRNA expression level of Klotho was observed in 46 patients with significant CAD, as compared with subjects without significant CAD (P < 0.01). Logistic regression analysis showed that Klotho expression was independently associated with lower risk for CAD.

Conclusions: Patients with significant CAD present lower concentrations of soluble Klotho, as well as reduced levels of Klotho gene expression in the vascular wall. Reduced serum Klotho concentrations and decreased vascular Klotho gene expression were significantly associated with the presence and severity of CAD, independently of established cardiovascular risk factors.

Funding: Government Support - Non-U.S.

SA-PO606
Bone FGF23 Expression Is Increased after Solid Organ Transplantation

R.C. Pereira, 1 Helena Liisa Valtta, 2 Hannu J. Jalanko, 2 Isidro B. Salusky, 1 Navdeep Kaur Tumber, 1 Outi Makitie, 2 Katherine Wesseling-Perry. 1 Pediatrics, UCLA, Los Angeles, CA; 2Univ of Helsinki, Helsinki, Finland.

Background: Expression of FGF23 in bone cells is increased in patients with all stages of CKD and bone immunoreactive FGF23 correlates with skeletal mineralization in both pre-dialysis CKD and dialysis pts. Immunosuppressive agents, particularly glucocorticoids, have been associated with higher circulating FGF23 concentrations; however, the effect of organ transplantation of bone FGF23 values remains unknown.

Methods: Bone histomorphometry was performed in 12 pediatric pre-dialysis CKD pts and in 22 pediatric solid organ transplant (tx) pts. All tx pts were treated with a calcineurin inhibitor, prednisone, an antimetabolite and vitamin D3 (400 or 800 IU/d). No pts received calcitriol or other active vitamin D sterols. Five micron sections of non-decalcified bone were incubated with antihuman FGF-23 (225-244) followed by biotinylated 2o antibody, then developed with ABC complex/HRP and AEC kit (Vector). Number of FGF-23 expressing osteocytes was normalized by tissue area.

Results: GFR was lower in kidney transplant recipients than in recipients of other solid organs; however, bone FGF23 expression did not differ based on the type of organ recipients. In bone, FGF23 binding to FGF receptors in the presence and absence of Klotho under normal (5mM) and hyperglycemic (25mM) conditions. Formation of reactive oxygen species (ROS) in HK2 cells was investigated by flow cytometry. Effects were inversely correlated with osteoid thickness (r = - 0.46, p < 0.01).

Funding: Government Support - Non-U.S.
SA-PO607

Renal Sclerosing Peritubular Nodule – How Rare Is It? Sajan Thomas, Nephrology, Goldcoast Hospital, Goldcoast, Queensland, Australia.

Background: Neurofibromatosis type 2 (NF2) is a rare autosomal dominant disorder. It affects about 1 in 25,000 people. Kidney involvement in NF2 has not been studied extensively. A relatively rare lesion, the renal sclerosing peritubular nodule (RSPN), was first described in a mother and 2 sons with NF2 who died and underwent autopsy in 1981.

Methods: A 53-year-old man with neurofibromatosis type II was referred for investigation and management of his deteriorating renal function. Physical examination revealed cutaneous manifestations of NF2. Serial blood tests showed declining renal function. Urine showed microscopic hematuria with no proteinuria. An ultrasound showed normal size kidneys and renal tract. A renal biopsy was performed.

Results: Light microscopy showed 3 out of 9 glomeruli globally sclerosed. Within the interstitium were paucicellular nodules, adjacent to tubules.

The nodules were lightly eosinophilic on H&E, PAS negative and argyrophilic on PAS.H. The nodules stained blue with Masson trichrome, resembling collagen. In the context of clinical history, the morphology of the collagenous nodules was consistent with RSPN. Histology of the kidneys revealed cutaneous manifestations of NF2. Serial blood tests showed declining renal function.

Conclusions: Therapy with immunosuppressive agents is associated with a marked increase in bone FGF23 immunoactivity, regardless of the type of allograft received and despite, in the case of liver and heart allograft, higher GFR. The implications of these findings for bone biology and systemic complications remain to be evaluated.

Funding: NIDDK Support, Private Foundation Support

SA-PO608

Necrotizing Crescentic Glomerulonephritis with Linear Anti-IgG Deposition in a Patient with Scleroderma: A Case Report Sarah Khan, Bhupinder Sangha, Karina Sulaiman, Neville R. Dossabhoy, Zulqarnain Abro. Nephrology, LSUHSC, Shreveport, LA.

Background: Scleroderma is a multisystem disease affecting the skin, lungs, esophagus, heart, kidneys, and other organs. It is marked by fibrosis and autoantibodies that may activate the immune system. Linear IgG deposition on the glomerular basement membrane is a well-recognized feature of scleroderma.

Methods: A 47-year-old Hispanic male presents with fatigue and lethargy. He has history of GPA, diabetes mellitus, hypertension, and hyperlipidemia. His medications include Zocor, lisinopril, azathioprine, and insulin. On exam, he is afebrile, vital signs stable. Remainder of physical exam is unremarkable. Laboratory data revealed creatinine 5.2 occurs in systemic sclerosis or localized scleroderma. Our patient, who did not meet the criteria for systemic sclerosis but had documented localized scleroderma on skin biopsy, with PAN seen on kidney biopsy and renal angiogram, could be the first reported case of ANCA negative vasculitis occurring in scleroderma.

Conclusions: The presence of anti-pr3 antibody supports recurrence of GPA. However, linear IgG staining favours anti-GBM disease. Anti-GBM disease and GPA both are treated with prednisone and cyclophosphamide. However, anti-GBM disease is also treated with plasmapheresis. In case of GPA, plasmapheresis is beneficial only in severe renal disease or pulmonary hemorrhage. Since our patient did not have detectable circulating anti-GBM antibody, decision was made not to proceed with plasmapheresis.

SA-PO610

ANCA Vasculitis Associated with Influenza Vaccination Megha Shah,1 Tanu Duggal,2 Paul E. Segal,3 Naima Carter-Monroe,4 Duvuru Geetha.1 1Dept of Medicine, Johns Hopkins Univ, Baltimore, MD; 2Dept of Medicine, Sinai Hospital of Baltimore, MD; 3Dept of Pathology, Johns Hopkins Univ, Baltimore, MD.

Background: Administration of influenza vaccine has been associated with development of auto antibodies and autoimmune rheumatic disease.

Methods: Two patients were diagnosed with AA at our institution 2 and 4 weeks following influenza immunization. Both patients had renal involvement, with one requiring hospitalization. Both patients improved after treatment. The patient was treated with intravenous methyl prednisolone 1 gm/day for 5 days followed by oral prednisone at 1 mg/kg/day, and monthly intravenous cyclophosphamide 15mg/kg. Patient had with partial renal recovery at 2 months.

The patient was treated with intravenous methyl prednisolone 1 gm/day for 5 days followed by oral prednisone at 1 mg/kg/day, and monthly intravenous cyclophosphamide 15mg/kg. Patient had with partial renal recovery at 2 months.
dialysis. Both patients were treated with cyclophosphamide (CYC) and prednisone (P) and in the patient with dialysis dependent renal failure plasmapheresis (PE) was added to the immunosuppressive regimen. Both patients achieved disease remission. The patient with initial dialysis dependent renal failure reached end stage renal disease. The characteristics and clinical outcomes of our 2 patients and 6 previously reported cases of AAV associated with influenza vaccine are reported in Table 1.

Conclusions: Renal involvement is common in AAV associated with influenza vaccine and treatment with conventional immunosuppression is successful in remission induction. While a causal role of vaccine in ANCA associated vasculitis cannot be confirmed with these case reports, the occurrence suggests a link. Further cases should be considered to determine the frequency of AAV associated with influenza vaccine.

SA-PO611 ANCA Associated Vasculitis Associated with Subacute Bacterial Endocarditis – A Match to Watch Out for Asifa K. Ansari, Diana L. Dietzer, Andres G. Chiesa-voetter. Cleveland Clinic Foundation.

Background: Infections such as subacute bacterial endocarditis (SBE) are seldom associated with elevated Antineutrophil cytoplasmic antibody (ANCA) titers and in some cases triggering features consistent with ANCA associated vasculitis (AAV). The presence of SBE and AAV in combination poses a clinical dilemma as therapeutic strategies are different. We report a challenging case of AAV associated with SIIH of mitral valve due to streptococcus mutans presenting with acute kidney injury (AKI).

Methods: 68 year old man presented with nonspecific symptoms of weight loss and weakness spanning 2 months. He was noted to have petechial rash on legs and a systolic murmur in mitral area on clinical examination. Laboratory studies showed hemoglobin of 7.6 mg/dl, platelets 70,000 cells/µl, LDH 384 U/L, with undetectable haptoglobins, low Complement C3 levels and negative ANCA. Serum creatinine was 3.6 mg/dl on admission and progressively worsened peaking at 6.88 mg/dl. Renal biopsy performed showed pan-nuclear crescentic glomerulonephritis with fibrinoid necrosis. Blood cultures were positive for streptococcus mutans, with echocardiography revealing mobile mitral valve (MV) vegetation. Patient was treated surgically with MV repair and excision of vegetation, intravenous ceftriaxone and corticosteroids. Patient briefly required renal replacement therapy and eventually had good clinical recovery.

Conclusions: Although rare, bacterial infections are being reported as triggers for AAV. This entity may be missed if appropriate investigations are not performed, resulting in inadequate therapy. Both SBE and AAV can result in AKI, and have an overlapping presentation and is often difficult to determine the underlying etiology. Optimal therapy in the presence of both conditions is not known, and immunosuppressive medications must be used judiciously as can potentially worsen sepsis. Elevated ANCA with low complement levels should raise the suspicion of AAV associated with SBE. Our case supports the use of corticosteroids for life-threatening AAV complicating SBE.

SA-PO612 Anti-Glomerular Basement Membrane Disease after Nephrectomy for Xanthogranulomatous Pyelonephritis in a Child Expressing HLA DR5 Major Histocompatibility Complex Antigens

Emma S. Hagon, Tamara Mallett, Karl McKeever, Mairead Convery. Paediatric Nephrology, Royal Belfast Hospital for Sick Children, Belfast, Co. Antrim, United Kingdom.

Background: The estimated incidence of Antiglomerular basement membrane (anti-GBM) antibody disease is 0.5 per million in adults but much rarer in children. We present the first reported case of a child with anti-GBM antibody disease following nephrectomy for Xanthogranulomatous Pyelonephritis (XGP).

Methods: A previously well 7 year old boy was treated with anti-microbials and required renal replacement therapy, and eventually had good clinical recovery.

Conclusions: While there is no evidence to support the duration of plasmapheresis that should be undertaken is unclear. KDIGO practice guidelines published June 2012 recommend Plasmapheresis for 14 days or until anti-GBM antibody titers are undetectable. These guidelines can be interpreted that a two week course of plasmapheresis is an adequate regimen for all anti – GBM disease.

Methods: The clinical course and data on 3 patients with anti-GBM disease without pulmonary involvement is presented. Two of the 3 patients required dialysis. All 3 patients were plasmapheresed until antibody titers became undetectable.

Results: The average number of exchanges required to achieve an undetectable anti-GBM antibody was 34. All 3 patients had improved renal outcome in follow up.

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

Underline represents presenting author/disclosure.
common in adults but represents a more severe clinical syndrome, with higher frequency of renal involvement. It is very rarely seen in association with cystic fibrosis with only 2 case reports on our literature search. Here we present one such rare association and discuss limitations in treatment.

**Methods:** 50 year old white male with history of cystic fibrosis, recurrent pulmonary infections, diabetes mellitus, Hypertension & CHF. He presented in October 2010 with abdominal pain & was found to have ileal inflammation on CT scan, ulceration on enteroscopy and Vasculitis on biopsy. Diagnosis of HSP was made but his kidney function was normal. In August 2011 he had microscopic hematuria. In April 2012 he had macroscopic hematuria, 1.3 gram proteinuria & increase in creatinine from 0.8 to 1.7. Serologic work up for proteinuria was negative and ultrasound showed normal size kidneys. In August 2012 He had nephrotic syndrome with 4.4 gm proteinuria & creatinine of 2.2. He was presumptively treated as IgA vasculitis with prednisone 1mg/kg & lisinopril. Despite 6 months of steroids his proteinuria increased to 6.6 grams & creatinine to 2.8. Kidney biopsy confirmed acute & chronic focal IgA glomerulonephritis. Cellcept was started cautiously as steroid sparing agent but discontinued a week later due to lobar pneumonia. He continues to be maintained on lower dose of prednisone.

**Conclusions:** Renal biopsy in Cystic fibrosis is technically difficult with inability to lie prone and respiratory reserve & coughing but can disclose a heterogeneous spectrum of nephropathies. Presented here is a case with typical demographics of Caucasian race and male sex for IgA vasculitis. Witnessed is the severity of illness with declining GFR and poor response to steroid therapy. Life threatening sepsis or infections limit the use of more aggressive immunosuppressive therapy in a group of patients particularly prone to resistant bacteria and recurrent infections.

**SA-PO616**

**IgA Nephropathy Precipitated after Hemi-Patectomy for Colorectal Metastasis Siddiq Anwar, Derek Larson, Muhammad A. Ashraf, Helen Liapis, Aubrey R. Morrison. Washington Univ School of Medicine, St. Louis, MO.**

**Background:** Mesangial IgA deposition in the renal glomerulus is a recognized complication of end stage liver disease (ESLD). We report a patient, who developed severe hematuria, acute kidney injury (AKI) and a lower legs rash suggestive of Henoch–Schönlein purpura (HSP) 8 weeks after a right hemichepatectomy. This was subsequently diagnosed as IgA nephropathy (IgAN).

**Methods:** A 50-year White male with a history of colorectal cancer developed AKI following his hemichepatectomy. This was initially attributed to a urinary tract infection and acute tubular necrosis, however he subsequently developed a ‘rash’ and proteinuria which raised the suspicion for a glomerular entity. Patient was readmitted with AKI 4 weeks later and an initial ultrasound revealed mild hydropneumonia. Urology was consulted for stenting, however even after stenting, the patient continued to have an increase in his serum creatinine (SC). This was initially attributed to a urinary tract infection which was presumptively treated as IgA vasculitis with prednisone 1mg/kg and losartan. Despite 6 months of steroids his proteinuria increased to 4.2 grams & creatinine to 2.4. Kidney biopsy confirmed acute & chronic focal IgA glomerulonephritis. Cellcept was started cautiously as steroid sparing agent but discontinued a week later due to lobar pneumonia. He continues to be maintained on lower dose of prednisone.

**Conclusions:** Renal biopsy in Cystic fibrosis is technically difficult with inability to lie prone and respiratory reserve & coughing but can disclose a heterogeneous spectrum of nephropathies. Presented here is a case with typical demographics of Caucasian race and male sex for IgA vasculitis. Witnessed is the severity of illness with declining GFR and poor response to steroid therapy. Life threatening sepsis or infections limit the use of more aggressive immunosuppressive therapy in a group of patients particularly prone to resistant bacteria and recurrent infections.
Methylprednisone 1gm daily for 3 days followed by oral prednisolone at 60 mg/day. Four drug anti tuberculosis treatment (H, R, E, Z) was started. Despite steroids and AKT patient continued to have worsening azotemia and was initiated on haemodialysis after 7 days.

Conclusions: There is evidence to suggest that tuberculosis, in addition to other conditions associated with mucosal exposure to antigens producing an IgA immune response can result in IgA nephropathy. This glomerulopathy is reported as a potential renal complication of concurrent mycobacterial infection. IgA nephropathy due to MOTT in kidney is rare.

SA-PO619
A Unique Case of IgA Heavy Chain Deposition Disease Prodeep Dhakarwal, Ashnil Kumar, Kathryn E. Usai, Nephrology Div, Lehigh Valley Hospital/USF, Allentown, PA.

Background: To our knowledge only 5 cases of IgA heavy chain deposition disease (HCDD) have been reported and 2 were female. We present a case of IgA HCDD and compare the clinicopathological features with earlier cases.

Methods: 65 year old white female was referred for edema, proteinuria and microscopic hematuria. She had history of hypertension and pulmonary embolism. Creatinine (Cr) at presentation was 0.81mg/dL. HB, calcium were normal and urine/Cre was 1.2mg/dL. Urine microscopy had dysmorphic RBCs and RBC cast. ANA, anti dsDNA, ANCA, anti GBM, and complements were negative. SPEP, UPEP was negative but serum and urine kappa/lambda was elevated. Renal biopsy light microscopy showed nodular sclerotic with mesangial nodules. IF had 3+ staining of mesangial nodules and 2+ linear staining of GBM. She was started on eye, bortezomib, and dexamethasone. Cr increased to 1.97 within one week of the first cycle and urine/Cre increased to 9.3. She underwent 6 plasma-exchange (PLEX) and Cr decreased to 1.05. The decision was based on possible aggressive disease.

Conclusions: All reported cases of IgA HCDD presented with hypertension, elevated Cr, microscopic hematuria, anemia and positive SPEP. 4 of 5 patients had nephrotic range proteinurias in presentation. In all cases kidney biopsy had crescentic features with nodular glomerulosclerosis; considered characteristic pattern in this subset of HCDD. Plasma cell dyscrasia was present in all patients. Our patient presented with normal Cr, 1.2g proteinuria, normal hemoglobin and negative SPEP. Renal biopsy had no crescents. This patient received PLEX with decrease in Cr. In summary, we report the sixth case of IgA HCDD, with multiple findings different from earlier cases, including an apparent response to PLEX.

SA-PO620
ACTH a Novel Treatment in IgA Nephropathy Vinh Q. Nguyen,1 Ashraf El-Meanawy,2 Nephrology, Medical College of Wisconsin, Milwaukee, WI; 2Nephrology, Medical College of Wisconsin, Milwaukee, WI.

Background: IgA nephropathy is the most non-infectious glomerulonephritis worldwide. Despite this, treatment options remains limited as current data on immunosuppressive therapy of MMF and cyclosporine have been inconclusive. This leaves supportive therapy and corticosteroids to be the cornerstone of current therapy for aggressive disease.

We report a case of IgA nephropathy treated with ACTH with improvement in proteinuria.

Methods: JB is a 38 y/o white male who was diagnosed with IgA nephropathy biopsy proven in his early 20’s when he presented with hematuria. He now presented to the clinic with worsening creatinine with proteinuria. On PE his BP was 129/85, HR: 68 and well built. The remainder of his exam was unremarkable other than trace bilateral edema. His creatinine at the time was 2.04 mg/dL with 0.9 g/g on spot P/C ratio. Patient was offered steroids and celex and he declined. He opted to have a second opinion at Mayo Clinic where a biopsy was performed showing positivity for IgA, IgM and moderate C3. He was treated with steroids. He returned to our clinic with worsening proteinuria of 3.3 g/g and a creatinine of 3.0 mg/dL and was started on celex. Subsequently his renal function and proteinuria did not improve and ACTH was initiated. He stopped his creatinine stabilize at 2.6-3.0 mg/dL with improvement of proteinuria down to 1.7 gms/gram.

Conclusions: ACTH is a therapy that has been considered in primary membranous nephropathy. However its role in IgA nephropathy has yet to be described. Besides the glucocorticoid effects, it has been thought that ACTH has anti-inflammatory and immune modulating properties. We believe that in selective patients who failed corticosteroids and MMF, ACTH is a viable option.

SA-PO621
Successful Treatment of Rapidly Progressive Immunoglobulin A Nephropathy with Human Immunodeficiency Virus Infection by Steroid Pulse Therapy and Tonsillectomy Daisuke Fujimoto,1 Yoshikazu Miyasato,2 Taku Miyoishi,1 Masataka Adachi,2 Kenichiro Kitamura.2 1Dept of Nephrology, Kumamoto General Hospital, Yatsushiro, Japan; 2Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.

Background: Several renal syndromes including Immunoglobulin A (IgA) nephropathy have been described in patients with human immunodeficiency virus (HIV) infection. Hotta et al. reported that renal syndrome combined with IgA nephropathy is an effective target for clinical recognition in patients with IgA nephropathy (Am J Kidney Dis, 2001). Here, we report a case of rapidly progressive IgA nephropathy with HIV infection treated successfully with steroid pulse therapy and tonsillectomy.

Methods: A 43-year-old man was referred to our department for rapidly progressive renal impairment, proteinuria, and hematuria. He was under treatment of acquired immunodeficiency syndrome (AIDS) with Highly Active Anti-Retroviral therapy (CD4 count >200x10^3, HIV RNA: undetectable). Kidney biopsy revealed IgA nephropathy with cellular crescents. Firstly steroid pulse therapy (methylprednisolone 0.5-1.0g/day for 3 consecutive days, 3 courses) was initiated and prednisolone (30mg/day) and mizorbine (initially 50mg/day, loaded up to 150mg/day) were orally administered as aftertreatment. Two months later, he underwent tonsillectomy. One course of methylprednisolone pulse therapy was added after tonsillectomy. During steroid pulse therapy, CD4 count dropped below 200x10^3, but no serious complication occurred. Serum creatinine (Cr) level increased up to 4.15mg/dL and gradually decreased to 1.1mg/dL. Although hematuria still exists, urinary protein declined from 3g/24h to 0.3g/24h during the 10 months treatment period.

Conclusions: Steroid pulse therapy combined with tonsillectomy dramatically ameliorated the rapid progression of IgA nephropathy in our current case and no serious complication occurred in such a highly immunocompromised host. This combined therapy could be considered in the treatment of rapidly progressive IgA nephropathy in patients with HIV infection.

SA-PO622
Resolution of C1q Deposition but Not of the Clinical Nephrotic Syndrome after Immunomodulating Therapy in Focal Sclerosis Michelle L. Blake,1 Eva Csongradi,1,2 Tibor Fulop.1 Internal Medicine, Univ of Mississippi Medical Center; 1Nephrology, Univ of Debrecen Medical and Health Science Center, Hungary.

Methods: A 30 year-old Caucasian female referred for further management of biopsy-proven C1q nephropathy (C1qNP) and nephrosis. She was normotensive but had severe, bilateral pitting edema, serum albumin of 1.4 g/dL and urine protein/creatinine (UPC) concentrations of 4800-133 mg/dL. Serologic work-up was negative, including complement C3 and C4 levels and anti-nuclear antibodies. A renal biopsy revealed minimal change nephropathy vs. focal sclerosis and C1qNP on immunopathology. She had failed a trial of high-dose oral prednisone. At follow-up she failed a regimen of mycophenolate mofetil 1,500 mg twice a day and prednisone 40 mg daily for 14 months and then monthly IV cyclophosphamide 750 mg x 9 cycles. She received the maximum tolerated ACE inhibitor and spironolactone therapy. Her random UPC ratio ranged 5-35 g/mg/day, serum creatinine (sCr) progressively rose from 1.0 mg/dL to 1.4 mg/dL. Two years after her initial visit we faced the dilemma of ongoing nephrotic-range proteinuria failing maximized therapy. The dilemma was made to repeat the diagnostic histology to reassess the underlying disease. A repeat biopsy revealed focal sclerosis but no C1q deposition. Combined diuretic and ACE inhibitor therapy was continued for symptomatic control; restarting immune-modulating therapy was felt likely to be of little benefit. She was lost to follow-up up till 16 months post biopsy, when sCr rose to 2.8 mg/dL and she remained severely nephrotic with a UPC ratio of 23.

Conclusions: How an underlying glomerulonephritis changes with treatment remains a relatively little explored subject. While clinical nephrosis did not change with immunosuppressive therapy, C1q deposition ceased, making the latter entity likely an immunologically mediated process. Our case illustrates at least two points: first, an established pathologic diagnosis does not obviate the need for repeated renal biopsy later on, should diagnostic uncertainty persist. Second, histological diagnoses may evolve over time, especially in a patient receiving active and powerful immune-modulating treatment.

SA-PO623
Late Recurrence of Light Chain Deposition Disease after Kidney Transplantation Treated with Bortezomib: A Case Report Tarig Javed, Abdul Moiz, Jorge C. Garces, Catherine G. Stafford-Coit. Ochsner Multi-Organ Transplant Institute, Ochsner Clinic Foundation, New Orleans, LA.

Background: Herein, we present a case of a patient who developed recurrence of LCDD, several years after kidney transplantation, leading to allograft dysfunction requiring renal replacement therapy. The patient had a significant improvement in her renal function after receiving bortezomib and was able to come off dialysis.

Methods: A 55 YO Caucasian female with history of Type 2 DM and HTN, ESRD secondary to LCDD underwent living-unrelated kidney transplantation. Her induction consisted of antilymphocytic antibody (thymoglobulin) and MMF 500mg in 3 doses.

She had immediate allograft function without the need of renal replacement therapy. Her creatinine stabilized between 0.8-1.0mg/dL. After 6 years of transplantation routine labs showed a Cr of 1.8mg/dL and nephrotic range proteinuria (9.5g/g) on spot protein to creatinine ratio. She subsequently underwent a kidney biopsy. A diagnosis of recurrent
light-chain deposition disease was made based on the biopsy findings. Oncology was consulted and a bone marrow biopsy was performed which was consistent with a plasma cell dyscrasia and she met criteria for multiple myeloma. Patient initially received five cycles of plasmapheresis without any improvement. She eventually required renal replacement therapy three times a week. She then received one cycle of Bortezomib (Velcade 1.3mg/m² intravenously) along with IV dexamethasone. She received 4 doses of Bortezomib every 1, 4, 8, and 11. There was no immediate clinical response to the treatment and she remained dialysis dependent. She was discharged to a rehabilitation center due to significant debility and deconditioning. Her renal function was closely monitored while she remained on dialysis. She gradually exhibited signs of renal recovery after staying on dialysis for 2 months. Dialysis was held when her urine output improved (> 1L/day), and her creatinine eventually settled between 1.5-1.7 mg/dl.

**Conclusions:** Bortezomib may provide an alternative to currently available treatment options in patient with LCDD after transplantation.

**SA-PO624**

**Heavy Chain Deposition Disease: A Case Report**

Sassan Ghazan-Shahi, Iain D. Young, Ralph M. Meyer, Christine A. White. Internal Medicine - Nephrology, Queen’s Univ, Kingston, Canada.

**Background:** Heavy Chain Deposition Disease (HCDD) is a rare condition with few case reports in the literature. It is one of the three subtypes of monoclonal immunoglobulin deposition disease (MIDD) in the kidney. The most common clinical features are hypertension, microscopic hematuria, nephrotic range proteinuria, and variable degrees of renal insufficiency. The characteristic histopathological finding of HCDD is nodular glomerulosclerosis.

**Methods:** Case Presentation: An 82 yo female with proteinuria and microscopic hematuria presented to the clinic. She reported increased bilateral leg edema, shortness of breath on exertion and generalized fatigue. There was no gross hematuria. She denied any other constitutional symptoms including fever, night sweats, weight loss or loss of appetite. There were no symptoms suggestive of a vasculitic or connective tissue disorder. Past Medical History: COPD and peripheral vascular disease. Her medications were perindopril/indapamide, metoprolol, ASA.

**Physical examination:** BP=170/80 mmHg, clear lungs, broad and displaced PMI, S3 gallop and VI/VI systolic ejection murmur over the aortic area, bilateral leg edema and anasarca. No signs or organomegaly.

**Table 1** shows categorized list of the investigations. Image 1 and Image 2 show light microscopy and immunofluorescence microscopy of the kidney biopsy.

**Outcome:** She was started on Chlorambucil and Prednisone cycles. The response to therapy over 9 months was favorable by improved proteinuria and serum M-Protein.

**Conclusions:** Almost all reported cases of HCDD are in patients with advanced renal insufficiency. Despite the severity of biopsy findings, the renal function in this case was reasonably well preserved on presentation and throughout the follow up period. Given the echocardiographic findings of possible cardiomyopathy, we are proposing possibility of cardiac decompensation.

**SA-PO625**

**A Case of Membranoproliferative Glomerulonephritis (MPGN) with Type I Cryoglobulinemia Associated with Monoclonal Gammopathy of Undetermined Significance (MGUS)**

Shoko Hasegawa, Toshiaki Nakano, Akihiro Tsuchimoto, Kazuhiko Tsuruya, Takanari Kitazono. Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

**Background:** The association of cryoglobulinemia and renal involvement is well known. Renal involvement usually is reported in mixed (type II or III) cryoglobulinemia, mostly associated with chronic hepatitis C infection. Renal involvement in monoclonal, type I cryoglobulinemia is unusual. We report the a rare case of a patient exhibiting pathological characteristics of MPGN, which was induced by type I cryoglobulinemia associated with MGUS.

**Methods:** A 36-year-old Japanese woman was admitted because of proteinuria, hematuria and skin ulcers on the both legs. Urinary protein to creatinine ratio was 3.0 g/gCr and urinary sediment analysis revealed red blood cell of 60-70/high power field and other various casts. The histopathology of skin biopsy showed an obstruction of superficial blood vessels with cosinophilic amorphous materials. Immuno-electrophoresis revealed a monoclonal immunoglobulin (Ig) G-K, type I cryoglobulin. Serum IgG was 1.3 g/dl (<3 g/dl), and a bone marrow biopsy demonstrated 4% of plasma cells. The cryocrit was 35%. A renal biopsy showed mesangial hypercellularity, endocapillary proliferation, and double-contour formation of the glomerular basement membrane. Electron microscopic examination revealed a deposition of annular or curved cylinder tubular material in the glomerular basement membrane. The final diagnosis was MPGN caused by type I cryoglobulinemia associated with monoclonal gammopathy of undetermined significance (MGUS) and skin ulcers with type I cryoglobulinemia associated with MGUS. The hematia and proteinuria improved after therapeutic dose of prednisolone.

**Conclusions:** Renal histopathology of type I cryoglobulinemia shows generally noninflammatory glomerulopathies, including thrombotic and hypocellular lesions, without evidence of vasculitis (Karras A et al. Am J Kidney Dis 2002). We described a rare case of MPGN and skin ulcers with type I cryoglobulinemia associated with MGUS. The hematuria and proteinuria improved after therapeutic dose of prednisolone.
HIV, ANA, anti-DNA and ANCA were all negative, fraction of the complement C3 was normal and C4 reduced. Renal findings included renal failure with proteinuria and hematuria. Ultrasound demonstrated normal kidney size and cortical-medullary relationship preserved. Cryoglobulinemia was suspected and subsequent serum cryoglobulin levels were positive. The peripheral blood smear showed characteristic findings and renal biopsy confirmed the diagnosis of cryoglobulinemic vasculitis.

The peripheral blood smear showed characteristic findings and renal biopsy confirmed the diagnosis of cryoglobulinemic vasculitis.

The patient was treated with steroids and monthly pulse of cyclophosphamide, with recovery of renal function after the second month of treatment and disappearance of the skin lesions.

Conclusions: This case demonstrates that in patients with suspected vasculitis, even with negative serology for hepatitis C, essential cryoglobulinemia should be considered, as early diagnosis and therapy promotes a higher chance of better outcome.

SA-PO628

The Cool Side of Acute Kidney Injury: Type 1 Cryoglobulinemic Glomerulonephritis in a Patient with Waldenstrom’s Macroglobulinaemia

Manita Shah,1 Rahul Mutneja,1 Sparsha Kakunoor,1 Dhwani Vyas,1 Andre A. Kaplan.2 Internal Medicine, Univ of Connecticut, Farmington, CT; 1Nephrology, Univ of Connecticut, Farmington, CT.

Background: Renal manifestations of Waldenstrom’s Macroglobulinaemia (WM) include amyloidosis, glomerular/interstitial IgM deposition, cast nephropathy, intracapillary IgM deposition and cryoglobulinemic glomerulonephritis (GN). Type 1 cryoglobulinemic GN has been infrequently described.

Methods: 64 year old female with WM, not on treatment, presented with vomiting and blurry vision. She was found to be hypertensive with acute renal failure (Creatinine-5.2 mg/dL). Random urine protein was >600 mg/dL. Labs 2 weeks prior showed a creatinine (Cr) of 0.6 mg/dL, cryoglobulins of 29% and IgM of 1330 mg/dL. She underwent immediate therapeutic plasma exchange (TPE) and hemodialysis (HD) for presumed hyperviscosity and renal failure. Serum viscosity drawn prior to TPE returned normal (1.5 U). Following HD and TPE Cr fell to 3.4mg/dL. 4 days later she received only TPE following which Cr was 2.5 mg/dL. with concomitant decline of cryoglobulins (6%) and IgM (301 mg/dL). Renal biopsy on day 4 revealed type 1 cryoglobulinemic GN (courtesy Dr. Herlitz).

She was started on bortezomib, rituximab and steroids and was sent home with follow up. Cr at discharge was 0.6 mg/dL.

Conclusions: Cryoglobulinemia (cryo) is present in 8-18% of WM patients. Cryo associated Raynaud’s, palpable purpura or GN is seen in less than 5% of these patients. Symptoms related to hyperviscosity and cryo are indications for WM treatment. Bortezomib, rituximab and dexamethasone have been most studied. The rapid improvement in renal function post TPE, before immunosuppressive/stereoid therapy is suggestive of rapid re-cannulation of cryoglobulin-clogged glomerular arterioles as is commonly seen with TPE treatment of cryo associated coalescing purpura of the skin.

SA-PO629

Sustained Remission of Refractory Membranoproliferative GN (MPGN) Associated with Monoclonal Gammopathy (MGUS) following Bortezomib/Dexamethasone Therapy

Marvin Aiko Schwarz,1 Yoon-Ishun Ko,1 Thorsten Wiech,2 Jürgen Floege,1 Karl August Brensing.2 Cardiology and Nephrology, RWTH Univ Hospital Aachen, Aachen, NRW, Germany; 1Nierencentrum Bonn, Bonn, NRW, Germany; 2Dept of Pathology, Univ Hospital Eppendorf, Hamburg, Germany; 3Center of Oncology, Johannis Krankenhaus Bonn, Aachen, NRW, Germany.

Background: MPGN type I is known to be associated with monoclonal gammapathy of undetermined significance (MGUS). However, the causal relationship between the two entities is not well established.

Results: A 63-year-old man presented in 2005 with arterial hypertension, microscopic hematuria, proteinuria of 7.4 g/day and a GFR of 99 ml/min. Renal biopsy disclosed MPGN type I. An extensive screen for conditions associated with MPGN type I only revealed an MGUS IgG kappa in serum and Bence-Jones-proteinaemia. From 2005 to 2012 the patient was treated with cyclosporine and low-dose steroids. While he initially responded with a partial remission of proteinuria, in 2011 and 2012 proteinuria relapse to full nephrotic syndrome (proteinuria 10-13 g/day, serum creatinine 1.3 mg/dL). GFR decreased to about 55-60 ml/ min. In view of the MGUS, no therapy with MMF was attempted. In 2012 his MGUS had remained stable with a maximal proportion of plasma cells of 10-12% in a bone marrow biopsy. Given this situation and the lack of alternative treatment recommendations in the 2012 KDIGO guidelines, in June 2012 we decided to target treatment with bortezomib and dexamethasone (Bort/Dex). Proteinuria decreased from 10.5 g/day to 1.9 g/day within 5 months and to 1.1 g/day at 12 months after chemotherapy. GFR increased to 105 ml/min and the patient had full clinical remission. Chemotherapy was well tolerated. The maximal proportion of plasma cells decreased to 2.4%-3% in 2014. A repeated kidney biopsy 3 months after 4 Bort/Dex courses therapy revealed almost complete regression of immunooactivity markers.

Conclusions: Our case suggests that the MGUS was indeed the cause of MPGN type 1 here. However, we cannot fully exclude that Bort/Dex might have also acted directly on the kidney disease. Bort/Dex therapy warrant further investigation in similar situations.

SA-PO630

Hepatitis C Negative Cryoglobulinemic MPGN after Two Decades of Rheumatoid Factor Positivity

Ingrid Callistil, Liliana E. Rios Rojas, Joseph Mattana, Nobuyuki (Bill) Miyawaki. Internal Medicine, Div Nephrology, Winthrop Univ Hospital, Mineola, NY.

Background: Membranoproliferative glomerulonephritis (MPGN) is a lesion often associated with cryoglobulinemic (CG) glomerulonephritis in hepatitis C (HCV) infection yet rare cases of HCV negative CG MPGN have been documented. We present a case of an elderly female without clinical features of rheumatoid arthritis (RA) or HCV who had a positive rheumatoid factor (RF) titer as a surrogate for CG for 20 years and eventually developed CG MPGN with monoclonal IgM kappa deposits.

Methods: A 67 year old female with hypertension, intermittent microhematuria and gradually worsening proteinuria over eight years from 500mg/day to 3000mg/day despite angiotensin receptor blockade and acceptable blood control was initially observed conservatively with serologies and biochemical testing given her preserved creatinine of less than 0.9/mg/dL. She had a persistently positive RF since an arthritis assessment done nearly 20 years ago without any clinical features of RA. Her serologies were otherwise negative, including complement levels and HCV by PCR and antibody. Only one of numerous agricultural assessments ordered through the years was transiently and faintly positive for IgM kappa. Quantitative immunoglobulin levels were unremarkable. Once her urine protein reached 3000mg/day a kidney biopsy was done and revealed MPGN with positive IgM and kappa deposits. Testing for cryoglobulins was positive.

Conclusions: Many cases of MPGN remain idiopathic but associated cases are often linked to HCV and the immune complex deposits, complement dysregulation, and thrombotic microangiopathies. Membranoproliferative glomerulonephritis, in the presence of paraproteinemia, have also been described in MPGN both with and without CG. Monoclonal IgM anti-IgG autoantibodies, commonly referred to as RF, are often considered a surrogate marker for CG. We speculate that this patient’s slowly progressive course was likely due to years of low-grade production of IgM kappa. This case illustrates the possibility that isolated RF positivity in the setting of microscopic hematuria and proteinuria may signal the presence of an underlying paraproteinemic process.

SA-PO631

Membranoproliferative Glomerulonephritis (MPGN) and Central Venous Catheter (CVC) Infections

John Sy,1 Cynthia C. Nast,2 P.T.T. Pham,2 P.C. Pham.1 Nephrology, Olive View MC, Sylmar, CA; 2Nephrology, UCLA MC, LA, CA; 3Pathology, Cedars Sinai MC, LA, CA.

Background: Chronic indwelling infected CVCs have been reported to be associated with MPGN via activation of the classical complement pathway. We report a case of recurrent MPGN in a patient with recurrent CVC infections. To review the literature for common clinical manifestations that may aid clinicians in early identification of both conditions. A 23-year-old male with prior small bowel resection due to trauma and chronic total parenteral nutritional support (TPN) via a CVC since the age of 17 presented with anasarca and low grade fevers.

Evaluation: Urinalysis: 2+ blood, no casts, 2.0 g proteinuria, creatinine (Cr) 1.9 (baseline 1.4 mg/dL),
SA-PO632
Membranoproliferative Glomerulonephritis with Background Non-Collapsing Focal and Segmental Glomerulosclerosis in Untreated HCV Infection

Zaid Brikian,1 Raafat Farag Makary,1 Leighton R. James.1 1Dept of Medicine/Nephrology and Hypertension, Univ of Florida, Jacksonville, Jacksonville, FL; 2Dept of Pathology and Laboratory Medicine, Univ of Florida, Jacksonville, Jacksonville, FL; 3Dept of Medicine/Nephrology and Hypertension, Univ of Florida, Jacksonville, Jacksonville, FL.

Background: Membranoproliferative Glomerulonephritis (MPGN) is uncommon in patients with HIV-associated Nephropathy (HIVAN). The most common feature in HIVAN is a picture of collapsing Focal Segmental Glomerulosclerosis (FSGS).

Methods: We report the case of a young African American man with a history of cocaine use, who presented to the hospital with worsening 1-month lower extremity edema, 2 years after being diagnosed with HIV. Apparently, he never started recommended therapy, and was not on any medications at the time of admission. He was found to have reduced CD4+ cells (81 cells/mL) and elevated creatinine (4.4 mg/dL). Urinalysis revealed blood (small) and protein (650 mg/dL). Urine microscopy showed white blood cell casts, high power field (hpf), red blood cells (2 hpf) and hylane casts (12 hpf). He had nephritic range proteinuria (24 gm/24 hours), but negative workup for SLE and Hepatitis. Accordingly, a kidney biopsy was performed. Light microscopy demonstrated mesangial sclerosis, thickened basement membranes, membranocapillary basement membrane (GBM), marked tubular atrophy and marked tubular dilatation. Immunohistostchemistry showed no specific immunoglobulins or complement deposits. Electron microscopy revealed mesangial expansion, increased cellularity, thickened subendothelial GBM, with subendothelial electron dense deposits along with tubulocapillary inclusions in the endothelium of interstitial blood vessels, all consistent with MPGN and non-collapsing FSGS. The patient was started on combined antiretroviral therapy (cART) and has maintained stable renal function without need for renal replacement therapy or immunosuppression.

Conclusions: This case demonstrates a rare presentation of MPGN in the setting of HIVAN with background non-collapsing FSGS, and highlights the importance of early initiation of cART therapy.

SA-PO633
Successful Antiviral Tripel Therapy in a Longstanding Refractory C Virus (HCV) Infection with an Acute Exacerbation (MPGN I with Acute Nephritis and Cryoglobulinemic Vasculitis)

David Callau, Joerg Latus, Niko Braun, Mark Dominik Alscher, Martin Kimmel. Dept of Internal Medicine, Div of Nephrology, Robert Bosch Hospital, Stuttgart, Germany.

Background: The HCV infection is a very common disease with about 170 million chronically infected patients worldwide. In almost 80% of the cases the infection passes into a chronic form with possible hepatic and extrahepatic manifestations. Before 2011 the standard therapy for patients with a genotype 1 changed. In 2011 the standard therapy for patients with a genotype 1 changed to a protease-inhibitor based triple therapy with telaprevir in 2011 the standard therapy for patients with a genotype 1 changed. In 2011 the standard therapy for patients with a genotype 1 changed to a protease-inhibitor based triple therapy, Kidney biopsy: MPGN type 1. Fourteen years later, he had a similar presentation with recurrent MPGN.

Conclusions: Literature review identified 3 similar cases; in all, the CVC was used for TPN for short bowel syndrome. All cases had multiple CVC infectious episodes prior to the first kidney biopsy. Renal presentations ranged from incidental microscopic hematuria, non-nephrotic proteinuria, +/- cellular/granular casts, to relatively rapid to insidious rise in Cr, ranging from 0.5-2 months, in association with active urinary sediments. Extra-renal manifestations included edema/anasarca, fever, and/or palpable purpura (leukocytoclasia vasculitis). Complement levels were depressed in all but one case. Blood cultures in 3 out of 4 cases revealed Staph. Epidermidis. Following CVC replacement and antibiotic therapy, Cr, proteinuria, and hematuria improved in all patients. Proteinuria improved within days and Cr within 2 weeks. Complete kidney function occurred within 3-10 months. Recurrent inulin clearance in a patient with recurrent MPGN was associated with a causal relationship by the former. MPGN is associated with repeated episodes of CVC infections and may be predicted with surveillance urinalysis, Cr, +/- components. Kidney injury may herald or coincide with CVC infections.

SA-PO634
Clinical and Histopathologic Maintenance of Disease Remission off Eculizumab in Two Patients with Recurrent C3 Glomerulopathy


Background: Eculizumab, a monoclonal Ab against C5, has emerged as a potential treatment for C3 glomerulopathies (C3G). Duration of therapy with this agent, however, remains an unresolved issue.

Methods: In 2012, we reported the 1st trial of eculizumab in C3G. Six subjects received the drug for 1 year:2 failed treatment,2 were re-started on eculizumab due to relapse, and 2 subjects remained off the drug with no evidence of relapse. We reviewed their clinical course and protocol biopsies performed before, upon completion, and one year after completion of eculizumab therapy.

Results: Both patients were white males, aged 20 and 42, with recurrent C3G in the allograft diagnosed within 2 months prior to initiating eculizumab therapy. Maintenance immunosuppression of MMF and FK506 was unchanged while on and off eculizumab. Genetic and autoAb testing revealed a mutation in MCP and a C3NeF in patient 1; patient 2 had no detectable mutation or autoAb. Patient 1’s Cr fell from 2.0 to 1.4 mg/dl by completion of therapy. One year later, Cr remained 1.2-1.4 mg/dl with no proteinuria. Biopsy done at completion of therapy showed minimal mesangial proliferation with no evidence of endocapillary proliferation or exudative features. Patient 2’s proteinuria fell from 10.6 g/g by UPyC to 1.8 g/g by completion of therapy with stable creatinine. One year later, UPyC remained 1.4 g/g. Biopsy done at completion of therapy showed decreased mesangial proliferation and resorption of electron dense deposits on EM compared to pre-treatment. Biopsy performed 1 year later showed similarly mild mesangial proliferation and further resorption of deposits. Notably, in both patients, the de novo IF staining for kappa-restricted IgG, and IgG4 (binding of eculizumab to C5 in renal tissue), present in biopsies performed at completion of therapy, was no longer seen one year of therapy.

Conclusions: In 2 patients with recurrent C3G, 1 year of treatment with eculizumab was associated with clinical and histopathologic remission that persisted after discontinuation of therapy.

Funding: Pharmaceutical Company Support - Alexion

SA-PO635
Atypical Hemolytic Uremic Syndrome Treated with Eculizumab


Background: This case report of aHUS illustrates the efficacy of plasma exchange and Eculizumab in the treatment of thrombotic microangiopathy resulting from a mutation of MCP.CD46.

Methods: 23 yo male presented with non-bloody diarrhea and “wine-colored” urine with a rise in creatinine (Cr) to 1.9mg/dl. No prior history of renal dysfunction nor family history of renal failure. On exam, he was hypertensive with a blood pressure of 160/90, μthrombocytopenia (platelets 28/L), and LDH 1800 U/L. Urine microscopy revealed white blood cell casts, high power field (hpf), red blood cells (2 hpf) and hylane casts (12 hpf). He had nephritic range proteinuria (24 gm/24 hours), but negative workup for SLE and Hepatitis. Accordingly, a kidney biopsy was performed. Light microscopy demonstrated mesangial sclerosis, thickened subendothelial GBM, with subendothelial electron dense deposits along with tubulocapillary inclusions in the endothelium of interstitial blood vessels, all consistent with MPGN and non-collapsing FSGS. The patient was started on combined antiretroviral therapy (cART) and has maintained stable renal function without need for renal replacement therapy or immunosuppression.

Conclusions: This case demonstrates a rare presentation of MPGN in the setting of HIVAN with background non-collapsing FSGS, and highlights the importance of early initiation of cART therapy.

Funding: Private Foundation Support
SA-PO636

Dermatomyositis-Induced Minimal Change Disease: A High Interferon State

Shailaja Chidella,1 Hitesh H. Shah,1 James M. Pullman,2 Kenar D. Jhaveri.1 1Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY; 2Pathology, Montefiore Medical Center/ Albert Einstein School of Medicine, Bronx, NY.

Background: Dermatomyositis (DM) is an autoimmune disease that characterized by involvement of proximal musculature and skin. Renal involvement is uncommon in dermatomyositis compared to other autoimmune disorders such as SLE. We report a patient who developed proteinuria in the setting of active DM.

Methods: A 60-year-old Hispanic female was referred by rheumatology for evaluation of proteinuria. Three weeks prior to presentation, she had been diagnosed with DM based on skin biopsy findings and systemic complaints. On presentation, she was normotensive and had trace lower extremity edema. She had normal lupus and other connective tissue serologies. A 24-hour urine collection revealed 2g of proteinuria. Both serum albumin (3.7g/dL) and serum creatinine were normal. Viral panels including hepatitis B and C, HIV, parvo virus B19 were negative. She has no history of diabetes mellitus or HTN. She denied any NSAID use. A kidney biopsy revealed normal light microscopy, normal IF but EM showed minimal change disease (MCD) with diffuse foot process effacement. In addition, significant number of tubulocapillary junctions (TRIs) were noted. She had never received any interferon (IFN) therapy. Of all the connective tissue diseases, MCD has the highest IFN production. Given the podocyte effacement with presence of TRI, a secondary cause of MCD was considered. Given her recent diagnosis of DM and new onset proteinuria, an association with DM and MCD was made. At that point, she was started on oral steroids for treatment of DM and MCD and her proteinuria is currently improving. Typically, it is not known to cause renal disease. We report a case of MCD secondary to DM along with TRIs on kidney biopsy suggesting that active DM is a high IFN signature state that can lead to the glomerular disease in these patients.

Conclusions: DMS along with TRIs on kidney biopsy suggesting that active DMS is a high IFN signature state that can lead to the glomerular disease in these patients.

SA-PO637

Minimal Change Disease Associated with Waldenstrom’s Macroglobulinemia

Olga Kuchmak1 William L. Clapp,2 A. Ahsan Ejaz.3 1Div of Nephrology, Hypertension and Transplantation, Univ of Florida, Gainesville, FL; 2Dept of Pathology, Univ of Florida, Gainesville, FL; 3Div of Nephrology, Hypertension and Transplantation, Univ of Florida, Gainesville, FL.

Background: Waldenstrom’s macroglobulinemia (WM) is a cancer of the B-lymphocytes, whereas minimal change disease (MCD) has been postulated to be associated with a Th2 immune response. MCD is common in children and WM is rare even in the adult predilection group. Occurrence of MCD associated with WM is rare, as described in this case report.

Methods: 73 year-old WM with history of diastolic dysfunction presented with generalized anasarca and recent 50 lbs weight gain. Labs were significant for the following: BUN 52mg/dL, Creat 2.58mg/dL, Total Prot 5.7g/dL, Alb 0.7g/dL, normal C3, C4, negative serology for hepatitis, HIV, ANCA and ANA. UA showed protein 3+, WBC 11/HPF, RBCs 2/hpf; random UPCr 12; UPEP and SPEP were positive for M (monoclonal) protein. Viral panels including hepatitis B and C, HIV, parvo virus B19 were negative. She has no history of diabetes mellitus or HTN. She denied any NSAID use. A kidney biopsy revealed normal light microscopy, normal IF but EM showed minimal change disease (MCD) with diffuse foot process effacement. In addition, significant number of tubulocapillary junctions (TRIs) were noted. She had never received any interferon (IFN) therapy. Of all the connective tissue diseases, MCD has the highest IFN production. Given the podocyte effacement with presence of TRI, a secondary cause of MCD was considered. Given her recent diagnosis of DMS and new onset proteinuria, an association with DMS and MCD was made. At that point, she was started on oral steroids for treatment of DMS and MCD and her proteinuria is currently improving. Typically, it is not known to cause renal disease. We report a case of MCD secondary to DMS along with TRIs on kidney biopsy suggesting that active DMS is a high IFN signature state that can lead to the glomerular disease in these patients.

Conclusions: DMS along with TRIs on kidney biopsy suggesting that active DMS is a high IFN signature state that can lead to the glomerular disease in these patients.
Tip Variant Focal Segmental Glomerulosclerosis (FSGS) Associated with Interferon-β Treatment of Multiple Sclerosis (MS)

Rhys David Russell Evans, Pandora Rudd, Andrew Rennie Hall, Mark Harber
Whittington Hospital and UCL Centre for Nephrology, London, United Kingdom.

Background: The nephrotic syndrome is a rare complication of treatment with Interferon. Minimal change disease and collapsing FSGS have been reported to occur in association with Interferon-b. We report a case of the nephrotic syndrome caused by tip variant FSGS in the setting of Interferon-b treatment of MS.

Methods: A 43 year old woman presented to the emergency department with swelling of her hands and feet. She had MS and had been treated with Interferon-b for the last 15 months without significant side effect. Other medical problems included migraine, oesophagitis, obesity and depression. She had been well until one week prior to presentation when she developed swelling of her hands and feet. She was hypertensive (199/110) with pitting oedema to the knee. Urine dipstick was positive for blood (3+) and protein (4+). Her creatinine was 64μmol/L with an albumin of 27g/L, cholesterol 8.8mmol/L, and urinary protein:creatinine (PCR) 1284mg/mmol consistent with the nephrotic syndrome. ESR was 62mm/hour (CRP 8mg/L) with an otherwise unremarkable renal screen. A renal biopsy demonstrated tip variant FSGS. Her Interferon was held and she was treated with an ACE inhibitor, diuretics and tacrolimus. Her proteinuria and albumin have improved with latest urinary PCR 100mg/mmol and albumin 30g/L. Her creatinine has risen to 119umol/L in association with the above. Her oedema is resolving and she remains well in herself without recurrence of any neurological symptoms.

Conclusions: Minimal change disease and collapsing FSGS are rare complications of Interferon-b treatment of MS. This is the first report of the nephrotic syndrome caused by the tip variant of FSGS in this setting.

Thrombotic Microangiopathy in a Patient Treated with a Protease Inhibitor Based Regimen for Hepatitis C

Rhys David Russell Evans, Mathena Pavan, Deepak Suri, Mark Harber. Whittington Hospital, London, United Kingdom.

Background: Current evidence advocates the use of triple therapy (pegylated interferon, ribavirin and a protease inhibitor) for the management of Hepatitis C genotype 1. We report a case of thrombotic microangiopathy in the setting of triple therapy with full recovery of renal function in response to cessation of antivirals and plasma exchange.

Methods: A 43 year old woman presented to the emergency department with swelling of her hands and feet. She had MS and had been treated with Interferon-b for the last 15 months without significant side effect. Other medical problems included migraine, oesophagitis, obesity and depression. She had been well until one week prior to presentation when she developed swelling of her hands and feet. She was hypertensive (199/110) with pitting oedema to the knee. Urine dipstick was positive for blood (3+) and protein (4+). Her creatinine was 64μmol/L with an albumin of 27g/L, cholesterol 8.8mmol/L, and urinary protein:creatinine (PCR) 1284mg/mmol consistent with the nephrotic syndrome. ESR was 62mm/hour (CRP 8mg/L) with an otherwise unremarkable renal screen. A renal biopsy demonstrated tip variant FSGS. Her Interferon was held and she was treated with an ACE inhibitor, diuretics and tacrolimus. Her proteinuria and albumin have improved with latest urinary PCR 100mg/mmol and albumin 30g/L. Her creatinine has risen to 119umol/L in association with the above. Her oedema is resolving and she remains well in herself without recurrence of any neurological symptoms.

Conclusions: Minimal change disease and collapsing FSGS are rare complications of Interferon-b treatment of MS. This is the first report of the nephrotic syndrome caused by the tip variant of FSGS in this setting.

Diabetic Nephropathy without Diabetes: A Case Report

Sara A. Combs, J. Pedro Teixeira, M. Scott Lucia, Richard J. Johnson. Univ of Colorado, Aurora, CO.

Background: Diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD) in the US. We present a case of a 45 year-old Hispanic man with no known history of diabetes who presented with renal failure and nephrotic syndrome and had advanced DN on biopsy.

Methods: The patient presented to the ED with progressive dyspnea, chest pain, and lower extremity swelling over 3-4 weeks. Exam revealed a blood pressure of 220/100 mm Hg and generalized edema. His BMI was 29.9 kg/m2, though he reported a 50-100 pound weight loss in the past few years. Serum creatinine was 7.5 mg/dL (eGFR by MDRD of 8 mL/min), potassium 5.8 mEq/L, bicarbonate 15 mEq/L, serum albumin 2.0 g/dL, BUN 101 mg/dL, phosphorus 6.1 mg/dL, calcium 6.8 mg/dL, and hemoglobin 9.3 g/dL. Urine microscopy revealed 10 to 20 RBCs per hpf with few granular casts. Urinary protein was measured at 11 g by 24 hour collection. Fasting glucose was in the normal to impaired range (average 94, range 80-110 mg/dL) with normal random glucose levels. Hemoglobin A1c was 5.9%. SPEP and UPEP, serum lambda/kappa ratio, HIV and HCV antibodies, HBV surface antigen, and ANA were all negative. Renal ultrasound revealed normal kidney size and ecchogenicity. Hemodialysis was initiated with improvement in the patient’s symptoms. Renal biopsy demonstrated marked nodular glomerulosclerosis, felt to be consistent with advanced DN. Dilated fundoscopic exam revealed severe bilateral diabetic retinopathy.

Conclusions: Whilst TMA complicating interferon treatment of Hepatitis C has been documented, this is the first description of TMA complicating triple therapy. Protease inhibitors may exacerbate the side effects of interferon.

Diabetic Nephropathy as a Manifestation of Chronic Graft versus Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation

Yul Hee Cho, Ji Hee Lim, Min Young Kim, Myung Hyun Lee, Ji Hyun Yu, Keun Suk Yang, Seun Deuk Hwang, Chul Woo Yang, Yong-Soo Kim, Cheol Whee Park. Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea, College of Medicine, Seoul, Republic of Korea.

Background: Membranous nephropathy (MN) is the most common glomerular disease after allogeneic hematopoietic stem cell transplantation (HSCT). The pathogenesis of MN after allogeneic HSCT is not well understood. We described the clinical and histopathological characteristics and outcomes of 12 patients with post HSCT MN.

Methods: We investigated the renal pathologic and clinical findings of 12 patients who developed MN after HSCT at Seoul St. Mary’s Hospital. We also measured the anti-PLA2R (M-type phospholipase A2 receptor) antibodies using commercial antigen specific ELISA kit in the serum samples from the seven patients at the time of renal biopsy.

Results: Of the 12 patients, all had chronic Graft Versus Host Disease (cGVHD) and indication of biopsy was proteinuria (>1g/day) without microscopic hematuria, in 58% (7/12) of patients with nephrotic syndrome. Overall response rate, including complete remission (urinary protein level < 0.3g/day)and partial remission (urinary protein level
SA-PO644
Membranous Nephropathy Post Allogeneic Haematopoietic Stem Cell Transplant – A Case Series
Karen Lok Yue Kung, Subramanian K. Kurnar, Nephrology, Gosford Hospital, Gosford, NSW, Australia; Nephrology, Westmead Hospital, Westmead, NSW, Australia.

Background: Membranous nephropathy is a rare complication following allogeneic haematopoietic stem cell transplantation, and clinical observations to date suggest an association between chronic graft versus host disease (cGVHD) and membranous nephropathy in this setting. Whether this is a secondary process and perhaps a manifestation of graft versus host disease in the kidney is difficult to verify. Primary membranous nephropathy is a possibility, but there have been no published case reports of serum PL2R antibody testing in these patients.

Methods: Here, we describe 5 cases of membranous nephropathy following allogeneic haematopoietic stem cell transplantation; serum anti-PL2R antibody testing was available at the time of diagnosis for two of these patients.

Results: A history of GVHD involving variable sites was identified in all five patients. All patients were treated with prednisolone with or without other agents after biopsy proven membranous nephropathy. At the time of last follow up, two patients had developed end stage renal failure and were dialysis dependent; two achieved complete remission proved membranous nephropathy. At the time of last follow up, two patients had developed end stage renal failure and were dialysis dependent; two achieved complete remission

Conclusions: The presence of a cGVHD history in all five of our patients with membranous nephropathy supports the findings in other cases series that there is likely an association between the two, but the exact nature of this relationship is difficult to establish. The absence of serum anti-PL2R antibody in both patients in which the test was performed, suggests an alternative antigen to PL2R is the target in patients with membranous nephropathy post allogeneic haematopoietic stem cell transplant. Furthermore, since the prevalence of the anti-PL2R antibody supports the diagnosis of primary membranous nephropathy, the negative result in both cases would support the diagnosis of membranous nephropathy in this clinical context as a secondary process.

SA-PO645
Response to Oral Corticosteroids in Relapsing Membranous Nephropathy with Acute Kidney Injury following Influenza Vaccine  Chinnay P. Patel, Hitesh H. Shah. Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY.

Background: Membranous nephropathy (MN) is one of the most common forms of nephrotic syndrome in adults. Here, we describe a unique case of relapsing MN with acute kidney injury (AKI) following 2009 H1N1 influenza vaccine with management and long term follow-up.

Methods: A 60-year-old female presented with 1 week history of acute onset lower extremity edema 5 days after receiving 2009-10 influenza vaccine. Patient had refused influenza vaccination in the past as her father had died from Guillain-Barre syndrome after receiving influenza vaccine. She denied NSAID use. Physical exam was significant for hypertension and lower extremity edema. Laboratory data revealed AKI with serum creatinine (Scr) of 10.2. Her spot urine total protein to creatinine ratio (TP/CR) was 28. At this point, patient underwent repeat kidney biopsy which showed stage 1MN with acute interstitial nephritis (AIN). She was started on daily oral prednisone (0.75mg/kg) with tapering doses over the next 2 months. 5 weeks after initiation of oral prednisone, her Scr had normalized (0.9) and spot urine TP/CR decreased to 1.3. However 1 week after completion of prednisone therapy, patient was found to have elevated Scr of 2.3. Her spot urine TP/CR increased to 28. At this point, patient underwent repeat kidney biopsy which showed MN with resolution of AIN. Daily oral prednisone was initiated in all patients. Her Scr decreased to 0.9 and spot urine TP/CR decreased to 1.3. Since then, she remained in complete clinical remission with stable renal function and spot urine TP/CR of 0.2. The etiologic link of the two syndromes is unknown. In both patients who underwent testing for serum anti-PL2R antibody, the result was negative.

Conclusions: The presence of a cGVHD history in all five of our patients with membranous nephropathy supports the findings in other cases series that there is likely an association between the two, but the exact nature of this relationship is difficult to establish. The absence of serum anti-PL2R antibody in both patients in which the test was performed, suggests an alternative antigen to PL2R is the target in patients with membranous nephropathy post allogeneic haematopoietic stem cell transplant. Furthermore, since the prevalence of the anti-PL2R antibody supports the diagnosis of primary membranous nephropathy, the negative result in both cases would support the diagnosis of membranous nephropathy in this clinical context as a secondary process.

SA-PO646
Syphilis-Associated Membranous Nephropathy Mimicking Class V Lupus Nephritis Chinnay P. Patel, Aditya Kadiyalaya, James M. Pullman, Hitesh H. Shah, Kenar D. Jhaveri. Hofstra North Shore-LIJ School of Medicine, Great Neck, NY; Montefiore Medical Center, Bronx, NY.

Background: Syphilis is a well known cause of secondary membranous nephropathy (MN), but is not commonly diagnosed in the US. We present a case of secondary syphilis presenting with acute onset nephrotic syndrome with unusual kidney biopsy findings.

Methods: A 21-year-old Caucasian male was admitted with a 3 day history of worsening anasarca, facial edema & 10 lbs weight gain. He was recently diagnosed with a rectal fissure and was started on mesalamine for a presumed diagnosis of inflammatory bowel disease. He was homosexual. On physical exam, he was thin built, normotensive & had periorbital edema. The area around the perianal fissure showed bilateral erythematous macular rash. There was no leukopenia & the rest of the physical examination was unremarkable. Pertinent admission laboratory data showed normal CBC, liver enzymes & lipid panel. Serum creatinine was 2.1mg/dl & serum albumin was 2.1g/dl. A 24 hour urine revealed 15 gms of protein. Serological workup was positive for hepatitis B & C, HIV, ANA, & Anti-dsDNA antibody. C3, C4 were in normal range. Patient had a positive RPR and FTA-Ab. In his kidney biopsy, LM showed thickening of glomerular basement membranes with no other changes. If showed a “full-house” pattern with granular staining in the capillary walls & mesangium for IgG, IgA, IgM, C3 and C4q. EM showed extensive foot process effacement & many small subepithelial electron dense deposits diagnostic of MN. Clinical criteria for SLE were otherwise absent. The final diagnosis was syphilis-related MN with similarities to class V lupus nephritis. The patient’s nephritic syndrome went into remission within 2 weeks of treatment with 3 doses of benzathine penicillin, supporting syphilis as a primary cause. Six months after treatment, the patient remains in remission.

Conclusions: The presence of a “full-house” IF pattern on renal biopsy, usually characteristic of lupus nephritis, did not preclude the diagnosis of syphilis-associated MN. Despite its rare occurrence, syphilis associated renal diseases should be considered in the differential diagnosis of “lupus-like nephritis” especially in high risk patient groups.

SA-PO647

Background: The Hypereosinophilic Syndrome (HES) is a group of disorders characterized by persistent eosinophilia without an identifiable cause, and usually with eosinophilia-related end organ damage. Skin, gastrointestinal, heart, and lung involvement are common, renal manifestations are rare. We report a case of HES with Membranous Glomerulopathy.

Methods: A 63 year old white man presented with pruritic diffuse erythematous dermatitis and eosinophilia with no identifiable cause. He had mild eosinophilia during the previous 10 years. Skin biopsy suggested psoriasisform dermatitis. Four months later he had explosive new-onset nephrotic range proteinuria (9 g/day) with serum creatinine 1.3mg/dl. Absolute eosinophils were 1400/mm3 and peaked at 4300/mm3 over one year. Serum IgE was 50,000 IU/ml. Studies including, ANA, anti-DNA, ANCA, serum/urine protein electrophoresis, complement, hepatitis B/C serologies, and HIV were negative or normal. Studies for parasites and malignancy were negative, and he was on no medications. Bone marrow showed increased eosinophils (30%) without abnormal myeloid maturation, increased total population or a lymphoproliferative disorder (absence of TIP1, PDGFR, JAK2-V617F, BCR-ABL and 4q12 mutations). Renal biopsy showed classic Membranous Nephropathy (MN). Tubulointerstitial nephritis with eosinophils was not present. Cyclosporine and steroids induced a full remission of nephrotic syndrome and resolution of erythema and eosinophilia.

Conclusions: This is the third case in the medical literature describing the association of membranous nephropathy with HES, in this case HES lymphocytic variant. The close temporal onset of both HES and MN, and their resolution with treatment suggest a close relation, not merely a coincidental association. Both HES and the nephrotic syndrome responded to cyclosporine and steroids. The etiologic link of the 2 syndromes is unknown.

Funding: Private Foundation Support

SA-PO648
IgG4-Related Tubulointerstitial Nephritis with Minimal Change Disease Shiba Khorsandi, Joshua Kaplan, Michael Yudd, Nitin Behl, Arshia Abbasi, Deepthi Karanam, Salvatore Chillemi, Reza Amerinashab,

Background: IgG4-related tubulointerstitial nephritis (TIN) is a newly recognized clinicopathologic entity. We report a rare case of IgG4-related TIN with minimal change disease in a patient who has Sjogren’s syndrome.

Methods: A 44 year-old Indian woman presented with bilateral leg swelling. Past medical history included autoimmune hepatitis, in remission on prednisone 5 mg daily. Her blood pressure was 140/77 mm Hg, and the physical examination was unremarkable other than 2+ pitting edema in her lower extremities. She was found to have proteinuria (17.9 g/24hr). Serum Cr was 2.7 mg/dl with baseline Cr level of 0.8 mg/dl. Antinuclear

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
antibodies titers was > 1.640. Anti-SSA and SSB antibody were elevated, confirming the diagnosis of Sjogren’s disease. Complement studies showed normal C4 and decreased C3. Anti-dsDNA, ANA, hepatitis B/C were undetectable. Serum IgG level was high. Urinalysis revealed 3+ protein with no red or white blood cells. Renal biopsy showed extensive foot process effacement and dense interstitial plasma cell infiltrates. No immune complex mediated glomerular lesions are identified. Staining for IgG4 was positive in plasma cells. Tubuloreticular pattern with cytoplasmic IgG4-related TIN superimposed on minimal change disease. One hypothesis is that the proliferating plasma cells produce IgG4 that is auto-reactive against podocyte antigens. The mainstay of treatment is glucocorticoids, and nephrologists need to be aware of this entity that responds well to steroid therapy.

**SA-PO649**

Kaposi’s Sarcoma in a 78-Year-Old Female with Membranous Glomerulonephritis

Hanna Bartosik,1 Magdalena Krajewska,1 Agnieszka Halon,1 Krzysztof Letachowicz,1 Katarzyna Jakuszko,1 Katarzyna Madziarska,1 Wacław Weyde,1,2 Marian Klinger.1

Methods: A 78-year-old Caucasian HIV-negative female with the history of diabetes mellitus type 2 was admitted to Nephrology Department due to severe nephrotic syndrome (total protein level 41 g/l, albumin level 14 g/l) which had occurred 2 months earlier. The patient was treated with ACE inhibitors and diuretics. ANA, ANCA vaculities were excluded. Anti-PLA2R antibodies were negative twice. All performed diagnostic tests did not reveal possible cause of nephrotic syndrome. Kidney biopsy was performed showing membranous nephritis of mild expression (the first stage in histological classification). Due to severe course of the disease and acute kidney injury (creatinine level 4.1 mg/dl) intravenous steroids, diuretics together with albumin were introduced. ACE inhibitors were stopped after 1 week. Remission treatment was started. Due to deterioration of kidney function, and no remission of nephrotic syndrome cyco phosphorin was substituted with a low-dose of tacrolimus (2 mg per day blood level 4 ng/ml). After 2 weeks of treatment improvement was noticed. After next 2 weeks skin changes were found, mainly on the left lower limb. Biopsy was taken. The diagnosis was Kaposi’s sarcoma. A dose of tacrolimus was reduced to 1.5 mg per day and everolimus treatment was started 10 days later (0.75 mg per day).

After 3 weeks of the regimen regression of sarcoma is observed. Remission of nephrotic syndrome and mild renal function impairment (creatinine level 1.7 mg/dl) is still maintained.

Conclusions: There is still a question whether Kaposi’s sarcoma is connected with immunosuppressive treatment or membranous glomerulopathy is the first sign of the disease.

**SA-PO650**

Lupus Nephritis with a False Positive Antiglomerular Basement Membrane Antibody

Ekamol Tantisattamo,1 Satyanarayana Chekuri.2

Methods: A 33 year-old man with history of nephrotic range proteinuria for 5 years and new onset of scrotal swelling for 3 weeks. Physical exam showed marked inflamed scrotum consistent with cellulitis. His BP was 123/75 mmHg. He was found to have AKI with a serum creatinine (SCR) of 6.8 mg/dl. Baseline SCR was 2.1 mg/dl. 7 months earlier. He refused renal biopsy due to severe course of the disease and acute kidney injury (creatinine level 4.1 mg/dl) intravenous steroids, diuretics together with albumin were introduced. ACE inhibitors were stopped after 1 week. Remission treatment was started. Due to deterioration of kidney function, no remission of nephrotic syndrome cyclo phosphorin was substituted with a low-dose of tacrolimus (2 mg per day blood level 4 ng/ml). After 2 weeks of treatment improvement was noticed. After next 2 weeks skin changes were found, mainly on the left lower limb. Biopsy was taken. The diagnosis was Kaposi’s sarcoma. A dose of tacrolimus was reduced to 1.5 mg per day and everolimus treatment was started 10 days later (0.75 mg per day).

After 3 weeks of the regimen regression of sarcoma is observed. Remission of nephrotic syndrome and mild renal function impairment (creatinine level 1.7 mg/dl) is still maintained.

Conclusions: There is still a question whether Kaposi’s sarcoma is connected with immunosuppressive treatment or membranous glomerulopathy is the first sign of the disease.

**SA-PO651**

How to Interpret Repeat Renal Biopsies in Lupus Nephritis? Lessons from the Transplantation of a Donor Kidney with Lupus Nephritis

Michael McRae, Mathieu Rousseau-Gagnon, Isabelle Houde, Julie Riopel, David Philibert, Sacha A. De Serres. CHUQ - Hotel-Dieu de Quebec, Univ Laval.

Methods: We describe the histological evolution of a kidney from a donor with proliferative mesangial LN at the pre-implantation biopsy, transplanted to a recipient with chronic kidney disease due to vescico-ureteral reflux. This case provides an opportunity to assess the clearance of immune lesions over time in a kidney explanted from its lupus environment.

Results: The donor was a 50-year old male, with past medical history limited to high blood pressure. Urine sediment showed mild proteinuria, but no hematuria. At pre-transplant histology there was 4+ glomerulosclerosis, mild mesangial enlargement, and mild hypercellularity, tubular atrophy and interstitial fibrosis. Immunofluorescence (IF) revealed moderate to strong mesangial IgG, IgA, IgM, C1q and C3. Electron microscopy (EM) showed numerous mesangial immune complex deposits and a single tubulocapillary inclusion. The recipient was a 26-year-old man who received induction with daclizumab and maintenance therapy with prednisone, mycophenolate mofetil and tacrolimus. A for-cause Bi at 1 month posttransplant showed light microscopy findings similar to pre-implant Bi, and a slight attenuation of all IF stainings. A protocol Bi at 8 months showed stable mesangial expression, but persistent IgM, C3 and C1q staining. A for-cause Bi at 33 months displayed normal mesangium and completely negative IF. Nine years post transplant, the patient maintains a stable renal function.

Conclusions: This case suggests that the resolution of histological LN lesions is a slow process. Persistent lesions after 6 months of treatment may be seen without ongoing systemic immune injury. Caution is advised in the interpretation of early biopsies following initial therapy for LN.

**SA-PO652**

Risks of Therapy in Lupus Nephritis – 3 Cases of Central Serous Retinopathy

Raquel Vaz,1 Maria Francisca Barros,1 Ana Teresa Nunes,1 Inês Castro Ferreira,1 Ricardo Neto,1 Edite M. Pereira,2 Eva Borka Mariz,1 Isabel Tavares,1 Nephrology, CHSJ, Porto, Portugal;3 Internal Medicine, CHSJ, Porto, Portugal;4 Rheumatology, CHSJ, Porto, Portugal.

Background: Steroids are highly effective but associated with important morbidity. Central serous retinopathy (CSR), resulting from fluid accumulation behind neurosensory retina, is a rare but reversible condition described during treatment with steroids. We report 3 cases.

Methods: Case1: A 27-year-old female presented in May 2012 with lupus nephritis(LN) class IV and thrombotic microangiopathy(TMA), treated with 5 pulses of methylprednisolone(MP) followed by oral prednisolone(PDN) 1 mg/Kg/d, intravenous(IV) cyclophosphamide(CYC) and plasma exchange(PE). As no improvement was observed she was given rituximab. TMA eventually relapsed but she developed bilateral CSR. PDN was tapered to 7.5mg/day and mycophenolate mofetil(MMF) added. Eye lesions resolved and she maintained remission and haematological remission. Case2: A 32-year-old female developed LN class IV+V in 2010 treated with IV CYC and PDN 1mg/Kg/day. CYC was later switched to MMF, by then on PDN 20mg/day. 7 months later CSR was diagnosed. PDN was reduced to 2.5mg/day. Her eye symptoms improved but lupus disease exacerbated. Tacrolimus was added to MMF and PDN withdrawn. 1 year later she is in renal and extrarenal remission, with new eye lesions. Case3: A 46-year-old female was admitted in 2001 with LN class IV. She was treated with 3 pulses of MP followed by oral PDN(1mg/Kg/day) and IV CYC. In 2005 PDN dose was increased and azathioprine(AZA) initiated due to renal flare. In 2007 she had a new flare PDN was increased and AZA switched to MMF. She was kept on low-dose PDN and stopped MMF in 2012. In January 2013 she presented with a new flare. MMF was restarted and PDN dose increased(0.5mg/Kg/day). She developed CSR and PDN was reduced to 10mg/day. Eye lesions improved and she maintains renal remission.

Conclusions: Discontinuation or reduction of steroid dose is essential in approach CSR and differential diagnosis with inflammatory disorders or toxicity from other drugs is mandatory. CSR highlights the need for new and less toxic therapies for lupus, including steroid sparing strategies.

**SA-PO653**

Catastrophic Antiphospholipid Syndrome in a Small Child


Background: Catastrophic antiphospholipid syndrome (CAPS) is rare but associated with high mortality. We report a child with CAPS and multi-organ system failure with hepatic thrombotic microangiopathy (TMA) and markedly elevated antiphospholipid antibodies (aPL). Multimodal therapy including plasma exchange and Rituximab led to a full recovery.

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

Underline represents presenting author/disclosure.
Methods: A healthy 5 year old female presented with fever and gastrointestinal symptoms. Acute kidney injury, liver failure, and hemolytic anemia were revealed. Acute respiratory distress syndrome necessitated mechanical ventilation. Continuous renal replacement therapy was initiated for oliguric renal failure. Serratia marcescens bacteremia and metaphenovirus pneumonia were noted. Therapeutic plasma exchange was initiated for thrombocytopenia associated multi-organ failure. After 3 sessions, her clinical status improved. Liver biopsy noted microthrombs in the portal vein. aPL were markedly elevated. A diagnosis of CAPS prompted methylprednisolone pulse therapy. Proteinuria and an elevated Cystatin C led to a renal biopsy which showed acute tubular necrosis without TMA. She was started on enoxaparin prophylaxis and angiotensin blocker for hypertension and renoprotection. A cumulative dose of Rituximab 1.5g/m2 was given and aPL subsequently decreased.

Conclusions: The patient showed complete recovery from CAPS with early initiation of multimodal therapy with plasma exchange, corticosteroids, Rituximab, and anticoagulation. The kidney biopsy did not show evidence of TMA despite the acute renal failure. This may reflect recovery of kidney injury after treatment or sampling error. Pediatric CAPS is uncommon, but a high index of suspicion allows for prompt diagnosis and treatment.

SA-PO654
A Case of a 62-Year-Old Male with IgG4-Related Disease Complicated by Systemic Lupus Erythematosus Xiaohu Shi, Xuemei Li, Mingxi Lee, Xuewang Lee. Dept of Nephrology, Peking Union Medical College Hospital, Beijing, China.

Background: IgG4 related Disease(IgG4-RD) was considered as an autoimmune disease which complicated by Autoimmune Pancreatitis, Mikulicz’s disease. But it rarely involved SLE. We report a case of IgG4-RD complicated by SLE in a patient with chronic glomerulonephritis and progressive renal failure.

Methods: 62 y/o Asian male with a history of intermittent fever, hyperglobulinemia and increased Scr(0.78 to 4.24mg/dL) for 2yrs without any effect by kinds of antibiotics. On admission, Scr kept increasing(3.88 to 5.52mg/dL) in 2ws. PE revealed mild edema and generalized lymphadenopathy. Lab work revealed: globulin 70g/L while albumin 38g/L, dsDNA to negative. In 7Ms follow-up, Prednisone gradually reduced to a dose of 50mg/d prednisone and 100mg CTX. SCr was improved to 1.6mg/dL, IgG4 to 1224mg/dL. Conclusions: Our patient showed complete recovery from CAPS with early initiation of multimodal therapy. There were few cases described in the literature of HIVAN in association with ITG, half of which were associated with viral hepatitis. We report the 4th case of HIVAN and ITG with negative viral serology leading us to question whether ITG could be triggered by factors related to HIV. To our knowledge, this is the first case describing the clinical presentation and kidney biopsy evidence of HIVAN, DILS, and ITG. Our case demonstrates the importance of renal biopsy for HIV infected individuals presenting with AKI.

SA-PO655
Atypical IgA Nephropathy with Membranous Features in a Patient with HIV Sarah E. Panzer, Shalini Tayal, Jessica B. Kendrick. Univ of Colorado Denver; Denver Health Medical Center.

Background: IgA nephropathy can exhibit a broad degree of plasticity in the clinical presentation, pathologic manifestations, and disease progression. The defining histologic lesion in IgA nephropathy is mesangial deposition of IgA; however, the findings on light microscopy can be quite variable. In this case report we describe an unusual histologic finding of a severe form of IgA nephropathy with membranous features in a patient with HIV.

Methods: A 63 year-old Caucasian male with HIV and new-onset hypertension was referred to the renal clinic for evaluation of nephrotic range proteinuria in a patient with HIV infection, whose kidney injury (AKI) with nephrotic range proteinuria in a patient with HIV infection, whose biopsy showed diffuse infiltrative lymphocytosis syndrome (DILS) and immunotactoid glomerulopathy (ITG) in addition to HIVAN.

Conclusions: Our case represents an atypical form of IgA nephropathy presenting with diffuse global thickening of the glomerular basement membrane and a ‘spike and dome’ pattern identified on methenamine silver stain (Figure 1A and 1B).

SA-PO656
Immunofluorescent staining showed strong IgA deposition in the glomerular basement membrane and mesangium (Figure 1C). Electron microscopy demonstrated numerous mesangial, intramembranous, and subepithelial electron dense immune-complex deposits with intervening membrane spikes between subepithelial deposits (Figure 1D). The patient was initially managed with angiotensin converting enzyme inhibitor therapy. However, renal insufficiency developed and the degree of proteinuria remained in the nephrotic range. Thus, the patient was treated with a six month course of alternating cyclophosphamide and prednisone and had a partial response to treatment.

Conclusions: Our case represents an atypical form of IgA nephropathy presenting with a mesangial pattern histologically. Data regarding this form of IgA nephropathy is scarce and it is unclear whether the presence of histologic features of membranous incurs a worse prognosis. To our knowledge this is the first reported case of this constellation of histologic findings in a patient with HIV.

Funding: NIDDK Support

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

778A
SA-PO657
Idiopathic Hypocomplementemteme Immune Complex -Mediated Tubulointerstitial Nephritis: An Unattended Differential Diagnosis for Sub-Acute Renal Insufficiency in Elderly Patients 
Fahima Nasreen,1 Ana Paula Rossi,1 Douglas M. Dressel,2 James C. Wasserman. 1Nephrology, Maine Medical Center, Portland, ME; 2Pathology, Maine Medical Center, Portland, ME.

Background: Immune complex (IC) deposits in renal tubular basement membrane (TBM) are commonly encountered with glomerular diseases. However, tubulointerstitial (TI) IC deposit occurs without significant glomerular pathology. TBM are commonly encountered with glomerular diseases and ANCA. LM showed 49% globally sclerosed glomeruli with extensive tubular atrophy. Diffuse interstitial infiltrate with reactive lymphoid cells and interstitial fibrosis. IF exposed granular deposits of IgG, C3, C1q, and kappa and lambda light chains in the interstitium and TBM. The patient was started on prednisone 1mg/kg/d with excellent response. Clinical improvement was associated with improved renal function, which has been stable for 2 years post-diagnosis (SCr 1.1 mg/dl, spot UPCR 0.1g/g).

Conclusions: IC-mediated TI nephritis is a relatively new and rare entity with clinical features that may include sinustitis, anorexia, weight loss, and renal insufficiency. TI IC deposition and interstitial plasma cell infiltrates appear to be involved in local IC formation. Idiopathic IC mediated TI nephritis may occur in elderly patients presenting with acute or sub-acute kidney injury and, therefore, should be considered in the differential diagnosis of elderly patients presenting with renal insufficiency.

SA-PO658
Idiopathic Granulomatous Interstitial Nephritis Responding to Mycophenolate Mofetil Therapy 
Nanat Leeaphorn, Patompong Ungprasert, William W. LeCates. Internal Medicine, Bassett Medical Center, Cooperstown, NY.

Background: Granulomatous interstitial nephritis (GIN) is a rare histologic disease. Many etiologies have been reported such as sarcoidosis, drugs, and infections. Idiopathic GIN is diagnosed by exclusion. GIN generally responds well to steroids, but there is limited data with therapy other than corticosteroids.

Methods: A 68-year-old Caucasian man presented with fever. He was found to have acute renal failure (SCR of 3.7mg/dl normal 4 months earlier) with bland urine sediment. Renal biopsy showed granulomas consistent with GIN. Oral methylprednisolone was initiated with good response, SCR 1.9mg/dl. However, he developed hyperglycemia from exposure to prednisone. The patient was then started on mycophenolate mofetil and prednisone, and additional imaging was not performed. After two months of prednisone therapy, the patient’s proteinuria began to worsen (UPC 1.64). Cyclosporine and mycophenolate mofetil were added, and triple immunosuppressive therapy was continued for an additional three months with improvement in proteinuria (UPC 0.15). Six months after her diagnosis of nephrotic syndrome, the patient developed lower back pain. Computed tomography revealed large masses located in her liver, skeleton, and lung. Biopsy showed a high-grade pleomorphic sarcoma consistent with metastatic leiomyosarcoma. Immunosuppressive were held, and chemotherapy with gemcitabine and docetaxel was initiated. A decrease and stabilization of tumor burden was observed. Nine months after the initiation of chemotherapy, the patient continues to demonstrate stable tumor burden and a complete remission of the nephrotic syndrome.

Conclusions: Leiomysarcoma may lead to MCD and the nephrotic syndrome. Reduction in tumor burden achieved via targeted chemotherapeutic agents may result in a complete and sustained remission of MCD associated with leiomyosarcoma.

SA-PO660
Granulomatous Interstitial Nephritis: A Potential Precursor to Paucl-Imune Small Vessel Vasculitis 
Liliana F. Rios Rojas,1 Vladimir Liberman,1 Ingrid Calliste,2 James Drakakis,2 Joseph Mattana,2 Nobuyuki (Bill) Miyawaki.2 1Internal Medicine, Winthrop Univ Hospital, Mineola, NY; 2Internal Medicine, Div of Nephrology, Winthrop Univ Hospital, Mineola, NY.

Background: Granulomatous interstitial nephritis (GIN) is a rare entity with a poor outcome. Little is known about the etiology, nor whether it may be a precursor to other renal pathologies. We present a case of GIN in which a repeat kidney biopsy revealed a pauci-immune small vessel vasculitis.

Case: A 57 year old woman with malaise and fever, without infection, was admitted with acute kidney failure (SCr of 3.7mg/dl normal 4 months earlier) with bland urine sediment. Renal biopsy showed granulomas consistent with GIN. Oral methylprednisolone was initiated with good response, SCR 1.9mg/dl. However, he developed hyperglycemia from exposure to prednisone. The patient was then started on mycophenolate mofetil and prednisone, and additional imaging was not performed. After two months of prednisone therapy, the patient’s proteinuria began to worsen (UPC 1.64). Cyclosporine and mycophenolate mofetil were added, and triple immunosuppressive therapy was continued for an additional three months with improvement in proteinuria (UPC 0.15). Six months after her diagnosis of nephrotic syndrome, the patient developed lower back pain. Computed tomography revealed large masses located in her liver, skeleton, and lung. Biopsy showed a high-grade pleomorphic sarcoma consistent with metastatic leiomyosarcoma. Immunosuppressive were held, and chemotherapy with gemcitabine and docetaxel was initiated. A decrease and stabilization of tumor burden was observed. Nine months after the initiation of chemotherapy, the patient continues to demonstrate stable tumor burden and a complete remission of the nephrotic syndrome.

Conclusions: GIN is a poorly understood, rare entity associated with a poor outcome despite steroid treatment. This case suggests the possibility that some instances GIN may be a precursor to the development of pauci-immune small vessel vasculitis, hence treatment failure or a rising SCr after an initial favorable response to steroids might be an indication for re-biopsy. The possibility of missing or developing pauci-immune small vessel vasculitis may explain, in part, the poor overall outcome of GIN with steroid treatment.
Methods: The patient is a 48 yr old man with a history of HIV for 10 yrs compliant with antiretroviral therapy at Atripla and Kaposi’s Sarcoma initially referred to renal clinic for a rise in proteinuria, hematuria, and weight gain. On admission, he was found to be hypertensive and 40 pounds above his baseline weight with peripheral edema and anasarca. Lab data was notable for a Creatinine of 1.97mg/dl from a normal baseline, 10.2g of protein on 24 hour urine collection, Albumin of 2.0, CD4 count 321 and viral load of 55. Urine sediment showed hemosiderin laden renal tubular epithelial cells and occasional lipid droplets in casts. He was admitted to the hospital for emergent renal biopsy illustrating ischemic ATN in addition to a podocytopathy most consistent with Minimal Change Disease with subclinical IgA deposition. Tenoflovir was held. His Creatinine continued to rise, peaking at 7.2 at which time he received IV pulse dose steroids before continuing oral Prednisone 60mg daily. Over three weeks, his Creatinine and proteinuria fell to 1.8 and 918mgm respectively. While his proteinuria continued to decline with the lowest microalbumin to creatinine ratio of 151 mg/mg, he noted cutaneous lesions consistent with prior relapses of Kaposis’s in addition to thoracic and abdominal compression. Therapy with liposomal Daunorubicin was initiated with good initial response. After 6 weeks, his Prednisone dose was tapered over four weeks to 10mg daily. Despite the rapid taper, weekly microalbumin to creatinine ratios remained relatively between 151 to 361.

Conclusions: Treatment of Minimal Change Disease is not infrequently complicated by adverse complications of high dose steroid therapy including hyperlipidemia and glucose intolerance. We present a case of a patient with a history of HIV on antiretroviral therapy and Kaposi’s sarcoma in remission whose treatment was complicated by recurrence of Kaposi’s sarcoma prompting a rapid taper of his oral Prednisone in addition to chemotherapy with liposomal Daunorubicin.

SA-PO662 Primary Sjogren Syndrome with Minimal Change Disease Xiaoxiao Shi,1 Zhou Zhang,1,2 Yubing Wen,1 Hang Li1, Xuemei Li,1 Xuewang Lee,1 Limeng Chen.1 1Nephrology, Chinese Academy of Medical Sciences & Peking Union Medical College Hospital, Beijing, China; 2No.4 Dept of Internal Medicine, Guizhou Hospital, Foshan City, China.

Background: Glomerular involvement in primary Sjogren Syndrome (pSS), especially minimal change disease (MCD), has rarely been reported. We report four cases of pSS with MCD.

Methods: Four cases of MCD confirmed by renal biopsy in pSS patients were enrolled as pSS-MCD group. Ten pSS patients with membranoproliferative glomerulonephritis (MPN) of the same period were enrolled as control group (pSS-MPN group). Medical records were summarized and compared.

Results: The four pSS-MCD patients were mainly middle-aged females (37-61y; male: female=3:1). They were diagnosed as pSS by dry mouth, dry eyes, positive anti-SSA, anti-SSB antibodies, and labial gland biopsy. They all clinically presented as nephrotic syndrome, with severe proteinuria (3.0-19.02g/d) and remarkable hypoalbuminemia (12-19g/L). They also showed mild microscopic hematuria and leukocyturia but normal blood pressure. Only one female, who had the most severe proteinuria (19.02g/24h), showed renal function impairment (Scr 200µmol/L). None of them showed renal tubular acidosis.

Compared with pSS-MPN group, pSS-MCD patients had more severe hypoalbuminemia (15.0g/L vs. 26.5g/L; P=0.009), but no significant differences were shown in other clinical characteristics. In renal biopsy, they all showed typical glomerular lesions of MCD and focal distribution of tubulo-interstitial injury, which presented as thickened TBUM, tubular atrophy, mild interstitial fibrosis and interstitial infiltration of mononuclear inflammatory cells. Besides the injuries of kidney and exocrine glands, the two cases with hypokalemia (3.0 and 3.2mmol/L) also showed hematomatologically involved with decreased white blood cell count of 3.32×10^9/L and 3.36×10^9/L. Steroid (1mg/kg/d) was given to all patients and great improvement of proteinuria was observed.

Conclusions: We report the 4 cases of pSS with MCD with typical nephrotic syndrome, severe hypoalbuminemia and good response to steroid.

Funding: Government Support - Non-U.S.

SA-PO665 C3 Glomerulopathy in a Young African American Adult Julio C. Chirinos, Devasmita Choudhury. Nephrology, UT Southwestern Medical Center, Dallas, TX.

Background: Membranoproliferative Glomerulonephritis (MPGN) is a pattern of glomerular injury recognized easily by light microscopy. Electron microscopy allows sub grouping in MPGN types I, II and III by localizing the area in which the electron dense deposits, and immunofluorescence detects immunoglobulin in MPGN type I and III, but not in type II. All 3 forms stain positive for C3. This sub grouping led to confusion, because of the presence of immunoglobulin negative MPGN I and III. These entities along with Type II MPGN are now under the subgroup of C3 glomerulopathy (C3G).

Methods: 35 year old man with PMHx of HTN diagnosed 3 years ago, on amiodipine only, referred by PCP for hyperkalemia and worsening renal function. Patient had no complaints at all, just that the last 1-2 months has been feeling more tired than normal but was because he has been exercising more for intentional weight loss. Reports he makes normal amounts of urine, but foamy for the last few months. PE: BP: 180/91 HR: 81; No distress. S1S2 normal. Labs: BMP: K 6 ; CO2; 19 mmol/L; Cr 59/4.42 (last Scr 1.4 in 2011); Hb 10. UA: No RBCs, no WBCs, P/C: 5 grams. Renal US: Bilateral hydronephrosis. CT: 3C ++ no Ig. EM: Effacement of visceral epithelial cell foot processes. Multiple mesangial proliferation.

Conclusions: This case give us the example of why a new classification for MPGN was needed.
on Immunoabsorption (IA). To prevent new AAB development we started a medication found. Eculizumab was stopped after 10 doses. 3 months after diagnosis the child was set
Consistent with dysregulation of C3 convertase an autoantibody against this protein was
low levels of C3 (0,08g/l min-0,8gl max) and an increase of SC5b-9 of 936 (<320) ng/ml.
the chronic antigenemia. The focus in C3G in contrast should focus on the dysrregulation
different. In types I and III therapy is focused in underlying disease triggering and driving
MPGN II. Additional
- 80% of patients have autoantibodies (AAB) as complement activating agent.
plasma creatinine levels (from 7,26mg/dl to 1,80mg/dl) markedly decreased and diuresis
remained impaired though plasma C3 levels increased. With the beginning of Eculizumab
preserve renal function and to control proteinuria. So far it remains open, if monitoring of
however it might be challenging to identify the individual dose and frequency of IA to
diagnosed with polymyositis, started on treatment with corticosteroids and subsequently
SA-PO667
Retinal Cotton Wool Spots and Renal Impairment Associated with Interferon Beta 1 Alpha Therapy for Multiple Sclerosis Eleni Chelioti,1 Evangelia Gkaitsiou,1 Evdokia Efthimiou,1 Maria Sotiraki,1 Spyridon Fradelos,2 Alexia Papaalexandrou,1 Maria Tsilivigou,1 Gabriel Papadakis,1 1Dept of Nephrology, General Hospital of Piraeus, Greece; 2Dept of Ophthalmology, General Hospital of Piraeus, Greece.
Background: Interferon is now the mainstream of maintenance therapy for multiple sclerosis (MS). Retinopathy is a well-known adverse effect of interferon-alpha in patients treated for hepatitis C. On the other hand, retinal lesions are rarely related with subcutaneous interferon beta 1 alpha (IFNβ1a) in MS. IFNβ1a nephrotoxicity is also an extremely rare side effect. We report a case of IFN-associated retinopathy and nephropathy in a patient with MS receiving subcutaneous INFβ1a.
Methods: A 42-years old female with a history of MS was on treatment with IFNβ1a (44μg/3times a week) for 10 years. She presented with anaemia, thrombocytopenia, albuminuria, mild elevation of liver enzymes and renal impairment. She displayed sudden hypertension without visual disorders. Ocular fundus exam showed several retinal cotton wool spots indicating IFN-retinopathy and interron was discontinued. Subsequent imaging exploration revealed normal sized kidneys. Further biochemical and immunological analyses were negative for autoimmune renal diseases. The retinopathy disappeared without specific therapy 2 months after discontinuing IFNβ1a and kidney function reached normal levels. IFNβ1a resumed 16 weeks after stopping treatment due to MS relapse. On an iterative fundus exam 3 months after resumption of IFNβ1a, no further cotton wool spots have recurred.
Conclusions: Our case supports that both complications resolved after drug cessation and the diagnosis of IFNβ1a retinopathy and nephropathy was retained due to the lack of any other etiology. There are only eight reports on MS related interferon-β retinopathy. Likewise there is only one case of IFNβ1a associated retinopathy and nephropathy. To our knowledge this represents the second case of IFNβ1a associated cotton wool spots and renal impairment and the first in the English-language ophthalmic literature. Given this limited number of cases no safe conclusions regarding causality, screening, dose related issues, severity and treatment options can be made.

SA-PO668
The Transplant Triumphs – Rapid Reversal of Nephrotic Range Proteinuria of Native Kidney Origin after Live Donor Kidney Transplant Dhananjay P. Kulkarni, Ismail M. Qattash. Internal Medicine/Nephrology, The Univ of Illinois at Urbana- Champaign, Urbana, IL.
Background: Proteinuria after renal transplantation increases both risk for graft failure and risk for death. In this case report we describe a finding of reversal of nephrotic range proteinuria after renal transplantation.
Methods: A 62 y/o Caucasian female with uncontrolled diabetes mellitus type 2, severe hypertension, coronary artery disease status post bypass grafting was referred to our clinic for abnormal renal function and proteinuria. Chronic kidney disease stage IV (GFR 16 ML/ MIN/1.73 M-2) with nephrotic range proteinuria and high urinary protein-creatinine ratio was noted. Patient had findings consistent with diabetic process including ophthalmopathy and nephropathy. She continued to have heavy proteinuria and had a hospital visit for severe nausea and vomiting. Creatinine peaked at 3.4 and urea was 66. She was started on hemodialysis and her symptoms resolved. After 3 months patient underwent a living donor kidney transplant donor was her son with native kidneys in situ. Patient was on immunosuppressant therapy with mycophenolic acid and tacrolimus. TMP/SMX and valganciclovir were also administered. After 1 month post-transplant her creatinine return to normal and a complete resolution of proteinuria in 3.5 weeks from transplant. On follow-up at 2 years, patient remained free of any proteinuria and had normal renal function parameters.

Conclusions: Our case supports that both complications resolved after drug cessation and the diagnosis of IFNβ1a retinopathy and nephropathy was retained due to the lack of any other etiology. There are only eight reports on MS related interferon-β retinopathy. Likewise there is only one case of IFNβ1a associated retinopathy and nephropathy. To our knowledge this represents the second case of IFNβ1a associated cotton wool spots and renal impairment and the first in the English-language ophthalmic literature. Given this limited number of cases no safe conclusions regarding causality, screening, dose related issues, severity and treatment options can be made.

SA-PO669
Scleroderma Renal Crisis as an Initial Presentation of Systemic Sclerosis in a Patient with Underlying Polymyositis Yuara R. Cheema, Cybele Ghosssein. Nephrology, Northwestern Univ; Feinberg School of Medicine, Chicago, IL.
Background: Systemic sclerosis (SSc) is a relatively rare connective tissue disease affecting 200 to 1 million adults. About 20% of patients with systemic sclerosis also have clinical or serologic evidence of another connective tissue disease. Of those with an overlap syndrome, 40% have evidence of both SSc and inflammatory myositis. Typically, patients with SSc/polymyositis overlap syndrome present first with signs of SSC and are diagnosed with polymyositis later in the course. Here we present the case of a patient initially diagnosed with polymyositis, started on treatment with corticosteroids and subsequently presenting with scleroderma renal crisis as the only manifestation of systemic sclerosis.
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Renal biopsy demonstrated vascular changes and focal thrombotic microangiopathy consistent with scleroderma renal crisis. Patient was started on escalating doses of captopril, amiodarone and aliskiren for BP control. CR initially stabilized at 4.5 mg/dL but renal functions continued to worsen over ensuing 4 months, ultimately requiring initiation of hemodialysis.

Conclusions: In patients with an underlying connective tissue disease, the development of renal dysfunction particularly following initiation of corticosteroid therapy should raise suspicion for possible overlap syndrome and scleroderma renal crisis.

SA-PO670

Unusual Systemic Manifestations of Levamisole Induced Cocaine Vasculitis: Rapidly Progressive Glomerulonephritis

Rona S. Smith,1 Ryan Jesseck,2 Annel Kumar,1 Laura D. Carbone,1 Lekha K. George,1 1Univ of Tennessee Health Science Center, Memphis, TN; 2Duke Univ, Durham, NC.

Background: Levamisole exposure with tainted cocaine causes cutaneous vasculitis that has distinct lab and clinical features distinguishing it from classical ANCA associated vasculitis. We report an unusual sequela of this syndrome – Rapidly Progressive Glomerulonephritis (RPGN) and discuss the potential role of Rituximab in its management in a patient with a history of chronic cocaine use who developed vasculitides manifestations of midline facial lesions, neutropenia, skin lesions, and pulmonary and renal manifestations.

Methods: A 30 year old female, with long history of intranasal cocaine use, presented with worsening skin ulcers. Physical examination showed violaceous, eschar-like skin lesions in various stages of healing on her hands, knees, and thighs along with upper airway midline lesions. Lab findings on admission showed an increase in serum creatinine from 0.8 (baseline) to 5.4 mg/dL, leukopenia (WBC count 2,200/μL), positive C-ANCA (13.4 U/mL) and positive P-ANCA (15.9 U/mL). Urinalysis showed gross hematuria, and proteinuria (150 mg/dL). Antineutrophil elastase, specific for levamisole associated cocaine vasculitis, was also positive.

Results: CT scan showed paranasal sinus disease, septal defects, and a noncalcified nodule of the lung. Renal biopsy showed focal necrotizing and crescentic glomerulonephritis consistent with pauci-immune ANCA vasculitis. The patient was treated with total of 3 gm (1 mg/kg/day) of methylprednisolone. Due to fertility concerns, cytopenia, relapsing nature of disease with systemic manifestation, rituximab 375 mg/m² was also given. This resulted in disappearance of skin lesions, lung nodule, and improvement in serum creatinine to 1.6 mg/dL and WBC count to 4,200/mm³.

Conclusions: This case of levamisole-induced vasculitis with palpable purpura, leucopenia, and positive ANCA and antineutrophil elastase along with RPGN, responded well with a regimen of high dose steroids and Rituximab. This response suggests a potential role of Rituximab in the management of such vasculitides with renal involvement.

SA-PO671

Renal Amyloidosis in Skin Poppers – Revisited

Vasili Peey,1 Ruchir R. Chokshi,2 Mario Carlos Ponce,1 David B. Thomas,3 Jair Munoz Mendoza,1 1Div of Nephrology and Hypertension, Univ of Miami; 2Dept of Medicine, Univ of Miami; 3Div of Pathology, Univ of Miami, Miami, FL.

Background: Renal amyloidosis secondary to long-term subcutaneous (SC) drug use (“skin popping”) originally described in African American population in New York in the 1980s, is nowadays rarely diagnosed despite the growing number of intravenous drug users. Methods: A 47 year-old Caucasian male with history of hepatitis C, recurrent skin abscesses due to drug use, and diabetes, was referred for deep-seated renal mass. Immunohistochemistry of the biopsy showed diffuse staining for lambda immunoglobulins.

Conclusions: In this case, we believe that this is the first description of renal amyloidosis secondary to cocaine in an intravenous drug user in the USA, as our patient has only used intravenous cocaine. Furthermore, this case underlines the importance of routine skin checks in patients on chronic skin poppers to prevent skin complications.

SA-PO672

Resolution of Syphilis Induced Rapidly Progressive Crescentic Glomerulonephritis (RPGN) with Penicillin Therapy

Deepak K. Nandikanti,1 Rona S. Smith,1 Annel Kumar,1 Barry M. Wall,1 Lekha K. George,1 1Univ of Tennessee Health Science Center, Memphis, TN; 2VAMC, Memphis, TN.

Background: Renal manifestations of Syphilis are variable, with membranous nephropathy being the most commonly described lesion. We describe a patient with RPGN secondary to latent Syphilis, which resolved after Penicillin (PCN) treatment in the absence of immunosuppressive therapy.

Methods: A 28-year old black male with a history of HIV never on HAART therapy presented with one week of nausea, vomiting and abdominal pain. He was treated for STDs in past but never diagnosed or treated for Syphilis. He was afebrile and normotensive. Physical examination was normal. Serum Creatinine (SCr) was 7.2 mg/dL (1.1 mg/dL one prior). Urinalysis: 3+ protein, WBC 15-20/HPF, many RBCs, and RBC casts. Spot urine protein to creatinine ratio (UPC) was 4.0. CD4 count was 412 with undetectable HIV viral load. Serologies for ANA, ANCA, anti-ASO, hepatitis B and C, and anti GBM, C3, C4 were negative or normal. RPR was positive with titer of 1:32. Treponema pallidum particle agglutination assay was reactive, confirming Syphilis diagnosis. CSF was negative for neumophathies. Ultrasound showed normal sized kidneys. Kidney biopsy LM showed focal and segmental necrotizing lesions and crescents. IF showed mesangial granular staining for C3 (3+) and IgM (1+). EM showed effacement of foot process without deposits. He received weekly Benazathine PCN for 3 wk. RPR titers decreased to 1:4. SCR rapidly improved with the first dose of PCN. UPC improved to 2.0 after 3 weekly doses of PCN. His SCR was 1.1 mg/dL and RPR titers 1:4 at 3 months follow up. These dramatic improvements in renal function occurred in the absence of any immunosuppressive therapy.

Conclusions: RPGN with crescents typically leads to ESRD in the absence of effective treatment, which usually includes immunosuppressive therapy. Our patient had dramatic renal recovery with PCN treatment, a finding which to our knowledge has not been previously reported. We strongly recommend that Syphilis be considered in the differential diagnosis of all patients with proteinuria or suspected glomerulonephritis, particularly in high risk populations.

SA-PO673

A Case of Fibronectin Glomerulopathy with Rapidly Progressive, Severe Nephrotic Syndrome Leading to End-Stage Renal Disease

Kise Ishimoto,1 Eisei Sohara,1 Eisaku Ito,1 Motoko Chiga,1 Soichiro Imoro,1 Tomikazu Okado,1 Tatsumitsu Rai,1 Shinichi Uchida,1 Sei Sasaki,1 1Dept of Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan; 2Dept of Pathology, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Fibronectin glomerulopathy occurs between the second and fifth decades of life in most patients, and it is known to be slowly progressive with mild proteinuria leading to kidney failure. The case of a 78-year-old woman with a rapid course of nephrotic syndrome due to fibronectin glomerulopathy is reported.

Methods: She had proteinuria that rapidly increased to 6.8 g/day in a month and microscopic hematuria. A renal biopsy specimen showed lobular glomerulopathy and membranoproliferative glomerulonephritis-like lesions on light microscopy. There was scanty staining for immunoglobulins and complement. Electron microscopy revealed granular deposits with fibril formation, which is 12-16 nm in diameter and typically arranged in an irregular fashion, indicating fibronectin glomerulopathy. Immunohistochemistry of the fibronectin showed intense staining in the mesangium and peripheral loop. Therefore, the case was diagnosed as fibronectin glomerulopathy. The kidney function was rapidly decreased, necessitating hemodialysis two months after renal biopsy.

Conclusions: To the best of our knowledge, such a rapid clinical course of nephrotic syndrome has not been previously reported in fibronectin glomerulopathy. In addition, this case is interesting because proteinuria occurred at 78 years of age, the oldest onset of fibronectin glomerulopathy reported to date. Taken together, it is important to consider fibronectin glomerulopathy in the differential diagnosis of nephrotic syndrome in older people.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
SA-PO674

**Ipilimumab-Induced Immune-Related Nephritis**

**Thuy-Trang T. Ngo, 1 Charles K. Minn, 1 Maen Abdelrahim, 2 Ala Abudayyeh, 3 Nephrology, The Univ of Texas Medical School at Houston; 2Nephrology, The Univ of Texas Medical School at Houston; 1Internal Medicine, Baylor College of Medicine; 2General Internal Medicine, Section of Nephrology, Univ of Texas-MD Anderson Cancer Center, Houston, TX.**

**Background:** Ipilimumab, a fully human monoclonal IgG1 antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) expressed on the surface of activated T cells and monocytes, offers a new therapeutic option in the treatment of metastatic melanoma. By inhibiting CTLA-4, ipilimumab increases anti-tumor immune response. Since CTLA-4 plays a major role in regulating immune tolerance to self-antigens, its blockade can result in autoimmune destruction of tissues by enhancing T-cell response in peripheral organs. Common immune-related side effects such as dermatitis, enterocolitis, hepatitis, and endocrinopathies are widely documented. However, renal involvement has rarely been described with only one case of ipilimumab-induced acute renal failure reported in the literature to date.

**Methods:** A 62 year old male presented with a history of uveal melanoma which progressed to metastatic disease was treated with ipilimumab (10mg/kg) which resulted in immune mediated nephritis in the presence of peripheral eosinophilia, enlarged kidneys, rash, colitis, autoimmune transverse myelitis, and uveitis.

**Conclusions:** Immune-related adverse effects from ipilimumab are generally dose dependent and typically occur between 3 to 12 weeks after drug administration. At the current approved ipilimumab regimen of 3 mg/kg every 3 weeks for four doses, immune-related adverse events occur in approximately 60% of patients. High-dose steroid therapy has been shown to effectively control side effects associated with ipilimumab immune stimulation. Greater awareness of this rare autoimmune nephritis may facilitate early recognition and prompt administration of corticosteroids.

SA-PO675

**Primary Myelofibrosis Causes Glomerulopathy**

**Thuy-Trang T. Ngo, 1 Manjunath Kottalgi, 1 William F. Glass, 1 Ala Abudayyeh, 2 Nephrology, The Univ of Texas Medical School at Houston; 2Pathology, The Univ of Texas Medical School at Houston; 3Section of Nephrology, The Univ of Texas- MD Anderson Cancer Center.**

**Background:** Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders in which proliferation of one or more of the myeloid lineages occur resulting in fibrosis of the bone marrow. Renal involvement by MPN is infrequent. Glomerular abnormalities in primary myelofibrosis (PMF) patients have rarely been described.

**Methods:** A 66 year-old Caucasian male recently diagnosed with primary myelofibrosis (PMF) (on JAK-2 inhibitor) presented with increased leg swelling, poorly controlled hypertension,23 grams of proteinuria, and worsening serum creatinine. Renal pathology revealed diffuse mesangial matrix expansion and mild mesangial hypercellularity, effaced podocyte foot processes, and glomerular intracapillary megakaryocytes without immune deposits on immunofluorescence. These findings are consistent with myeloproliferative neoplasm-related glomerulopathy.

SA-PO676

**Puci-Immune Crescentic Glomerulonephritis Associated with Oropharyngeal Cancer**

**Amaka Edeani, Derek M. Fine. Div of Nephrology, Johns Hopkins School of Medicine, Baltimore, MD.**

**Background:** Glomerulopathies of many forms have been described in association with solid and hematological neoplasms, most common is the association of membranous glomerulopathy with solid tumors. We report a case of ANCA-negative crescentic glomerulonephritis (GN) in a patient with oropharyngeal cancer.

**Methods:** A 52 year old male with tonsillar squamous cell carcinoma, diagnosed in 2011, treated to remission with tonsillectomy, radiation therapy and cisplatin. In January of 2012, he was diagnosed with a likely new squamous cell carcinoma of the right lateral tongue. He underwent resection and restarted a course of cisplatin and radiation therapy, completed in November 2012. He was admitted in December 2012 with gross hematuria and a serum creatinine of 1.7mg/dL, attributed at the time to cisplatin-induced nephrotoxicity. Hematuria spontaneously resolved and he was discharged with a creatinine of 1.9mg/dL. Three weeks later, he presented with recurrent hematuria, with creatinine now 4.5mg/dL and 24h proteinuria of 5.24 gram. Serologic workup revealed negative anti-GBM, p-ANCA, c-ANCA, anti-streptolysin O, anti-myoeloperoxidase antibodies and Hepatitis serologies. Urine and serum electrophoreses were negative. Renal biopsy revealed necrotizing crescentic glomerulonephritis with cellular crescents and acute tubular necrosis, with no immune complex deposits. Diagnosed with an ANCA-negative pauci-immune GN, he received pulses of steroids; however, renal failure worsened (creatinine up to 5mg/dL) and in addition to ongoing oral steroids, cyclophosphamide 75mg once daily was initiated with rapid improvement in renal function, with creatinine down to 3.3mg/dL by day of discharge 3 days later and 1.5mg/dL 4 weeks later.

**Conclusions:** Biava et al in 1984 described a case series of patients suggesting an increased incidence of solid tumors in those with pauci-immune crescentic glomerulonephritis. Subsequent observations have demonstrated these to be ANCA-associated. Associated tumors include prostate, lung, gastric and bladder cancer, and some hematologic malignancies. We describe here an immunopositive case of ANCA negative disease which has responded well to cyclophosphamide based therapy.

SA-PO677

**Single Center Experience with ACTH for the Treatment of Resistant Nephrotic Syndrome**

**Arafat Y. Melhem, Paul G. Schmitz. St. Louis Univ, St. Louis, MO.**

**Background:** ACTH injection was approved by the FDA in 1952 for the treatment of the nephrotic syndrome (NS). Its use was largely abandoned with the development of oral corticosteroids. However, 2 recent case series in patients with NS revealed that ACTH induced a remission in >50%. In this report we examined our experience with ACTH for resistant NS.

**Methods:** We retrospectively examined 5 cases of resistant NS between 2011-2013 that received salvage therapy with ACTH. The age ranged between 23-59 years and the histology revealed: MCD (n=1), MN (n=1), or FSGS (n=3). The subjects had been receiving multiple immunosuppressive agents (IS) at the time of initiation (mean ± 3.3 IS). The duration of NS in our subjects was 4-16 years. The duration of ACTH administration was 7.4 ± 3 months. Complete remission (CR) was defined as stabilization of the serum Cr. coupled with a protein excretion of <0.5 g/24h. A partial remission (PR) was defined as a protein excretion between 0.5-3.5 g/24h. ACTE/ARBS and diuretics were employed in all patients.

**Results:** 2 of the 5 patients achieved CR and one exhibited a PR (but met the definition of a CR 2 months after stopping ACTH). The average follow-up was 11.8 months with a range of 7-16 months. Importantly, 2 patients with CR were disease free 6 months after

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

Underline represents presenting author/disclosure.

783A
discontinuing ACTH treatment. Proteinuria decreased from an average of 6.2g/24h to 3.4g/24h. In addition, the eGFR increased from a mean of 63.8 mL/min to 71.4 mL/min. Most patients experienced skin pigmentation, weight gain, worsening diabetes and cushinoid features. This patient remained on therapy, since she had failed 6 IS. While on therapy her Cr. decreased from 6.3 to 3.5 mg/dl and proteinuria declined from 6.7g/24h to 3.5g/24h. Another patient experienced gastroesophageal reflux, which was controllable with conservative medical therapy. No other adverse events were reported.

Conclusions: In our center, we observed remarkable improvement in several patients who were highly resistant to IS. Our remission rate was comparable to previously published studies (60%). Moreover, the remissions persisted for up to 6 months after discontinuing therapy. Subsequently, ACTH is a unique and promising alternative to standard IS in patients with resistant NS.

SA-PO678
Proteinuria relapse before recovery of B Cells and Responsiveness to Rituximab in a Patient with Idiopathic Focal Segmental Glomerulosclerosis
Ilse M. Rood,1 Job Huussen,2 Jeroen Deegen,2 Jack F. Wetzels.3 1Dept of Nephrology and Transplantation, University Medical Center, Utrecht, Netherlands; 2Dept of Clinical Nephrology, UMCU, Utrecht, Netherlands; 3Dept of Clinical Hematology, University Medical Center, Utrecht, Netherlands.

Background: Focal segmental glomerulosclerosis (FSGS) is one of the most common causes of nephrotic syndrome (NS) in adults. FSGS is a heterogeneous disease with many underlying causes. A potential cause is the production of permeability factors by lymphocytes. This has been the rationale for targeted B-cell-therapy using rituximab (RTX). Several case reports showed remission of proteinuria in patients with idiopathic FSGS (fISFS). We present a patient with a relapse before recovery of peripheral B cells, who achieved remission after renewed RTX therapy.

Methods: A 65-year old woman presented with proteinuria of 3.0 g/24h and a serum albumin of 24 g/l. Renal function was normal (serum creatinine 51 μmol/l). A renal biopsy showed lesions consistent with FSGS. After ruling out secondary causes, fISFS was diagnosed. Treatment with prednisone was effective in inducing a partial remission. However, over the years these multiple relapses necessitating repeated courses of prednisone. Treatment with cyclophosphamide or ciclosporin did not result in a lasting remission. Because of side effects of the therapies, RTX treatment was given at the time of new relapse (1000mg on day 1 and 15). A renewed partial remission occurred. Seven months later she had a new relapse (proteinuria 4.2 g/24h, serum albumin 24 g/l, serum creatinine 144 μmol/l). At that time B-cell CD19+ count was 0.01x10^9/L. Although B-cells were not recovered, a new dose of RTX was given, resulting in a new partial remission (proteinuria 1 g/24h, serum albumin 32 g/l).

Conclusions: This is the first reported case of a relapse of the NS after treatment with RTX when there was no evidence of B-cell recovery. Interestingly, a new dose of RTX resulted again in a partial remission. This case illustrates either that B-cells in secondary lymphoid tissues can still activate T-cells or that B-cell independent mechanisms of RTX are involved in the relapse (by directly affecting podocyte function).

SA-PO679
Successful Treatment with Dexamethasone and Bortezomib for Proliferative Glomerulonephritis with Monoclonal IgG Deposits in Multiple Myeloma
Meenu Gaba,1 Mark Birkenbach,2 Iris J. Lee.1 1Dept of Nephrology, Temple Univ School of Medicine, Philadelphia, PA; 2Dept of Hematology/Oncology, Temple Univ, Philadelphia, PA.

Background: The pathophysiology of proliferative glomerulonephritis with monoclonal IgG deposits (PGN-MID) remains unknown. In 30% of PGN-MID cases, there was a monoclonal component detectable in the serum, but only two cases of myeloma were reported previously. Now we present the first case of PGN-MID leading to the diagnosis of multiple myeloma and subsequent successful treatment.

Methods: A 75 year old male with hypertension presented with progressive leg edema and fatigue. He was found to have nephrotic range proteinuria (13 grams on a spot protein-creatinine ratio) and hypoaalbuminemia of 2.8 g/dL. His serum creatinine was 1.39 mg/dL. His urine showed 30–49 RBC/hpf, but no dysmorphic cells or cellular casts. On serum and urine protein electrophoresis, he had monoclonal spikes in both the serum and urine. CRYOGLOBULIN test for serum resulted negative. Renal histopathology demonstrated lobular mesangial proliferation with moderate tubular atrophy and negative Congo red staining. Glomeruli showed granular capillary staining for IgG, C1q and C3 with light chain isotype restriction limited to kappa by immunochemistry, although tubular deposits were absent. Analysis for IgG subclass confirmed restriction to IgG1 subtype. Granular electron dense deposits were present in subendothelial and mesangial locations. Bone marrow examination revealed 17% of IgG kappa positive monoclonal plasma cells. A diagnosis of PGN-MID in multiple myeloma was made and we started on bortezomib and dexamethasone. Patient had significant positive response within 3 months with improvement of proteinuria to 0.66 grams/day and serum albumin to 3.4 mg/dL.

Conclusions: Redondo-Pachon et al. reported a case of PGN-MID and multiple myeloma refractory to treatment. However, we first demonstrated in this case that treatment for myeloma is effective for PGN-MID when plasma cell dyscrasia is involved in the pathogenesis.
polypagitis was the most common diagnosis with 58%, and 34% suffered from microscopic polypagitis (including renal-limited form). Cumulative organ involvement involved kidney in 89%, lungs in 61% and ENT in 38%. Mean S-creatinine at diagnosis was ≥161 μmol/L, 161 patients required dialysis. Cyclophosphamide was used in 89% of the patients, plasma exchange in 232 (36%) and biological therapy in 34 (5%). The estimated 5-year survival was 81.5% (95% CI = 78.1–84.9%) and was higher in patients aged >65 years than in the other ones (85% vs. 67%, p < 0.01) with better renal function at diagnosis compared to those with S-creatinine ≥ 200 and ≥ 500 μmol/L (91%, 80% and 67%; p < 0.05 and p < 0.001, respectively). During follow-up, 41% of the patients relapsed. Last available VDI (Vasculitis Damage Index) ranged between 0 and 16 (median 4).

Conclusions: In the studied population, GPA was the most common AAV, reflecting the northern European type. Older age and severe renal involvement were associated with higher mortality. Long-term survival was similar to previous studies, often associated with a significant morbidity.

SA-PO684
Infection, Relapse and Mortality in Antineutrophil Cytoplasmic Antibody Associated Vasculitides Julie-Anne G. McGregor, Caroline J. Poulton, Jason M. Kidd, Suzanne L. Katzanos, Lindsey R. Goetz, Yichun Hu, Patrick H. Nachman, Ronald J. Falk, Susan L. Hogan. UNC Kidney Center, Chapel Hill, NC; Hospital Universitari de l’Anoia, Barcelona, Spain; CHUQ, Québec, Canada.

Background: Study goal was to evaluate risk factors for infections, relapse and death within 2 years (ys) of diagnosis in a cohort with biopsy-proven antineutrophil cytoplasmic antibody associated vasculitides (AAV) (1992-2011).

Methods: All received immunosuppression. Infection (inf), relapse and death within 12 & 24 mos (mos) were assessed. Severe inf (intravenous antibiotics, intensive care unit, or cause of death) and prophylactic therapy was recorded. Inf number was grouped as no inf, 1-2 or >3 inf. Fisher exact or Kruskal-Wallis tests were used with Cox regression to estimate hazards ratios (HR) and 95% confidence intervals.

Results: 490 patients (median age 59 yrs; 47% male, 55% MPO-ANCA) were followed for a median of 2.8 yrs. Within 12 mos, 55% had inf, 19% relapsed and 8% died. Within 24 mos, 66% had inf, 36% relapsed and 12% died.

More in inf in 12 mos were associated with age (median age 57yrs with no inf, 60yrs with 1-2 inf and 65yrs with ≥3 inf; p = 0.02) and steroid-induced diabetes mellitus (DM) (19% in those with no inf, 27% in those with 1-2 inf, and 44% in those with ≥3 inf; p = 0.002). Female sex was the sole risk for more inf in 12-24 mos (39% with female vs 52% with ≥2 inf, 57% with ≥3 inf, p < 0.01), with urinary tract infections (UTI) most frequent (31% vs men 10%; p < 0.001). Prophylactics did not reduce inf.

Relapse in 12 mos was more common in females (60% vs males 40%, p = 0.014) and less likely with renal limited AAV (8% vs. GPA 33% and MPA 58%, p < 0.019). Only PR3-ANCA was associated with relapse in 12-24 mos (p = 0.005 vs. MPO).

Death was associated with more inf in 12 mos (0%; 1-2 inf 11%; ≥3 inf 13% p = 0.002). A severe inf within 24 mos was a risk for death from any cause in this timeframe (HR 5.6, 95% CI 1.2, 27.2).

Conclusions: Elderly patients and those with steroid induced DM must receive less aggressive immunosuppression. UTI in females needs to prompt prophylaxis. This information on inf, relapse and death in the first 1-2 years following AAV diagnosis can guide immunosuppressive strategies.

SA-PO685
Use of Cyclophosphamide in ANCA Associated Nephritis: Experience of a Tertiary Care Center Philippe Lachance, David Phihlbert. Nephrology, CHUQ, Québec, Canada.

Background: Cyclophosphamide (CYC) at 2mg/kg is the cornerstone of induction therapy in ANCA associated nephritis (AAN) with a 50 to 90% remission rate but with infection and leucopenia in up to 50% of cases. The aim of this study is (1) to describe retrospectively the safety and efficacy of reduced CYC regimen in our center and (2) to examine potential predictors of irreversible kidney injury (IKI).

Methods: Single arm retrospective study which included all ANCA affected patients from January 2009 to July 2012 at Hotel-Dieu de Québec, a tertiary nephrology center. CYC dose, rate of remission, infection (from the medical file) and leucopenia (WBC<4) were reported and compared to those in the literature. Complete remission was defined as stable or normalizing creatinine with bland urinary sediment while it was considered partial if erythrocytes were present. IKI was defined by need for chronic dialysis. All renal biopsies were reviewed. A damage score including tubular atrophy, glomerulosclerosis and interstitial fibrosis (0 to 3 pts each) was created. Patients with IKI were compared to the others to determine which features predict irreversible kidney injury (IKI).

Results: Twenty-six (26) patients (median age 59 (51, 70) years) were included with a median creatinine of 604 (263,880) μmol/L. Seven (27%) also had pulmonary manifestation. The median CYC induction and total doses were 1.13 (0.83, 1.38) mg/kg and 12 (7, 7.7) g respectively. Fourteen (54%) patients received plasmapheresis. After a median follow-up of 9 (4, 21) months, eighteen patients (70%) were in partial or complete remission. Infections and leucopenia occurred in six (23%) and nine (35%) patients respectively. IKI was correlated with peak serum creatinine (r=0.67). The histopathologic score correlated with IKI (r=0.52). AUC for this score was 0.85. A score > 5 yielded a 86% sensitivity and 74 % specificity.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Conclusions: Lower doses of CYC yielded remission rate similar to the literature with probably less infection and leucopenia. Peak serum creatinine seems to correlate well with KiJ as well as histopathologic findings. However, combination of these two features is probably needed to accurately predict patients with IkiJ. More data are needed to draw firm conclusion.

Funding: Clinical Revenue Support

SA-PO686

Crescentic and Focal Necrotizing Glomerulonephritis in Patients with Normal Serum Creatinine

Methods: We conducted a retrospective review (1995-2011) of all adult patients who presented with native renal biopsy proven FN/CGN and normal sCr (<120 micromol/l).

Results: 38 patients were identified, median age 57 years (range 17-78), 29% male. Biopsies showed median 14 glomeruli (4-33), with 32% (4-100%) of glomeruli affected by necrosis/crescents. All patients received immunosuppression in accordance with local protocols. Median duration of follow-up was 45 months (2-184). Clinical features and outcomes are summarised in the Table below. The majority of patients had good outcomes at one year and at last follow-up. Only 18% of patients had pre-existing diagnoses of autoimmune disease associated with GN. 2 patients progressed to ESRF (both due to lupus nephritis, at 21 & 29 months) and 4 patients died during follow-up (2, 12, 96 & 122 months).

Diagnosis Number of Cases (%) + Crescents/Necrosis (range)
---
Crescentic GN 11 (29%) 32% (4-100%)
Lupus nephritis 5 (13%) 50%
Anti-GBM disease 4 (10%) 90% (26-47%)
GA Nephropathy 3 (8%) 50%
B cell biopsies 21 (Biopsy 1 year 2) At last Follow-Up
Biopsy 1 (50-15) At 12 (14-18) At 24 (7-29)
Biopsy 2 (10-40) At 30 (40-40) At 12 (22-43)
DN (membranous) 3 (10%) 90% (39-52)

* censored for death/dialysis

Conclusions: This is the first reported series of severe renal pathology in patients presenting with normal creatinine. Low threshold of suspicion for FN/CGN, prompt renal biopsy and additional testing may prevent irreversible kidney damage and improve long-term outcomes in these patients.

SA-PO687

Analysis of 70 Patients with Severe ANCA Vasculitis Requiring Plasma Exchange at MGH: 2005-2013

Background: Anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis is a systemic autoimmune disease characterized by small vessel inflammation caused by pathogenic autoantibodies primarily directed against proteinase 3 (PR3) and/or myeloperoxidase (MPO). Rituximab is an FDA-approved humanized monoclonal antibody that depletes CD20-positive B cells. There is increasing evidence that chronic B cell depletion can lead to hypogammaglobulinemia. Our group currently manages over 400 patients with ANCA vasculitis, the majority of which receive rituximab every four to six months to maintain durable remission; thus, we sought to investigate the effect of prolonged rituximab exposure on immunoglobulin concentrations.

Methods: We conducted a systematic retrospective analysis of ANCA vasculitis patients from 2006-2013 who were treated with rituximab maintenance therapy and developed LOH. Continuous B cell depletion was performed in all patients by scheduled rituximab infusion every four months. Complete blood counts with differentials (CBC) were checked every two months. Patients who developed neutropenia from cocaine use as well as patients with both MPO- and PR3-ANCA were excluded from this analysis.

Results: 215 patients treated by our group from April 2006 through June 2013 underwent continuous CD20-positive B cell depletion with RTX. 17 patients developed LOH (defined as absolute neutrophil count (ANC) < 1000 cells/mm3). Median ANC nadir was 350 cells/mm3. Four episodes resolved without intervention by the time of repeat bloodwork; however, thirteen episodes were treated with granulocyte colony-stimulating factor (GCSF). Four patients had associated fever and were hospitalized for intravenous antibiotics. In all patients, neutropenia resolved in less than one week and in no patient was RTX discontinued due to this effect.

Conclusions: A serious and under recognized adverse feature associated with RTX use appears to be LOH and concomitant risk of infection. Fortunately, LOH resolves with GCSF use and typically does not recur with continued RTX use. A CBC with differential should be checked in every RTX-treated ANCA vasculitis patient every two months and immediately upon onset of fever.

Funding: Clinical Revenue Support

SA-PO689

Hypogammaglobulinemia in ANCA Vasculitis Patients Undergoing Continuous B Cell Depletion Using Rituximab

Background: Anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis is a systemic autoimmune disease characterized by small vessel inflammation caused by pathogenic autoantibodies primarily directed against proteinase 3 (PR3) and/or myeloperoxidase (MPO). Rituximab is an FDA-approved humanized monoclonal antibody that depletes CD20-positive B cells. There is increasing evidence that chronic B cell depletion can lead to hypogammaglobulinemia. Our group currently manages over 400 patients with ANCA vasculitis, the majority of which receive rituximab every four to six months to maintain durable remission; thus, we sought to investigate the effect of prolonged rituximab exposure on immunoglobulin concentrations.

Methods: We conducted a systematic retrospective analysis of ANCA vasculitis patients from 2006-2013 who were treated with rituximab maintenance therapy and who developed hypogammaglobulinemia.

Results: 215 patients treated by our group from April 2006 through June 2013 underwent continuous CD20-positive B cell depletion with rituximab. Hypogammaglobulinemia, defined as an IgG level of < 400 mg/dL, developed in only 17 patients. Rituximab was discontinued in none of these patients; however, none of these patients relapsed. As expected, the other eight patients, where rituximab was continued, also remained in remission. Six were hospitalized for infection or fever; however, three of these were associated with fever in the setting of late-onset neutropenia. Two patients received intravenous immunoglobulin (IVIg) for recurrent bronchitis.

Conclusions: Hypogammaglobulinemia was a rare, late and modest complication that improved with rituximab cessation and/or IVIg administration. There does not appear to be any apparent predictor or association for patients who develop hypogammaglobulinemia; however, as the size of this cohort grows, the power to identify an association may increase.

Funding: Clinical Revenue Support
Clinical Characteristics and Renal Outcome in ANCA Associated Vasculitides with Renal Involvement: A 6-Year Retrospective Cohort Analysis
Ping Fu, 1Department of Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China; 2Department of Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China; 3Department of Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China.

Background: Renal vasculitis is a common manifestation in antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AVV), and is an important cause resulting in ESRD. This study was to analyze clinical characteristics and renal outcome of patients with renal involvement of AVV.

Methods: Patients who presented to the West China Hospital with renal involvement of AVV were retrospectively recruited. All patients were followed up from 3 to 60 months. Among them, 49 patients were granulomatosis with polyangitis (GPA), 85.0% as MPA, 5.4% as PICGN. ANCA serology identification was not associated with the composite outcome of patient or renal survival (P=0.098 in Log-rank test and P=0.921 in trend test). In multivariate analysis, eGFR <15 ml/min (Subdivision hazard ratio (SHR) 1.85 (95% CI 1.43-1.96)) and severe chronicity (SHR per unit increase 1.10 (1.01-1.19)) were risk factors for renal death. Use of cyclophosphamide (SHR 0.3 (0.13-0.69)) and eGFR ≥ 15 ml/min (SHR 0.38 (0.15-0.97)) were significantly associated with patient survival after adjustment for age, ANCA type, and disease classification.

Conclusions: The new histopathologic classification alone is insufficient in assessing prognosis in ANCA-GN. A classification scheme that incorporates measures of tubulointerstitial damage may be of improved prognostic value.

SA-PO692
MPO-Positive Cells and Extracellular MPO Are Associated with Capillary Injury in Glomeruli in Lupus Nephritis
Sakokawashina, Shinya Kaname, Yoshinori Komagata, Yoshihiro Armura, Akira Yamada. First Dept of Internal Medicine, Kyorin Univ School of Medicine, Mitaka, Tokyo, Japan.

Background: We have recently reported that in human MPO-ANCA-associated glomerulonephritis (GN), MPO exists along the glomerular capillary walls near infiltrated MPO-positive cells, suggesting that MPO release from neutrophils directly causes capillary injury (Clin Nephrol 2013). Here we investigated the role of MPO in the pathogenesis of glomerular capillary injury in patients with lupus nephritis, in which neutrophil infiltration and vascular necrosis are also frequently observed.

Methods: We analyzed 589 renal specimens obtained from 27 patients with lupus nephritis class IV. Glomerular infiltration of MPO-positive cells, deposition of extracellular MPO in the glomeruli and endothelial cells injury. Co-localization of MPO and CD34 deposition was also examined by immunofluorescence staining.

Results: The infiltration of MPO-positive cells and MPO deposition were observed in some glomeruli, especially in the glomeruli at an active injury phase with severe inflammatory cell infiltration, whereas MPO was rarely stained in sclerotic/lobular glomeruli with high chronicity. MPO deposition was mainly located in the glomerular capillary walls near the infiltrated MPO-positive cells. Interestingly, there were various degrees of MPO deposition along the capillary walls, and necrotic lesions were strongly associated with diffuse MPO deposition that covered more than 50% of the capillary loops, but was rarely associated with limited-type MPO deposition where only a small part of capillary walls was involved. Moreover, in some parts of necrotic lesions with MPO deposition phenomenon of neutrophil extracellular traps (NETs) was suggested to occur.

Conclusions: These results indicate that MPO deposition released from infiltrated MPO-positive cells, particularly diffusely distributed lesions along the glomerular capillary wall, may play important roles in the pathogenesis of lupus nephritis.
Phases 1 and 2 Clinical Trial of CXCX168, an Orally Administered CsA-R Antagonist, in Patients with ANCA-Associated Renal Vasculitis (CLEAR)

Annette Bruchfeld, 1 Matthias Schaier, 1 Lorraine Harper, 1 Michel Y. Jadoul, 1 Marten Segelmakar, 2 Istvan Szombati, 2 Michael Venning, 2 Patrick Hamilton, 2 Christian Hugo, 2 Paul L.A. Van deel, 3 Ondrej Viklicky, 3 David R.W. Jayne, 1 Antonio Potarac, 1 Juan C. Jaen, 4 Thomas J. Schall, 5 Pieter Boberek, 1 Konstanz M. Institute, Sweden; 2 Univ Hosp Heidelberg, Germany; 3 Univ of Birmingham, United Kingdom; 4 Cliniques Saint-Luc, Belgium; 5 Linköping Medical, Czech Republic; 11 Univ of Cambridge, United Kingdom; 6 Medicine/Nephrology; Elmhurst Hospital Center, Elmhurst, NY; 7 Stony Brook Univ Medical Center, Stony Brook, NY.

Background: CXCX168 block C5a-induced neutrophil chemotaxis and CD11b expression in blood samples in Ph1. It markedly reduced glomerular crescent formation and necrosis, and proteinuria and hematuria in transgenic iC5aR mice with anti-MPO-induced GN.

Methods: This Ph2 trial tested whether CXCX168 could substitute, at least partially, for CsA. In Step 1, 12 pts were randomized 2:1 to 30 mg CXC168 BID + a reduced dose of prednisone (20mg/d) or placebo BID + a full dose of prednisone (60mg/d) for 12 wks. All patients received CYC 15 mg/kg IV up to 1.2g q2-3wk. If Step 1 were successful, in Step 2, 12 patients received the same treatments as Step 1, except the CXC168 group received no CsA. Eligible patients had GPA, MPA, or renal limited vasculitis, were anti-PR3 or MPO+ and had active renal vasculitis. Primary objective: safety and tolerability. Secondary objectives: feasibility of reducing Cs and effect of CXC168 on renal disease.

Results: Baseline characteristics are shown below.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dosing Group 1 (n=8)</th>
<th>Dosing Group 2 (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>20.1 ± 4.6</td>
<td>35.4 ± 12.0</td>
<td>0.008</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>6:2</td>
<td>8:2</td>
<td>0.43</td>
</tr>
<tr>
<td>New onset/Relapse</td>
<td>4/4</td>
<td>6/4</td>
<td>0.19</td>
</tr>
<tr>
<td>GPA/MPO+PR3</td>
<td>1/0</td>
<td>2/2</td>
<td>0.09</td>
</tr>
<tr>
<td>C-ANCA</td>
<td>0/1</td>
<td>3/9</td>
<td>0.004</td>
</tr>
<tr>
<td>P-ANCA</td>
<td>3/3</td>
<td>2/6</td>
<td>0.24</td>
</tr>
<tr>
<td>C-ANCA to P-ANCA</td>
<td>6/8</td>
<td>5/0</td>
<td>0.40</td>
</tr>
</tbody>
</table>

No SAEs related to CXC168 occurred in Steps 1 or 2. No rescue Cs was required in Step 1 in the treatment period and two rescue events in Step 2 (treatment still blinded).

Conclusions: CXC168 shows promise in the treatment of ANCA-associated renal vasculitis.

SA-PO696

Endothelial Cell Injury Contributes to the Formation and Development of Extracapillary Lesions in Crescentic Glomerulonephritis

Emiko Fujita, 1 Akira Shimizu, 1 Akiko Miyi, 1 Megumi Fukui, 2 Shuichi Tsuruoka. 1 Dept of Pathology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan; 2 Dept of Nephrology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.

Background: Glomerulonephritis (GN) with extracapillary lesions is known to have a poor prognosis. However, the endothelial injury has not been elucidated. In the present study, we aimed to assess the association of endothelial cell injury with the formation of extracapillary lesions and the development of crescentic GN.

Methods: Renal biopsy samples of crescentic GN including ANCA-related GN were included. Of 281 biopsies reviewed, crescentic GN represented 12% (34/281) of the total; 21.9% of all HISP biopsies (25/114) and 5.4% of all non-Hispanic biopsies (9/167). AAV was the second most common glomerulonephritis after SLE (21.9% vs. 23.7% in HISP. HISP, AAV, and non-Hispanics included 53.1 ± 3.4 years old, with proteinuria and eGFR of 3.4 ± 0.5 and 16.5 ± 21.9%, respectively. 28% of HISP (7/25) had hemoptysis. Among 25 HISP with AAV, 56% (14/25) had P-ANCA and 40% (10/25) C-ANCA. Of all HISP AAV, 61% were South American and only 15% Mexican. 70% of South Americans had P-ANCA. 44% of HISP-AAV are dialysis dependent.

Results: Of 281 biopsies reviewed: AAV represented 12% (34/281) of the total; 21.9% of all HISP biopsies (25/114) and 5.4% of all non-Hispanic biopsies (9/167). AAV was the second most common glomerulonephritis after SLE (21.9% vs. 23.7% in HISP. HISP, AAV, and non-Hispanics included 53.1 ± 3.4 years old, with proteinuria and eGFR of 3.4 ± 0.5 and 16.5 ± 21.9%, respectively. 28% of HISP (7/25) had hemoptysis. Among 25 HISP with AAV, 56% (14/25) had P-ANCA and 40% (10/25) C-ANCA. Of all HISP AAV, 61% were South American and only 15% Mexican. 70% of South Americans had P-ANCA. 44% of HISP-AAV are dialysis dependent.

Conclusion: Duration of hematuria does not predict eGFR at 1 year in ANCA-GN. We propose that among patients otherwise in clinical remission, the persistence of hematuria should not delay transition from induction to maintenance immunosuppression.

SA-PO698

Increased Risk for Antineutrophil Cytoplasmic Antibodies Associated Renal Vasculitis (AAV), Specifically Antimyeloperoxidase (P-ANCA) for Hispanic Patients (HISP) (Salwa Rhazouani, 1 George N. Coritsidis, 1 Aleek M. Rahman. 1 Medicine/Nephrology; Elmhurst Hospital Center, Elmhurst, NY; 2 Stony Brook Univ Medical Center, Stony Brook, NY.

Background: AAV is an uncommon diagnosis with most clinical observations arising from Europe, Japan and the United States. Recent data has suggested an increase in antineutrophil c-associated (C-ANCA) vasculitis in Mexicans. Since data from Central & South America is limited, a retrospective analysis of biopsies from our institution that serves a large immigrant Hispanic population was conducted.

Methods: All renal biopsies (1999-2012) were analyzed for: age, gender, proteinuria(g/d), MDRD glomerular filtration rate (eGFR,ml/min/1.73 m2), renal outcomes and histology at presentation. Data presented as average ± standard error of mean. Multivariate logistic regression models were used to determine odds.

Results: Of 281 biopsies reviewed: AAV represented 12% (34/281) of the total; 21.9% of all HISP biopsies (25/114) and 5.4% of all non-Hispanic biopsies (9/167). AAV was the second most common glomerulonephritis after SLE (21.9% vs. 23.7% in HISP. HISP, AAV, and non-Hispanics included 53.1 ± 3.4 years old, with proteinuria and eGFR of 3.4 ± 0.5 and 16.5 ± 21.9%, respectively. 28% of HISP (7/25) had hemoptysis. Among 25 HISP with AAV, 56% (14/25) had P-ANCA and 40% (10/25) C-ANCA. Of all HISP AAV, 61% were South American and only 15% Mexican. 70% of South Americans had P-ANCA. 44% of HISP-AAV are dialysis dependent.

Conclusion: Duration of hematuria does not predict eGFR at 1 year in ANCA-GN. We propose that among patients otherwise in clinical remission, the persistence of hematuria should not delay transition from induction to maintenance immunosuppression.

SA-PO699

Rituximab for Remission Induction of Recurrent ANCA Associated Glomerulonephritis Post Kidney Transplant

Duvuru Geetha, 1 Teresa K. Chen, 1 Pradeep Manoharan, 2 Duvuru Geetha. 1 Medicine/Nephrology; Elmhurst Hospital Center, Elmhurst, NY; 2 Stony Brook Univ Medical Center, Stony Brook, NY.

Background: Kidney transplantation (KTX) is the treatment of choice for patients with end stage renal disease (ESRD) due ANCA associated vasculitis (AAV). Relapses of AAV occur after KTX and may adversely affect allograft survival. Combined therapy with cyclophosphamide and rituximab and steroids. Mean time to hematuria resolution was 91 (77) days, and 34 (62%) patients had hematuria resolution prior to 90 days. Older age and lower baseline eGFR were associated with lower eGFR at 1 year (p=0.03 and p<0.001, respectively). Hematuria resolution (<90 vs. ≥90 days) was not predictive of eGFR at 1 year (p=0.89). In sensitivity analyses, age, gender, baseline eGFR, proteinuria, and ANCA type were not associated with timing of hematuria resolution.

Conclusion: Duration of hematuria does not predict eGFR at 1 year in ANCA-GN. We propose that among patients otherwise clinical remission, the persistence of hematuria should not delay transition from induction to maintenance immunosuppression.
a B cell depleting monoclonal antibody is approved for remission induction in AAV. We report the clinical presentation and outcomes of 5 KTX recipients who were treated for recurrent crescentic glomerulonephritis (GN) with RTX.

Methods: We identified 37 patients who underwent KTX for ESRD due to AAV between 1999 and 2012. Seven patients experienced recurrent GN and 5 were treated with RTX. We collected demographics, details of immunosuppression, clinical features at relapse and outcomes following RTX use in these patients.

Results: The median age at the time of KTX was 26 years (4 Caucasians, 3 females). The disease phenotype was microscopic polyangiitis in 3 and granulomatosis with polyangiitis in 2 patients (p-ANCA=3, c-ANCA=2). All patients were in remission with 4 being ANCA positive and 1 with negative ANCA. RTX received induction therapy and all were maintained on steroids, mycophenolate mofetaiol and tacrolimus. Biopsy proven recurrent GN occurred at a median of 26 months. All patients had rise in serum creatinine and hematuria and were ANCA positive at relapse. RTX was used with steroids in all 5 patients. Four patients achieved disease remission after RTX, the fifth patient was refractory to RTX and CYC. All patients showed evidence of B cell depletion and 2 patients were ANCA negative post RTX. Follow up biopsies in 3 patients showed resolution of active GN in 2 patients and persistent active GN in 1 patient. At the time of last follow up, 2 patients had reached ESRD, one to refractory vasculitis and one to nephritis and recurrent GN due to medication noncompliance.

Conclusions: RTX is an alternative to CYC for remission induction in recurrent AAV associated GN in KTX patients.

SA-PO700

ANCA-Associated Renal Vasculitis: Insights from an Observational Cohort Study

Mark N. Canney, Eoin O Sullivan, Philip Hugh Bredin, Michael Clarkson. Dept of Renal Medicine, Cork Univ Hospital and Univ College Cork, Ireland.

Background: ANCA-associated vasculitis (AAV) is a life threatening illness requiring robust immunosuppression that carries attendant risks of leucopenia and sepsis. Our unit is the sole tertiary referral centre for AAV in Southwest Ireland (population 650,000). Here we report the incidence and outcomes of renal AAV in an Irish population. Furthermore we explore the role of renal biopsy and IV vs oral cyclophosphamide (CYC) in the management of this condition.

Methods: The Cork Renal Vasculitis Registry captures all incident AAV patients in Southwest Ireland with clinical evidence of renal involvement. The period of interest was 2005-2012. Data was obtained from laboratory results and patient records, and analyzed using SPSS v16.0.

Results: 73 patients met the inclusion criteria giving an incidence of 15.4 cases per million patient years. The majority were male (59%), anti-MPO ANCA positive (64%) and received CYC as induction therapy (68%). One year patient survival was 88%. Patients who received oral CYC tended to develop more severe leucopenia than those who received IV CYC (p<0.01). Those who did not undergo renal biopsy had a higher creatinine at baseline (730.6 μmol/L vs 378.3 μmol/L, p=0.06). They received more plasma exchange (47% vs 10%, p=0.001) and pulse methylprednisolone (72% vs 42%, p=0.007) as induction therapy. Not having a renal biopsy associated with a higher risk of death and ESKD even after adjusting for confounding variables such as age, creatinine at presentation and initial BVAS (p=0.03). Intriguingly not having a biopsy associated with higher grade leucopenia (p=0.011) suggesting the potential of relative over-immunosuppression in more critically ill patients at presentation.

Conclusions: Induction with oral CYC may result in more severe leucopenia than IV CYC, in keeping with suggestions from clinical trial data. In severe renal AAV, not undergoing a renal biopsy associated strongly with more intense induction immunosuppression, higher grade leucopenia and higher risk of death/ESKD. Inability to perform a renal biopsy at presentation may be an important signal identifying patients at highest risk of adverse outcomes.

SA-PO701

In Sweden, ANCA Associated Nephritis Is a More Common and a More Severe Disease as Compared to Lupus Nephritis

Marten Segelmark,1 Maria Weiner,1 Christopher Sjöwall,2 Ola Nived,3 Per Eriksson,2 Aladdin Mohammad.3 1Nephrology, Linköping Univ, Linköping, Sweden; 2Rheumatology, Linköping Univ, Linköping, Sweden; 3Rheumatology, Lund Univ, Lund, Sweden.

Background: The aim of this study was to compare incidence rates and outcome between lupus nephritis (LN) and ANCA associated vasculitis (AAV) in Sweden. We perform a renal biopsy at presentation may be an important signal identifying patients at highest risk of adverse outcomes.

Methods: A prospective cohort study of all AAV pts. referred to our centre between 2000-2010 was performed. All pts. had AAV based on positive ANCA and a compatible clinical syndrome. 132 pts. were admitted and 118 followed for a mean of 5.7 years (range 0.2-12.3, 676 patient years) and 116 were kidney biopsed. 57% were male, 47% were MPO-ANCA positive. 36% had high creatinine >500, 40% were aged >65. 105 pts. were Plasma Exchange(PLEX)-d (mean 7 (5-11)) and the use was decided on severity of renal biopsy and ANCA titres. Immunosuppression consisted of prednisolone 1 mg/kg/day and a low dose of daily oral Cyclophosphamide (100 mg/day in pts. <65 years and 50 mg/day in pts. >65). AZA/MMF was given for maintenance of remission.

Conclusions: Following this classification, most of patients belong to crescentic class, followed by focal, sclerotic and mixed class. Patients of sclerotic class had the highest percentage of starting RRT, and focal class the least percentage. Highest mortality corresponded to mixed class. The severity of initial damage can predict evolution and renal survival.

SA-PO703

Impact of Renal Histological Classification on Long Term Renal Outcome in ANCA Associated Vasculitis

Wladimir M. Szpir,1 Elizabeth Krarup,2 Martin Egfjord.1 1Nephrology, Rigshospitalet; 2Nephrology, Herlev, Copenhagen, Denmark.

Background: The four histological subclasses in renal biopsies of patients with ANCA associated vasculitis (AAV) have been proposed and shown to have an impact on renal outcomes. We report the incidence and outcomes of renal AAV in an Irish population. Furthermore we explore the role of renal biopsy and IV vs oral cyclophosphamide (CYC) in the management of this condition.

Methods: This is a retrospective descriptive study. From renal biopsies made during the last 20 years we analyzed AAV, describing: age, sex and histological category. Patients were classified in four classes: "focal" (≥50 % normal glomeruli), "crescentic" (≥50 % glomeruli with cellular crescents), "mixed" (<50 % normal, <50 % crescentic, <50 % globally sclerotic glomeruli), and "sclerotic" (≥50 % globally sclerotic glomeruli), following clinical evolution.

Results: From 629 biopsies, 67 (10.6%) corresponded to AAV. Patients had a mean age of 62.5 ± 12.6 years. Men/women 34:33. Histopathological classification and evolution are represented in Table 1 and renal survival in Figure 1.

Conclusions: In Sweden AAN outnumber LN almost three to one, and outcome is considerably worse. In our country SLE is often diagnosed and treated early which in many cases can prevent the development of severe nephritis, while AAN is often diagnosed at later stages leading to severe consequences.

Funding: Private Foundation Support, Government Support - Non-U.S.
Results: The renal histological subclasses were classified into focal(≥50% normal glomeruli, n=30), mixed(<50% crescents and < 50% sclerotic, n=12), crescentic (≥50% crescents, n=66) and sclerotic(≥50 % sclerotic, n=5 - not shown). 6 biopsies were inconclusive due to few glomeruli. Furthermore interstitial fibrosis was scored and 75 biopsies were fibrosis free whether 41 had fibrotic changes. No significant differences were found between the classes, however at 5 years the best survival was found for mixed(89%), followed by focal (87%) and crescentic (73%) subclass, whether 3 out of 5 sclerotic kidneys were still functioning. Comparison of plus/minus fibrosis showed 5 years renal survival of 81% for non fibrotic kidneys compared to 72% with fibrosis (n.s.).

Conclusions: Only few renal biopsies showed chronic sclerotic picture and the biopsy findings including interstitial fibrosis were correlated to long term renal outcome, however the differences were not significant.

SA-PO704
Evaluating Lupus Nephritis with Serial Kidney Biopsies
Anthony Alvarado,1 Ana Malvar,2 Valeria Gabriela Alberton,3 Bruno Jorge Lococo,3 Maria Fernanda Toniolo,1 Brad H. Rovin,1 Ohio State Univ Wexner Medical Center, Columbus, OH; 2Hospital Fernandez, Buenos Aires, Argentina; 3C.D. Pathologico, Buenos Aires, Argentina.

Background: The effectiveness of lupus nephritis (LN) therapy is determined mainly by improvement in proteinuria and renal function. The histologic response to therapy is generally not evaluated because serial kidney biopsies are not usually obtained in patients who have improved. Also, stopping therapy in responders is a clinical decision, and renal pathology is not taken into account. In this study serial renal biopsies were correlated with clinical response to determine the concordance of clinical and histologic findings.

Methods: Biopsies were done in 25 Hispanic LN patients at LN diagnosis (BX1), after 6 months of induction therapy with either MMF (2.4g/d) or cyclophosphamide (1g/mo X6) (BX2), and during maintenance therapy with either MMF or azathioprine, after at least 42 months of total treatment, and 24 months of clinical inactivity (BX3). Biopsies were read by a single renal pathologist (VA) and NIH activity (AI) and chronicity (CI) indices were calculated. Serum creatinine (SCr) and proteinuria (PR) were measured serially.

Results: Between BX1 and BX3, SCr and PR improved significantly (1.0:0.4 vs 0.8:0.3 mg/dl and 3.3:2.1 vs 0.3:0.2 g/d respectively, P<0.001). From BX1 to BX3 AI declined (9.04 vs 1.9:1.7, P=0.001) and CI increased (2.8:1.4 vs 4.3:1.6, P=0.01). However in individual patients who were complete responders (n=16, SCr normal; PR<0.5g/d) only 6 had an AI of 0-1 at BX3, while 8 had an AI≥2 at BX3 (range 3-5). Multivariate modeling showed that improvement in AI at BX3 correlated with cyclophosphamide induction plus the decline in SCr between BX1 and BX2, or cyclophosphamide induction plus the increase in complement component C4 between BX1 and BX3.

Conclusions: These data demonstrate discordance between clinical and histologic responses in LN patients on immunosuppressive therapy for more than 3 years, with 50% of complete responders still having active histologic lesions. The implications of this continued low-level activity for discontinuation of therapy remains to be determined.

Funding: Other NIH Support - National Center for Advancing Translational Sciences

SA-PO705
Two-Year Maintenance Therapy with Tacrolimus for Class IV and V Lupus Nephritis Patients, Sub-Analysis of Post-Marketing Surveillance in Japan
Hirofumi Makino,1 Naoko Wakasugi,2 Tsutomu Takeuchi.3 1Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan; 2Astellas Pharma Inc., Japan; 3Keio Univ School of Medicine, Japan.

Background: Tacrolimus (TAC) is an immunosuppressive macrolide that blocks T cell activation, and it is widely administered following organ transplantation. Recently some small randomized controlled trials have shown that TAC is an effective maintenance treatment for lupus nephritis (LN), and a small open-label trial showed that TAC is effective in class V LN. However, in any trials, the sample sizes were small and the follow-up period was not sufficiently long, and the safety and efficacy with class IV LN has not been clear enough.

Methods: Post-marketing Surveillance has been conducted in Japan. The design was an open-label, non-comparative, non-interventional observational study. Patients were registered centrally between 2007 and 2010, and we have conducted an interim analysis included all the registered 1375 patients. To clarify the safety and efficacy of TAC for class IV and V LN, the sub-analysis was performed.

Results: Of 1375 patients, we studied the 214 patients with biopsy-proven Class IV and 159 patients with Class V. There was no difference in the safety by class. The patients with Class V had higher urine protein/creatinine ratio(P/C ratio) with higher e-GFR at baseline, but the improvement of P/C ratio two years after TAC treatment were almost equivalent, and the eGFR was maintained in both classes.

Conclusions: Sub-analysis of data from TRUST showed that 2 years TAC treatment was a safe and effective treatment in both Class IV and V LN. It seemed to take a longer time to complete remission in Class V compared to Class IV, we found that 2 years TAC treatment achieved the maintenance of remission in both classes, and the renal functions were maintained similarly in both classes.

Funding: Pharmaceutical Company Support - Astellas Pharma Inc.

SA-PO706
The Achilles Heel of Lupus Nephritis Treatment – Identifying Non Adherence Using Hydroxychloroquine Blood Levels

Background: Non adherence (NA) to lupus nephritis (LN) treatment (Rx) is the most important factor for non remission (NR) or renal relapses (RR). Hydroxychloroquine (HCQ) has very long half life, so low levels represent NA. In this first report in LN, we examined NA as defined by HCQ blood levels (HCQBL) ≤0.2mg/L and its correlation with clinical outcomes.

Methods: 145 patients (pts) with WHO class III, IV or V LN had HCQBLs measured during Rx. Complete remission (CR) was defined as protein creatinine ratio (PCR) <55mg/mmol and normal serum creatinine (SCr) or ≥15% increase in PCR or SCr requiring renal biopsy or change in Rx.

Results: Comparison of NA and adherent pts at HCQBL testing (table).

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

790A
SA-PO707

Soluble Forms of Intercellular Adhesion Molecule 1 (ICAM-1) and Vascular Cell Adhesion Molecule 1 (VCAM-1) Are High-Sensitivity Biomarkers for Lupus Nephritis Flare

Daniel J. Birmingham,1 George Sigal,2 Nicole Marie Reyes,1 Pankaj Oberoi,1 Brad H. Rovin,1 Lee A. Hebert,1

1The Ohio State Univ Medical Center, Columbus, OH; 2Meso Scale Discovery, Rockville, MD.

Background: Identifying biomarkers of lupus nephritis (LN) flare would help elucidate LN flare pathogenesis, and could lead to forecasters of impending flare to allow earlier treatment. Cross-sectional studies of urine samples have identified a number of candidates. However, little has been done to rigorously test how these candidate biomarkers temporally change relative to LN flare onset.

Methods: The present study sought to fill this gap by testing 18 different candidate biomarkers of LN flare in serially obtained urine samples leading up to flare. The samples were from the Ohio SLE Study (OSS), a prospective longitudinal study of recurrently active lupus patients. Soluble biomarker levels, normalized to urine creatinine levels, were determined from 24-hour OSS urine samples collected at 10, 8, 6, 4, and 2 months prior to, and at, LN flare (n=16).

Results: Using a mixed-effects stepwise regression model, incorporating repeated measures ANOVA, and accounting for other covariates such as WHO classiﬁcation, flare severity, age, race, and use of medications, 9 of the 18 biomarkers were found to be signiﬁcantly increased at the time of LN flare. The most sensitive of these were sICAM-1 and sVCAM-1 (both P < 0.0001), which increased by at least 25% at LN flare in 15/16 and 14/16 LN flares respectively. Both sICAM-1 and sVCAM-1 were also significantly increased at 2 months prior to LN flare. The next most sensitive biomarker was complement C5a (P=0.0002), which increased by at least 25% at LN flare in 9/16 LN flares. Notable biomarker candidates that did not change relative to LN flare included neutrophil gelatinase-associated lipocalin, beta-2-microglobulin, vascular endothelial growth factor, osteopontin, and cystatin C.

Conclusion: Increases in urine levels of sICAM-1 and sVCAM-1 occur prior to LN flare and identify LN flare with high sensitivity, suggesting that enhanced leukocyte adhesion is a key factor in the pathogenesis of LN flare.

Funding: NIDDK Support, Other NIH Support - PO1 DK55546, U1L RR025755

SA-PO708

Short Term Outcome of Induction Therapy in Pediatric Patients with Proliferative Lupus Nephritis

Murty Adabala,1 Rudolph P. Valentini,1 Rossana Baracco,1 Tej K. Mattoo.1

1Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 2Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 3Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 4Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI.

Background: Lupus Nephritis (LN) & its treatment are associated with morbidity & mortality. The objective of this study was to evaluate the clinical outcome at 6 months following induction therapy in pediatric patients with proliferative LN.

Methods: Retrospective chart review (23 patients) of LN patients with WHO class IV & severe class III followed at vasculitis clinic (2004-2011). All patients received the induction treatment with pulse Methylprednisolone followed by daily prednisone IV. Patients were considered to have LN if they had significant proteinuria (>1g/day) with or without cellular casts and a rise in serum creatinine. Induction therapy was continued for at least 8 weeks. All patients had at least 1 biopsy. All patients received either azathioprine (AZA) or mycophenolate mofetil (MMF). However, the cost-effectiveness of these two treatment strategies has not been reported.

Results: Using a third-party payer perspective, we constructed a Markov model with a 3-year time horizon to compare the cost-utility of generic formulations of AZA and MMF as maintenance therapy. We used individual-level simulations to account for patient age variability and probabilistic sensitivity analysis (PSA) to account for parameter uncertainty. We factored in drug adverse events and rescue therapy for LN relapse on either AZA or MMF. Probabilities, utility and disutility weights were based upon published studies, while costs of medications and health services were drawn from public sources. Model outcomes were costs, quality-adjusted life-years (QALY), incremental cost-effectiveness ratios (ICER) and net monetary benefit.

Results: Compared with AZA strategy, the ICER for MMF was $214,856/QALY gained. One-way sensitivity analysis showed that MMF is the favored strategy only if its yearly cost was less than $886, at a willingness-to-pay (WTP) $50,000/QALY. Results of PSA demonstrated that the probability that AZA was cost-effective compared to MMF was 90.9% at WTP $50,000/QALY.

Conclusion: Our state-transition model suggests that an AZA-based strategy is more cost-effective than MMF as maintenance therapy over a 3-year timeframe for proliferative LN. “The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense, or the US government.”

SA-PO710

Podocyte Lesions Involved in Lupus Nephritis Based on the 2003 ISN/RPS Classification System

Yan Wang, Di Song, Feng Yu, Suxia Wang, Minghui Zhao, Youkang Zhang. Renal Div, Dept of Medicine, Peking Univ First Hospital; Institute of Nephrology; Peking Univ.

Background: The podocyte lesions in lupus nephritis is still an intriguing controversy in ISN/RPS system. We assess the associations between podocyte lesions and clinicopathological features in a large cohort of lupus nephritis patients.

Methods: Clinicopathological data of 202 patients with renal biopsy proven lupus nephritis were reviewed. Morphometric analysis of podocyte foot process width (FPW) was performed to access the degree of podocyte injury, its correlations with clinical and pathological parameters were further analyzed.

Results: The podocyte foot processes in patients with lupus nephritis effaced variously, reflected by the FPW ranged from 626.16nm to 8253.78nm(median: 1397.39nm). 13 patients with lupus podocytopathy, including 9 with minimal change glomerulopathy and 4 with focal and segmental glomerulosclerosis pattern, met the histological criteria of lupus podocytopathy with a FPW of 2026mnm=1793nm. The degree of foot process effacement was positively correlated with proteinuria(a=0.509, P=0.001). The FPW of 1240nm can distinguish the nephrotic syndrome with sensitivity(81.5%) and specificity(62.7%). The degree of foot process effacement aggravated significantly from class I to class V, and patients with combined lupus nephritis presented with the severest podocyte lesions. The complete remission rate was significantly higher and the long-term renal outcome was better in group with calcineurin inhibitors than that with other regimens in patients with FPW higher than 1240 nm.

Conclusion: Podocyte damage was common in lupus nephritis. Lupus podocytopathy acted as an extreme form of lupus podocyte lesions. Podocyte injury mediated by immune complex deposits existed in different types of lupus nephritis, notably in class V and combined types. Hence, whether a subclass of lupus podocyte injury should be added to the ISN/RPS histopathological classification system for guiding therapy and judging prognosis, need further investigation.

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

Underline represents presenting author/disclosure.
SA-PO711

Spot Urine Protein/Creatinine Ratio Is More Unreliable in Estimating 24-h Proteinuria in Lupus Nephritis Than in Other Forms of Chronic Glomerular Diseases

Lee A. Hebert,1 Daniel J. Birmingham,1 Ganesh B. Shidham,1 Derek M. Fine,2 Roger A. Rodby,3 Giuseppe Remuzzi,4 Paul Louis Hurbert,2 Brad H. Rovin.1 1Internal Medicine, Ohio State Univ Wexner Med Ctr; Columbus, OH; 2Johns Hopkins Univ, Baltimore, MD; 3Rush Univ Medical Center; Chicago, IL; 4IRCCS-Istituto di Ricerca Farmacologiche Mario Negri, Bergamo, Italy; 5Univ of Washington, Seattle, WA.

Background: Spot urine protein/creatinine ratio (PCR) is often used clinically to estimate 24-h P. However, spot PCR shows considerable hour-to-hour variability. Spot collections (CI) reveal this variability. Longer CI conceal it. Spot PCR is useful in cohort studies where its variability is mitigated by averaging. However, clinical decisions often are based on a single spot PCR. Here, spot PCR variability is a liability. Here we compare spot PCR variability in lupus nephritis (LN) and chronic kidney disease (CKD).

Methods: For LN, we use the published works (N=3, 165 pts) that documented C content of the 24-h CI (studies A, B, C); for CKD, the REIN cohort (98 pts). Almost all spot were morning CI.

Results: Calibration plots show that most [spot PCR/24-h PCR] values fall well outside the limits of agreement with 24-h PCR.

Coefficient of variation (CV) of [spot PCR/24-h PCR] is greater in LN than CKD (mid CV (95%) LN versus CKD is 0.538 (0.459, 0.621) versus 0.335 (0.185, 0.456), p < 0.001). KDIGO and ACR recommend spot PCR but its variability is confounding, especially in LN. For example, 0.6 PCR increase is a BILAG-A renal flare. Spot PCR would not be reliably detect this change (see Figure). Also, spot PCR is not reliable for screening. It over and under estimates about equally.

Conclusion: Spot PCR testing is substantially inaccurate, particularly in LN. Its impact on clinical decision making, compared to 24-h PCR, needs further study.

Funding: NIDDK Support

SA-PO712

Lower Renal mir-150 Expression Levels Are Associated with Better Response to Treatment in Lupus Nephritis Patients

Hua Zhou,1,4 Sarfaraz Hasni,2 Howard A. Austin,3 James E. Balow,2 Ilas Alevizos,1 Gabor Illei.1 1NIDCR; 2NIAMS; 3NIDDK/NIH; 4Dept of Nephrology, The 1st Hospital, China Medical Univ, Shenyang, China.

Background: We recently reported that renal mir-150 expression correlated significantly with chronicity index (CI) in lupus nephritis (LN) patients and showed a causative role of mir-150 in promoting renal fibrogenesis. In this study, we examined the association of pre-treatment renal mir-150 levels and response to treatment (cyclophosphamide and corticosteroids) in LN patients.

Methods: 28 renal biopsies (formalin fixed paraffin embedded tissue blocks) obtained from patients with active proliferative LN before starting treatment with cyclophosphamide and corticosteroids. Based on their response to treatment at 24 months patients were classified as treatment effective (n=16) and ineffective group (n=12). Total RNAs were extracted from the biopsies and renal mir-150 expression was measured by TaqMan RT-PCR. The renal mir-150 level was expressed in relation to the expression of U68 (A:U48C1 – mir-150C1). Statistical analysis was done by Prism 5 software package.

Results: Consistent with our previous report in a different cohort of LN patients, renal mir-150 level positively correlated with CI (r=0.63, p<0.05) but not with activity index (r=0.12, p=0.49). Pre-treatment renal mir-150 level was significantly lower in treatment effective group compared to ineffective group (ACAT: 1.62 ± 0.22 vs. 2.72 ± 0.38, p=0.015, respectively). In a receiving operating characteristic analysis, renal mir-150 was an accurate predictor of treatment effectiveness in an area under the curve (AUC: 0.73, p<0.05).

Conclusion: Increased renal mir-150 levels are associated with an increased CI and poor response to immunosuppressive therapy in active proliferative LN patients. Pre-treatment levels of renal mir-150 have a good potential as biomarkers to predict the effectiveness of immunosuppressive treatment in LN, but its practical application needs further validation in larger cohort of patients. The potential use of mir-150 as a predictor of treatment response in proliferative lupus nephritis should be further assessed in noninvasive clinical samples such as urine and blood.

Funding: Other NIH Support - NIAMDS

SA-PO713

An Open Label Randomized Controlled Trial to Compare the Efficacy and Complication between Low Dose and High Dose Intravenous Cyclophosphamide for Induction of Remission in Thai Patients with Proliferative Lupus Nephritis

Ratana Chawasanuntaropo1, Boonyarit Cheunsuchon,2 Psal Parichatikanon,3 Kriengsak Vareesangthip,4 Chairat Shayakul.1 1Medicine, Siriraj Hosp.; 2Pathology, Siriraj Hosp., Mahidol U.

Background: Proliferative lupus nephritis (pLN) is a major organ involvement affecting the worse prognosis in SLE patient. The pathogenesis consists of genetic, environmental and immunology. The high incidence and poor prognosis are found in Asian, Afro-American [and Hispanic]. The cost and effective standard induction treatment, intravenous cyclophosphamide (IVCy) 0.75-1/gBSA (high dose, HDCCY) monthly for 6 doses provides the good response. The adverse effects are concerned: infection, gonadal toxicity and malignancy. The low dose intravenous cyclophosphamide (LDCCY) is effective in Caucasian with less complication. This study was to investigate the efficacy and complication of LDCCY comparison with HDCCY in Asian.

Methods: We randomly assigned 149 pLN patients to a HDCCY (G1) and LDCCY (G2) from Mar 2005 to Nov 2012. Median time to follow up was 40 months. Overall demographic data; age, blood pressure, onset, albumin, proteinuria, RPGN, activity and chronicity index were comparable. Median creatinine was 1.1 and 0.9 in G1 and G2, p=0.04. Induction treatment failure at 6 months was lower in G1, 24.7% compared to 34.3% in G2. The complete response at 12 months was significantly higher in G1, 76.5% compared to G2, 52.3%. Renal fibrosis was insignificantly low in G1, 35.5% and 45.2% in G2. 5 years renal and patient survival were comparable in G1 (90 and 83.2%) and G2 (89 and 86%). Regarding the complication including avascular necrosis, DM and infection were not different. There are 9 cases dead in each group and infection was a common cause. The gonadal toxicity was significantly higher in G1 and malignancy was found 2 cases in G1.

Conclusions: The low dose CYC could be the effective to induce response in pLN. However, the complete response at 12 months was significantly high in high dose CYC.

Funding: Government Support - Non-U.S.

SA-PO714

Latin American Lupus Nephritis Cohort: Maintenance Therapy with Mycophenolate Sodium

Vania Vazquez,1 Juan Jose Lopez,2 Bruno Jorge Lococo,3 Alicia Isabel Fayad,3 Marcelo Alejandro De Rosa,3 Vicente Altobelli.4 1Nefrologia, Hospital Simplemente Evita, Gonzalez Catan, Buenos Aires, Argentina; 2Nefrologia, Hospital Gobernador Centeno, La Pampa, Argentina; 3Nefrologia, Hospital Fernandez, Ciudad Autonoma de Buenos Aires, Buenos Aires, Argentina; 4Nefrologia, Hospital de Niños A. Gutierrez, Ciudad Autonoma de Buenos Aires, Buenos Aires, Argentina; 5Nefrologia, Centro Nefrologico Salta, Salta, Argentina.

Background: Mycophenolate has emerged as promising alternative in Lupus Nephritis(LN) treatment but its effects on Latin American(LA) population to maintain response induced by cyclophosphamide (CYC) has not been well defined.


Results: Induction:26% achieved CR,73.9% PR. Maintenance:all CR was sustained,50% PR switched to CR.End-study:63% achieved CR,36.9% showed PPR. PPR group showed 2 hypertension rate,Cr<1.2, moderate interstitial fibrosis(IF) and tubular atrophy(TA) vs CR group.Risk predictor variables of association to RRP: elevation of baseline sCr,moderate IF and TA.Most frequent AE:minor infections 36.6%,gastrointestinal intolerance 15.2%.

Funding: Other NIH Support - NIAID

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

792A
SA-PO715
Effects of an Intensified Treatment of Lymphocyte Depletion without Immunosuppressive Maintenance Therapy in Severe SLE over a Four Year Follow-Up
Dario Roccatello, Daniela Rossi, Carla Naretto, Simone Baldovino, Mirella Alpa, Savino Sciascia, Ilaria Salusolua, Vittorio Modena. Giovanni Bosco Hospital and Univ of Turin, Italy.

Background: B-lymphocytes (BL) play a critical role in Systemic Lupus Erythematosus (SLE). BL depletion therapy still remains an attractive option, despite the disappointing results of RCTs.

Methods: Twelve SLE patients [2 males, mean age 43.8 yrs (29-54)] with polyarthalgia and multiorgan involvement including class IV or V (ISN/RPS) glomerulonephritis (9 cases), skin lesions (7cases, with necrotizing ulcers in 3), polyneuropathy (7cases, with CNS involvement in 2), lymphoepithelioma (6) & polymyositis (5) have been treated with an intravenous BL depletion protocol for intolerance to conventional immunosuppressive therapy (6 cases) or as a front line therapy (6 cases). Protocol: Rituximab 375 mg/d on days 1,8,15,22, and 2more doses after one and two months, associated with 2 IV administrations of 10 mg/kg of cyclofosfamide and 3 infusions of methylprednisolone (15 mg/kg) followed by oral prednisone (0.8 mg/die, rapidly tapered to 5 mg/day in 10 weeks), without further immunosuppressive maintenance therapy.

Results: This protocol obtained a complete depletion of CD20+ BL for 12-18 months. Patients had been followed-up for 48.9 (25-93) months. ESR (baseline mean value: 54.2; 3 months: 27.5; end of follow-up: 17) and proteinuria (baseline: 4.9 g/24 hours; 3 months:0.97; end of follow-up: 0.22) significantly declined (p<0.05), while C4 values (baseline 11 mg/dl) significantly increased (p=0.05) after 3 months (22 mg/dl) and at the end of the follow-up (20 mg/dl). 3 patients relapsed after 36.41 and 72months respectively. They showed again a complete remission after retreatment over 13-48 months of observation.

Conclusions: These data confirm the opportunity to reconsider the regimens of BL depletion in the treatment of the most severe forms of SLE despite the disappointing results of RCTs.

SA-PO716
Oral Sirolimus Was More Effective Than Intravenous Cyclophosphamide in Patients with Proliferative Lupus Nephritis
Jian Hui Yang, Renal Div, Zhejiang Provincial People’s Hospital.

Background: To evaluate the efficacy and safety of sirolimus on refractory lupus nephritis.

Methods: Forty-eight patients with proliferative lupus nephritis who failed to response to prednisone, azathioprine and intravenous pulse cyclophosphamide were randomized to sirolimus group (SRL) or intravenous pulse cyclophosphamide (CTX). The patients’ ages, gender, hematuria, proteinuria and other clinco-pathological features were of no marked differences between two groups. The former group were administrated with 0.3–0.5mg/kg/day oral prednisone and 2 mg/kg sirolimus (NCP GENETECH BIOTECHNOLOGY CO. LTD) for 6 to 12 months. Sirolimus doses were adjusted so that the serum sirolimus concentration could be maintained between 4 to 10 ng/ml. The later group were given same dose of oral prednisone and intravenous CTX (0.6g/bimonthly).

Results: Three months after initiation of these therapy, the patients’ SLEDAI, DNA antibody, and 2 mg/d sirolimus (NCPC GENETECH BIOTECHNOLOGY CO. LTD) for 6 to 12 months.

Conclusions: Low dose of oral SRL was more effective and safer than CTX in patients with intestinal nephropathy or hypercholesterolemia in lupus nephritis was not the contradictions of sirolimus.

SA-PO717
Diffusion Weighted Imaging and Blood Oxygen Level-Dependent MR Imaging of Kidneys in Patients with Lupus Nephritis
Xiao Li, Nan Chen. Dept of Nephrology, Ruijin Hospital, Shanghai Jiao Tong Univ School of Medicine, Shanghai, China.

Background: To investigate the role of diffusion weighted imaging (DWI) and blood oxygen level-dependent (BOLD) magnetic resonance (MR) imaging in the assessment of renal involvement and pathological changes in patients with lupus nephritis (LN).

Methods: Thirty-eight patients with LN (34 biopsied) and 16 healthy controls underwent coronal echo-planar DWI and BOLD MR imaging of the kidneys with a single breath-hold time of 16s. The apparent diffusion coefficient (ADC) and R2* value of the kidneys was calculated with high b values (b=500 s/mm2). Image analysis was performed on a GE workstation (Sun Microsystems, ADW4.2) with FuncTool 2 image analysis software. The relation between the renal injury variables and the ADCs or R2* values were evaluated.

Results: The mean ADC values of kidneys in patients with LN were 2.41±0.25 x10–3 mm2/s, the mean R2* values of the renal cortex and medulla were 10.73±sec/1.74 and 13.48/1.36 respectively, which were all significantly lower than those in volunteers (p=0.048, p=0.048 and p=0.008, respectively). In the patients with LN, the mean ADC values were correlated with eGFR (r=0.558, p<0.05). There was a negative correlation between the ADC values of the right kidneys and pathological chronic indexes (r=-0.493, p<0.05). Moreover, the R2* values of the renal medulla were negatively correlated with 24 hours proteinuria (r=-0.344, p<0.05), the degree of tubulointerstitial lesions (r=-0.324, p<0.05).

Among 10 patients who repeated MR scan after treatment for 9 to 12 months, 7 patients got complete remission (CR) and 3 had no response (NR). The ADC and R2* values of kidneys were significantly higher than before in CR patients (all p<0.05), while the ADC and R2* values being lower than before in NR patients with no statistical significance (P>0.05).

Conclusions: The functional MR imaging showed lower ADC values and R2* values of renal cortex and medulla in patients with LN than normal controls, which were associated with renal function, proteinuria and pathological changes. DWI and BOLD MR imaging may be used to non-invasively monitor disease activity, evaluate therapeutics efficacy in lupus nephritis.

Funding: Government Support - Non-U.S.

SA-PO718
Severely Low 25-Hydroxyvitamin D Levels Are Associated with Worse Renal Outcomes in Proliferative Lupus Nephritis
Alcine Pires Gama, Luciana Loureiro Nardotto, Lectícia Jorge, Cristiane Bitencourt Dias, Rui Toledo Barros, Viktoria Woronik. Nephrology, Univ of Sao Paulo, Sao Paulo, Brazil.

Background: The associations between 25-hydroxyvitamin D(25OHD) levels and lupus nephritis(LN) are not clearly known. The aim of this study was to evaluate if very low serum levels of 25OHD in proliferative LN patients are associated with worse renal outcome.

Methods: Medical records from 2009 to 2012 of 72 subjects with biopsy-proven proliferative LN were retrospectively analyzed. Severe 25OHD deficiency was defined as <10ng/ml. The study’s endpoints were either progression of chronic kidney disease(CKD) - defined as a clearance reduction greater than 5ml/min/y - or progression to end-stage renal disease(ESRD).

Results: Median levels of 25OHD were low at baseline(16,5±7,9ng/ml). Clinical features, follow-up times, biopsy features and renal outcomes are shown on table 1.

<table>
<thead>
<tr>
<th>25OHD(ng/ml)</th>
<th>Clinical Features</th>
<th>Renal Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (≤10)</td>
<td>High (&gt;10)</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>16,5±7,9</td>
<td>27,5±14</td>
</tr>
<tr>
<td>Baseline</td>
<td>9±0,5</td>
<td>13,8±9,2</td>
</tr>
<tr>
<td>Activity</td>
<td>54±4,5</td>
<td>16,5±9,1</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>69±0,8</td>
<td>8,4±0,5</td>
</tr>
<tr>
<td>Hb</td>
<td>9,8±0,2</td>
<td>9,2±0,3</td>
</tr>
<tr>
<td>CR (10%)</td>
<td>25,7±5</td>
<td>7,6±5,5</td>
</tr>
<tr>
<td>CKD (%)</td>
<td>33,7±3,5</td>
<td>18,5±1,5</td>
</tr>
<tr>
<td>Follow-up/y</td>
<td>1,6±0,1</td>
<td>1,7±0,5</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>25,0±5</td>
<td>24,5±3</td>
</tr>
<tr>
<td>Activity</td>
<td>54±4,5</td>
<td>50,5±6,4</td>
</tr>
<tr>
<td>CKD (%)</td>
<td>33,7±3,5</td>
<td>18,5±1,5</td>
</tr>
<tr>
<td>Follow-up/y</td>
<td>1,6±0,1</td>
<td>1,7±0,5</td>
</tr>
</tbody>
</table>

Results: Among 10 patients who repeated MR scan after treatment for 9 to 12 months, 7 patients got complete remission (CR) and 3 had no response (NR). The ADC and R2* values of kidneys were significantly higher than before in CR patients (all p<0.05), while the ADC and R2* values being lower than before in NR patients with no statistical significance (P>0.05).

Conclusions: The functional MR imaging showed lower ADC values and R2* values of renal cortex and medulla in patients with LN than normal controls, which were associated with renal function, proteinuria and pathological changes. DWI and BOLD MR imaging may be used to non-invasively monitor disease activity, evaluate therapeutics efficacy in lupus nephritis.

Funding: Government Support - Non-U.S.

SA-PO719
Persistent Proteinuria as a Major Predictor of Renal Outcome in Lupus Nephritis Class V (LNV) Alcine Pires Gama, Luciana Loureiro Nardotto, Lectícia Jorge, Cristiane Bitencourt Dias, Rui Toledo Barros, Viktoria Woronik. Nephrology, Univ of Sao Paulo, Sao Paulo, Brazil.

Background: Natural history studies of LNV suggest a relatively low rate of progression to ESRD. The aim of this study was to review the prognosis and the predictors of renal outcome in LNV.

Methods: The medical records of patients (n=97) with biopsy-proven LN, WHO class V without any past history of proliferative lupus nephritis were reviewed retrospectively. The study endpoint was ESRD.

Results: Among 25OHD levels at baseline were associated with worse renal outcomes (either progression of CKD or progression to ESRD) in biopsy-proven proliferative LN patients, even though this group presented better biopsy features at baseline.
SA-PO720


Background: Renal biopsy is required to confirm the diagnosis of lupus nephritis (LN) according to the current ACR guidelines (Arthritis Care & Research 2012; 64: 797–808), in case of unexplained increasing serum creatinine level, proteinuria > 1.0 g/day or combinations of the following: a) proteinuria > 0.5 g/day plus hematuria, b) proteinuria > 0.5 g/day plus cellular casts.

The goal of this pilot study was to determine the value of renal biopsy in lupus patients presenting with glomerular hematuria and proteinuria below 500 mg/day with normal renal function.

Methods: Renal biopsies from 38 lupus patients with glomerular hematuria and proteinuria below 500 mg/day were evaluated by LM and immunofluorescence microscopy and classified according to the ISN-RPS 2003. No patients with renal failure or previous renal biopsy were included. Glomerular hematuria was considered at the presence of 3 or more dysmorphic RBCs per high-power field plus acanthocytes more than 5% and RBC casts. The urinary sediment corresponding to every patient was observed by nephrologists.

Results: The mean patient age was 35.5 years old (range 19 to 65) years. Male/female= 8/30. The 24hr proteinuria was negative in 2 pts. (5%), proteinuria trace in 16 pts. (42%), >1 g/day in 12 pts. (32%), >2 g/day in 7 pts. (18%), >3 g/day in 3 pts. (8%) and >5 g/day in 2 pts. (5%). The mean age in MMF group was 22.4±2.5yrs, AZA group 22.9±3.1yrs. There was one male in each of the treatment groups.

Conclusions: The present study shows that Class III, IV; V are present in a substantial proportion of lupus patients with mild clinical manifestations of renal disease and it may suggest a new potential indication for renal biopsy. In addition, since these histological classes of LN are associated with poor prognosis and require an early diagnostic and appropriate treatment, we think the data presented in this pilot study acquire importance.

Funding: Government Support - Non-U.S.

SA-PO721


Background: Very little is known on long term outcomes of patients treated with lupus nephritis with MMF as compared to induction with CyP. We have used MMF for induction and maintenance treatment from 1999. We report the outcomes of patients treated for >5yrs.

Methods: Retrospective analysis of all adult patients with biopsy proven LN between January 1999 and March 2013 and on MMF both for induction and/or maintenance therapy for >5yrs. A 64,348 patients were identified from our lupus biopsy database. Renal remission = normal serum creatinine or no worse than 20% above baseline, and urine PCR <50mg/mmol.

Results: Median follow-up 80.87mths (72.01-102.90). 32(50.8%) patients received CyP induction. The rest received rituximab+ MMF(10) or MMF alone(11) as first induction therapy. Most frequent additional maintenance drugs were prednisolone + hydroxychloroquine. Outcomes at latest follow-up: Maintenance prednisone treatment was stopped in 38 patients(67.9%). No patients died(7.5%) required RRT(0 of those whose urine PCR was<100 at the time of stopping prednisone). 46.5% had sustained doubling of serum creatinine (SDSC), remission was achieved in 82% and 58% had a relapse. Serum creatinine improved from 1.08±0.7 to 1.21±0.3 mg/dL respectively. After initiation of prednisone and MMF, IgG declined significantly from 1444.0±600.5 mg/dL to 1215.4±649.7 mg/dL, 914.5±362.4 mg/dL and 1034.6±452.5 mg/dL respectively. After initiation of prednisone and MMF, IgG declined significantly after 2 weeks, reaching a nadir at 8-week, then followed by gradual normalization.

Conclusions: Treatment with prednisone and MMF does not lead to clinically important IgG depression and excessive infection.

Funding: None.

SA-PO722

The Effect of Corticosteroids and Mycophenolate Mofetil Treatment on Serum Immunoglobulin G Levels in Lupus Nephritis Patients. Desmond Y.H. Yang, Susan Yang, Gary Chan, Daniel Tako Mao Chan. Medicine, The Univ of Hong Kong, Hong Kong, Hong Kong.

Background: Depressed serum immunoglobulin G (IgG) is associated with heightened infective risk. The effect of corticosteroids and mycophenolate mofetil (MMF) on circulating IgG levels in lupus nephritis (LN) patients remains unclear.

Methods: Active class III/IV-V LN patients who received prednisolone (0.8mg/kg/d) and MMF (1g bd) as induction treatment were included and their longitudinal IgG profiles analyzed.

Results: 46 patients were included. Prior to treatment, 34 (73.9%) patients (Group I) had normal or elevated IgG (1444.0±600.5 mg/dL) while 12 (26.1%) (Group II) had IgG below the lower limit of normal (567.8±160.9 mg/dL). The mean IgG at baseline, 6- and 12-month after treatment were 1215.4±649.7 mg/dL, 914.5±362.4 mg/dL and 1034.6±452.5 mg/dL respectively. After initiation of prednisone and MMF, IgG declined significantly after 2 weeks, reaching a nadir at 8-week, then followed by gradual normalization.

Figure 1.

SA-PO723

Maintenance Therapy with Mycophenolate versus Azathioprine in Lupus Nephritis. Pavan Kumar Rao Navya.1 Nephrology, Andhra Medical College, Vishakapatnam, Andhra Pradesh, India; 2Nephrology, Andhra Medical College, Vishakapatnam, Andhra Pradesh, India.

Background: Lupus nephritis is one of the commonest renal lesions affecting young women contributing to considerable morbidity and mortality. It requires long term treatment to preserve renal function. We tried to compare Mycophenolate mofetil, Azathioprine and Cyclophosphamide in Maintenance therapy of Lupus nephritis.

Methods: All biopsy proven Class 3 & 4 Lupus Nephritis patients in a Tertiary care centre in South East India were followed from May 2011 to May 2013. After initial induction with cyclophosphamide for 6 months, maintenance therapy was started with either Mycophenolate(MMF) or Azathioprine(AZA) or quarterly Cyclophosphamide pulses(CYP). The decision to opt for any of the treatment modalities was given to the patient/attender with prior counseling regarding fertility and malignancy risk. We had 52 patients during the period, 4 patients were lost to follow up. Of the 48 remaining, 19 received MMF, 22 AZA and 7 CYP.

Results: Among 48 patients, the mean age in MMF group was 22.4±2.5yrs, AZA group 24.5±3.4 yrs and in CYP group 22.9±3.1 yrs. There was one male in each of the treatment...
groups. At the start of the Maintenance therapy all the patients had attained either complete or partial remission. At the end of the study period 13 patients in the MMF group, 18 in AZA group and 5 in CFM group continued to be in remission. Four(21.1%) in the MMF group, 2(9.1%) in the AZA group and 1(4.3%) in the CFM group had died during the study period. 2 each in the MMF and AZA group and 1 in the CFM group progressed to ESRD during the study period. The commonest cause of death was infection due to pneumonia in 4 and cellulitis leg in 2, leading in septicemia. The incidence of flare either nephritic or nephrotic was 4 (21.1%) in the MMF group, 4 (18.8%) in the AZA group and none in the CFM group, all of which responded to treatment.

**Conclusions:** We found that in our population the remission was equally maintained in all treatment groups. The mortality rates were higher in MMF group compared to AZA and CFM groups. The incidence of flares was similar in all the groups. Although all modalities were efficient we need larger studies to ascertain higher infection rates in CFM group in our area.

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

## SA-PO724

**Lupus Podocytopathy: Clinical Characteristics, Pathology, and Therapy**

**Jason Coulb, Jose E. Navarrete.** *Nephrology, Emory Univ School of Medicine, Atlanta, GA.*

**Background:** Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) in systemic lupus erythematosus (SLE) patients has been described as the lupus podocytopathy. Lupus podocytopathy pathology is characterized by diffuse foot process effacement with a lack of significant immune complexes.

**Methods:** We are presenting nine cases in our clinical practice with varying clinical characteristics, pathology, and response to therapy.

**Results:** At the time of kidney biopsy four patients were new diagnosis, and in five patients the average duration of known lupus was 7.1 years. At time of presentation the average creatinine was 3.26 mg/dL, 7.8 grams of urine protein per day, and serum albumin of 1.5 g/dL. All patients presented with hematuria. Renal pathology showed significant diffuse foot process effacement in all cases. Two patients with FSGS only, one patient with MCD only, one patient with minimal mesangial lupus nephritis with MCD, three patients with mild mesangio proliferative lupus nephritis with MCD, and two patients with mild mesangio proliferative lupus nephritis with FSGS. Seven of nine patients were treated primarily with corticosteroids and other therapies included calcineurin inhibitors, cyclophosphamide, and plasmapheresis. The patients were followed for an average of 3.4 years, with three patients requiring dialysis and only one required dialysis indefinitely.

**Conclusions:** We analyzed nine cases with varying presentations of the same disorder in our clinical practice. There were no correlation between severity of renal dysfunction and laboratory findings such as double stranded DNA elevation, decrease levels of C3/C4, and degree of proteinuria. No correlation for pathological changes such as presence of tubular ectatic inclusion bodies or degree of interstitial fibrosis and atrophy, and amount of mesangial proliferation. The most severe renal dysfunction at time of presentation (creatinine > 5 mg/dL) was seen in the two patients with collapsing FSGS features. Our goal is to a complete analysis of all the cases of lupus podocytopathy in our large academic hospital system.

## SA-PO725

**Risk Factors to Not Achieve Complete Remission in Mexican Patients with Lupus Nephritis**

**Arreola Guerra Jose Manuel, Juan M. Mejia-Vilet, Rodrigo J. Rosado, Norma D. Uribe-Uribe, Luis E. Morales-Buenrostro.** *Nephrology & Pathology, National Institute of Medical Sciences and Nutrition S.Z, Mexico City, DF, Mexico.*

**Background:** The induction therapy in Lupus Nephritis (LN) has been changed. The aim of this study is to compare the efficacy (complete remission) of different options of induction therapy in incipient patients with LN.

**Methods:** Retrospective cohort study of all patients with biopsy proven LN in the period between mar/08 and Feb/13. We included 185 patients with at least 3 months of follow-up. We evaluated the remission status in the month 3, 6 and 12. Time to complete remission (CR) was evaluated with the univariate and multivariate Cox regression analysis.

**Results:** Seventy-six patients received cyclophosphamide (CFM), Mycophenolate Mofetil (MMF) and 43 Azathioprine (AZA). Univariate and multivariate analysis is shown in table 1. In the univariate analysis, the induction therapy with CFM was significantly less effective than MMF or AZA to achieve CR (p<0.029). In the multivariable analysis less effective than MMF or AZA to achieve CR (p<0.029). In the multivariable analysis.

**Conclusions:** In Mexican patients with LN we don’t find differences in the outcomes of the different groups of induction. Only the SLEDAI index was significantly related with CR. This represent the clinical practice of our center, were the most aggressive cases were biassed to receive CFM.

## SA-PO726

**Lupus Nephritis as the Main Histopathological Diagnosis in a Renal Biopsy Registry: Analysis of a Local Renal Biopsy Registry in Mexico**

**Juan M. Mejia-Vilet, Arreola Guerra Jose Manuel, Rodrigo J. Rosado, Norma D. Uribe-Uribe, Luis E. Morales-Buenrostro.** *Nephrology and Pathology Depts, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran, Mexico City, Mexico.*

**Background:** Renal biopsy (RB) results have been advocated worldwide to define the patterns of distribution of renal diseases.

**Methods:** Retrospective study of our institutional RBs registry, including 710 consecutively biopsied patients analyzed by the same pathologist, from 04/2008-04/2013.

**Results:** 710 native RBs were performed in 689 adult patients. Secondary glomerulopathies (SGN) comprise 416 (58.6%), being lupus nephritis (LN) responsible for 372 cases (96.3%) of SGN, followed by diabetic nephropathy (9.8%), amyloidosis (3.8%), hereditary nephropathies (2.9%). Primary glomerulopathies (PGN) comprise 181 cases (25.5%), with focal and segmental glomerulosclerosis (FSGS) in 34.8%, followed by membranous nephropathy (27.1%), IgAN (16.6%), minimal change disease (7%), mesangio proliferative GN (4.9%), membranoproliferative GN (3.9%).

Vascular pathologies comprised 9.3% (pauciimmune GN 90.9%) and tubulointerstitial pathologies 3.9% of the total.

## SA-PO727

**Clinico-pathologic Features of Lupus Nephritis in African Americans and Hispanics in an Inner-City Safety Net Hospital**

**Alberto M. Osei,** Richard A. Nunez Lopez,‡ Matilda Malm,§ Mark A. Kraus,‡ Peter D. Hart,› John H. Stroger Jr. Hospital of Cook County; Rush Univ Medical Center, Chicago.

**Background:** Systemic lupus erythematosus disproportionately affects women and ethnic minorities in the United States with renal involvement in nearly one half. To better understand lupus nephritis among African Americans and Hispanics, we reviewed the clinical and histopathologic features at the time of renal biopsy.

**Methods:** We retrospectively reviewed all renal biopsies from 2003 to 2012 at our institution to define patients with lupus nephritis. Cases were divided based on both the ISN/RPS classification and ethnicity. Tubulointerstitial involvement was classified as mild, moderate or severe if the corresponding percentages were less than 25, 25 to 50 or more than 50 respectively.

**Results:** Of 162 biopsies with lupus nephritis, 65% were performed in African Americans and 15% in Hispanics and, in each ethnicity the majority of patients were females (77% vs. males 23%). Mean age at the time of the biopsy was higher in African Americans compared to Hispanics (36.11 vs.33.10years, P<0.05). Initial serum creatinine was also higher in African Americans than Hispanics (2.21 vs 1.81 mg/dL, P<0.05). Degree of proteinuria, hypocomplementemia, and ANA panel did not differ.

In African Americans, ISN/RPS class V was the most frequent lesion (26%), then class IV (20%), IV + V (14%) and III (11%). In Hispanics class V was also the most frequent (25%), followed by class IV (23%), III (18%) and V + III (18%). The serum creatinine did differ between class V and class IV (1.41 vs. 2.82 mg/dl, p=0.05) and among tertials of tubulointerstitial fibrosis (severe 3.31±1.6; moderate 2.31±1.7; and mild 1.41±1.6 mg/dl p<0.001). No such differences was noted for the degree of proteinuria. Also, lower levels of bicarbonate predicted severity of tubulointerstitial fibrosis (mild 24.6±2.9; severe 22.5±3.3, p<0.001) and the same was true for hemoglobin (mild 10.61±1.6; severe 9.81±1.5 g/dl p<0.05).

**Conclusions:** African Americans with lupus nephritis compared to Hispanics were older, had higher initial serum creatinine and more class IV + V disease. Further studies are needed to understand the impact of these differences.

## SA-PO728

**African Americans with Mixed Lupus Nephritis Have Better Prognosis Than Pure Proliferative Glomerulonephritis at a Safety Net Hospital**

**Jane Vennik,** Richard A. Nunez Lopez, Mark A. Kraus, Peter D. Hart, Div of Nephrology, John Stroger Hospital of Cook County, Chicago, IL; Internal Medicine, Rush Univ, Chicago, IL.

**Background:** It has been described that adults with mixed Lupus Nephritis (combined membranous with focal or diffuse proliferative GN; MLN) have a worse clinical course than those with either segmental or diffuse proliferative lupus nephritis (PLN). Little information

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

Underline represents presenting author/disclosure.
is available regarding the outcome of African Americans with MLN. By reviewing our biopsy registry, we sought to evaluate if African Americans presenting with MLN had a different outcome than patients with PLN.

Methods: We retrospectively examined medical records of the patients biopsied at our institution between January 01, 2001 and May 30, 2012 and diagnosed with MLN or PLN based on either WHO or ISN/RPS classification. In patients who underwent multiple biopsies, only data related to the initial biopsy were included.

Results: Of the 769 biopsies performed, 141 had LN. 84 of these were identified as initial biopsies with MLN or PLN. 51 (60%) were of African American patients with 22 classified as MLN and 29 as PLN. The incidence of crescents did not differ significantly between the MLN (41%; N=9) and PLN (45%; N=13) groups (p=0.12). There was no significant difference among serum creatinine, degree of interstitial fibrosis and tubular atrophy, C3 and proteinuria at the time of biopsy.

All patients were induced with combination of high dose steroids and cytotoxic medications, with majority receiving cyclophosphamide and prednisone. Most of the patients were maintained on low dose prednisone and either Mycophenolate mofetil or Azathioprine.

A significant reduction in serum creatinine was noted in the MLN group at 1 year follow up (1.3±0.6 mg/dL, N=13) compared to the time of biopsy (2.4±2.4 mg/dL, N=22) (p=0.05). Creatinine remained stable in the PLN group (2.8±0.7 mg/dL to 2.8±0.7 mg/dL; n=20; p=0.9). Serum creatinine was significantly lower in MLN vs PLN at 1 year follow up (p=0.05).

Conclusions: African American patients presenting with mixed lupus nephritis (MLN) have a better serum creatinine at one year follow up than those with proliferative lupus nephritis (PLN).

SA-PO729
Diagnostic Significance Determining the Level of Urinary Neutrophil Gelatinase Associated Lipocalin in Patients with Lupus Nephritis Violeta Rabrenovic,1 Dragan Jovanovic,1 Milan M. Radovic.2
1Dept of Nephrology, Military Medical Academy, Belgrade, Serbia; 2Clinical Center of Serbia, Belgrade, Serbia.

Background: The aim of the study was to monitor and compare the parameters of activity of lupus nephritis, between the examined and controlled groups of 20 pts each, at baseline, and 2 and 4 months after the start of treatment.

Methods: The prospective study included a group of 40 patients who were homogeneous in terms of demographic data (gender, age, body weight, type of lupus nephritis and therapeutic modality) in which 20 were associated with lupus nephritis in remission, and 20 patients with active disease. We monitored and compared the parameters of the two groups in 3 visits over 2 months. : Proteinuria, the ratio of urinary protein and creatinine Up/Cr, SLEDAI / r score, complement C3, C4, ANA, dsDNA antibodies, Urinary neutrophil gelatinase associated lipocalin - uNGAL. All patients had creatinine clearance >120 ml / min. U NGAL was determined by CMA immunochromatographic test (commercial kits of Abbott Diagnostic on ARCHITECT ™ 8000 SR).

Results: A statistically significant difference (p<0.001) was observed for the comparison of anti dsDNA antibodies, proteinuria, Ur/Cre, SLEDAI index / r scores, uNGAL between these two groups of rounds. The UNGAL was significantly correlated with parameters of active disease p<0.001, the values of the area under the ROC curve (AUC) the maximum sensitivity of 95% sensitivity and 100% specificity expressed in u NGAL. The coordinates of the ROC curve for the u NGAL, limit: “cut off” was 52.95 ng / ml. With that value, all patients with uNGAL more than 52.95 ng / ml, should be in the group with active disease, and none in the group with lupus nephritis in remission.

Conclusions: The results show the importance in the diagnosis of disease activity, and in confirmation of remission of lupus nephritis, which can result in application of more appropriate therapeutic modality and individual approach to treatment. This study suggests that the determination of uNGAL in patients with lupus nephritis in daily clinical practice can contribute to the optimal effect of treatment.

SA-PO730
Vitamin D Is Negatively Correlated to Urinary MCP1 in Lupus Nephritis Patients
Aline Lázara Resende, Cristiane Bitencourt Dias, Fabiana Graciolli, Luciene dos Reis, Vanda Jorgetti, Viktoria Woronik. Sao Paulo Univ, Sao Paulo, Brazil.

Background: The association between vitamin D levels and SLE disease activity remains controversial. Urinary levels of Monocyte chemotactant protein-1 (uMCP1) are recognized as a specific biomarker of Lupus Nephritis (LN) activity. The aim of this study was to characterize the vitamin D status of newly diagnosed LN patients and its relationship to uMCP1 levels.

Methods: We included pre-menopausal female patients with ≤ 2 months of diagnosed LN attended from 2010 to 2012. The levels of uMCP1 were determined by specific ELISA (R&D Systems) and standardized to urine creatinine (Cr). 25-hydroxyvitamin D, 25(OH)D [M] were measured by chemiluminescence assay. Age-matched healthy female control’s samples were collected at the end of winter. Statistical analysis were performed by Mann–Whitney test, Spearman correlation coefficient and linear regression models.

Results: 34 LN patients presented a mean age of 29.5±10 years and were on glucocorticoid use for 34±12 days. Proxerative LN was observed in 86.6% of cases, with a mean proteinuria of 4.7±2.9 g/day and an estimated GFR of 37 (31-87) ml/min/1.73m². All SLE patients presented vitamin D insufficiency (9.9±4.4 ng/ml, range 4-20). Clinical and biochemical features of LN patients and controls are summarized below.

SA-PO731
Proliferative Lupus Nephritis-NIH Regimen versus Tacrolimus and Mycophenolate Combination

Background: Is multitarget therapy superior to NIH regimen?Future lies in individualizing therapy.


Results: Primary outcomes:CR&PR(p=0.21 and 0.33 respectively),non response(p=0.33) and mortality(p=1.00)were similar.Secondary outcomes:Arm I fared better over arm II with respect to mean change in serum creatinine n=0.017,eGFR(p=0.042),C3 (p=0.014), and histological activity index HA(p=0.036). The episodes of LRTI & UTI were higher in the arm I(p=0.019 & p=0.028 respectively).Steroid toxicity was higher in arm II p=0.001. GI intolerance was higher in arm II (p=0.046). Subgroup analysis: In arm I: HI of >/=15 predicted poor outcome( p=0.03) & in arm II a LDAI of >/=9 predicted poor outcome(p= 0.055).12 out of 14 patients in the arm I had a LDAI of >/=9. Dialysis dependence beyond 1 month of adequate immunosuppression predicted non responsiveness to therapy in both arms.3 of the 4 deaths in the arm II were amongst non dialysis requiring patients and 1 of them died after attaining PR,where as all 4 deaths in the arm I were among dialysis dependent patients.

Conclusions: Multitarget regimen should be reserved for patients with stable renal function, LDAI >/=9 and having contraindication to CYC.CYC arm had greater improvement in the C3 levels and HAI. HAI of >/=15 predicts poor outcome with CYC. Dialysis dependence after 1 month of either regimen should prompt one to withdraw/swich immunosuppression.Infection episodes & steroid toxicity were more in NIH arm but early fatal infection episodes in arm II raises concern over its safety.Larger trials are needed to validate the utility of LDAI or HAI in individualizing therapy,predicting outcomes & guiding when to choose alternatives at the outset.

SA-PO732
Managing Lupus Nephritis with Cyclophosphamide or Mycophenolate Mofetil in a Large Nephrology Centre
Hannah M.M. Burton, Tracey M.E. Salter, Rebecca Suckling, David Makanjuola, Fiona E. Harris. St. Helier Hospital, United Kingdom.

Background: Since the NIH trials of the 1980s cyclophosphamide has been the mainstay of induction therapy for lupus nephritis (LN). The Euro-Lupus Nephritis Trial (ELNT) then demonstrated the benefits of a low-dose cyclophosphamide regime. In 2012 a Cochrane review concluded that mycophenolate mofetil (MMF) was as effective as cyclophosphamide in inducing remission. We appraised our management of LN over two decades to ascertain if our protocol could be optimised.

Methods: We present our single centre observational data. We retrospectively analysed the records of patients presenting with LN from 1992-2012. Response to induction therapy was assessed at 1 year, with complete remission defined as serum creatinine ≥Cr <124μmol/L and urine protein:creatinine ratio (UPCR) ≤33g/mol, and partial remission defined as ≥50% increase in sCr from baseline and ≥50% reduction in UPCR to ≤150g/mol.

Patients were divided into 2 groups of 29 with 2% of them died after attaining PR,while as all 4 deaths in the arm I were among dialysis dependent patients.

Primary outcomes:CR≥25% increase in sCr from baseline and 50% reduction in UPCR to ≤150g/mol. GI intolerance was higher in arm II (p=0.046). Subgroup analysis: In arm I: HI of >/=15 predicted poor outcome( p=0.03) & in arm II a LDAI of >/=9 predicted poor outcome(p= 0.055).12 out of 14 patients in the arm I had a LDAI of >/=9. Dialysis dependence beyond 1 month of adequate immunosuppression predicted non responsiveness to therapy in both arms.3 of the 4 deaths in the arm II were amongst non dialysis requiring patients and 1 of them died after attaining PR.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Conclusions: The mean serum creatinine was 112.6± 38.9, and isotopic GFR measurements con-
mit with both furosemide and immunosuppressive treatment with reducing course corticosteroids and mycophenolate in
biopsies were obtained in 9 patients; all showed a diffuse diffuse lymphoplasmocellular of tubular proteinuria, the mean protein creatinine ratio was 46.3± 62.5 mg/mmol. Renal
No patients had evidence of Fanconi syndrome, no patients had glycosuria or evidence impaired renal excretory function in all patients with a mean GFR of 42.5 ± 9.02 ml/min).

SA-PO733
Renal Involvement in Sjögren Syndrome. Maryam Khesraei,1 Chris Laing,2 Stephen B. Walsh,3
1Royal Free & Univ College London Centre for Nephrology; 2Royal Free & Univ College London Centre for Nephrology, 3Royal Free & Univ College London Centre for Nephrology.

Background: Sjögren syndrome (SS) is an autoimmune disorder that has been estimated to affect as much as 1-2% of the adult female population. Epithelial cells are targets for a cell-mediated autoimmune response, in the lacrimal and salivary glands, as well as the renal tubulointerstitial compartment.

The involvement in SS has been estimated at approximately 30%. The renal manifestation of SS is classically of distal renal tubular acidosis (dRTA), decreased renal excretory function.

Methods: We characterised 13 patients with renal SS who presented to the UCL Centre for Nephrology.

Results: Of the 13 patients, all were female, the mean age was (55.6 ± 12.6 years).

Immunologically, All were positive for extractable nuclear antigens: 12 were Ro (SSA) positive, 9 were La (SSB) positive, 5 had hypocomplementemia (low C4), 1 had ANA, 7 had hypergammaglobulinemia (mean IGF 20.4± 8). All had urinary acidification (UA) tests with both fuurosemide and fludrocortisone and then oral ammonium chloride. The mean nadir urinary pH was 5.58 ± 0.47; all individual UA tests confirmed the presence of dRTA. The mean serum creatinine was 112.6± 38.9, and isotopic GFR measurements confirmed impaired renal excretory function in all patients with a mean GFR of 42.5 ± 9.02 ml/min.

No patients had evidence of Fanconi syndrome, no patients had glycosuria or evidence of tubular proteinuria, the mean protein creatinine ratio was 46.3± 62.5 mg/mmol. Renal biopsies were obtained in 9 patients; all showed a diffuse diffuse lymphoplasmocellular infiltrate of mononuclear cells with variable tubular atrophy. 8 patients were started on immunosuppressive treatment with reducing course corticosteroids and mycophenolate mofetil (mean dose 937.5 mg daily). 8 patients also required supportive treatment with sodium bicarbonate (mean dose 562.5 g daily) and potassium (mean dose 57.6 mmol/day).

Conclusions: dRTA in renal SS is common, and this is usually due to a pronounced decrease in tubular function.

SA-PO734
1Physiology and Biophysics, 2Medicine, 3Radiology, Univ of Mississippi Medical Center.

Background: Renal angioplasty and stenting (PTRAS) improves renal function in only 30% of patients with renovascular disease (RVD), underscoring the need for more effective therapeutic strategies. Because endothelin (ET)-A receptor blockade attenuates renal dysfunction and cardiovascular risk in chronic renal disease, we hypothesized that PTRAS followed by ET-A receptor blocker therapy would improve the renal outcomes in RVD. In addition, since little is known about the role of ET-B receptors in RVD, we performed for cohort comparison (p<.05 was statistically significant) by STATA.

Methods: Unilateral RVD was induced in 12 pigs by renal artery stenosis. After 6 weeks, single-kidney blood flow (RBF) and filtration (GF) was quantified in vivo in the stenotic kidney using multi-detector computed tomography (MDCT). Then, all pigs underwent PTRAS and blindly randomized in controls (RVD+PTRAS), and treated with ET-A blockers (Atrasentan, RVD+PTRAS+A) or with ET-A and ET-B blockers (RVD+PTRAS+AB, n=4 each). ET blockers/placebo were administered daily for 4 weeks and then in vivo MDCT studies repeated at 10 weeks.

Results: PTRAS relieved renal artery stenosis in all pigs and improved RBF and GF. However, improvements were greater in RVD+PTRAS+A at 10 weeks, leading to almost a full recovery of renal function. In contrast, combined ET-A/B blocker therapy abolished the beneficial effects of both PTRAS and PTRAS+A.

Conclusions: These results show that blockade of the ET-B receptors diminished the therapeutic effects of both PTRAS and ET-A blockade on RBF and GF, implying RVD insensitivity for a functional ET-1/ET-B pathway in the recovery of renal function in RVD. Furthermore, our study supports the potential therapeutic use of ET-A blockers to significantly improve the outcomes of PTRAS in RVD.

Funding: Other NII Support - NIH-NHLBI, Pharmaceutical Company Support - Unrestricted grant from Abbvie

SA-PO735
Oxidative Stress: The Role in the Pathogenesis of Cardiorenal Syndrome. Type 1 Grazia Maria Virzi,1 Alessandra Brocca, Massimo de Cal, Giacomo Mason, Sonya Day, Claudio Ronco. Nephrology Dep-IRRV, Vicenza, Italy.

Background: Cardiorenal Syndrome Type 1 (CRS1) is characterized by acute cardiac events leading to acute kidney injury. Loss of redox homeostasis in reactive oxygen species (ROS) and reactive nitrogen species (RNS) results in a proinflammatory and profibrotic milieu via distinct mechanisms which promotes cardiovascular and renal structural and functional abnormalities. This pilot study examined the putative role of ROS/RNS-linked oxidative stress as a pathogenic mechanism of CRS1.

Methods: Subjects were selected from a prospective community-based cohort study with HF (58%male, mean age 80±8yrs, median Crea 0.98mg/dl, IQR 0.87-1.15), CRS1 (54%male, mean age 76±10yrs, median Crea 1.34mg/dl, IQR 1.12-1.83). Quantitative determinations for IL6, Myeloperoxidase (MPO), Nitric Oxide (NO), Copper/Zinc Superoxide Dismutase (Cu/ZnSOD), and Endogenous Peroxidase Activity (EPA) were performed in HF (n=12), and CRS1 (n=11) patients. The Mann-Whitney U test was performed for cohort comparison (p<.05 was statistically significant) by STATA.

Results: CRS1 patients displayed significant augmentation in circulating ROS and RNS, as well as expression of inflammatory cytokines, as IL6. Quantitative analysis of all oxidative stress markers showed significantly lower oxidative stress levels in HF compared to patients with CRS1 (p<.05).

Conclusions: This pilot study demonstrates the significantly heightened presence of dual redox disequilibrium in CRS1 compared to HF patients: ROS/RNS production involving NADPH oxidase and MPO; superoxide production of hydrogen peroxide and NO; upregulation of proinflammatory mediators via peroxynitrite. Our findings indicate that oxidative stress is a potential therapeutic target, as it promotes inflammation by ROS/ RNS-linked pathogenesis. For the first time we demonstrate evidence for the delineation of 2 distinct oxidative roles in CRS1 pathogenesis.

SA-PO736
In Vitro Study of Cell Responses at Radiocontrast Medium. Grazia Maria Virzi,1 Alessandra Brocca, Massimo de Cal,1 Dinna N. Cruz,2 Claudio Ronco.1 Nephrology Dep-IRRV San Bortolo Hosp, Vicenza; 2Univ of California.

Background: Radiocontrast-induced nephropathy (RCIN) accounts for >10% of all causes of hospital-acquired renal failure, causes a prolonged hospital stay and represents a powerful predictor of poor outcome. Mechanisms of RCIN are not completely understood. In this in vitro study, we investigated the in vitro effects of Contrast Media (CM) on renal tubular cells (RTC's) in terms of cell viability, and cell damage. Moreover, we evaluated the relationship between NGAL and RCIN in these patients.

<table>
<thead>
<tr>
<th>Method</th>
<th>OSI</th>
<th>Cu/ZnSOD</th>
<th>Myeloperoxidase (MPO)</th>
<th>Nitric Oxide (NO)</th>
<th>Copper/Zinc Superoxide Dismutase (Cu/ZnSOD)</th>
<th>Endogenous Peroxidase Activity (EPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF 1898 &amp; 2388 days</td>
<td>4.9±2.9</td>
<td>184.5 (160.5-192.0)</td>
<td>505.6 (421.7-547.8)</td>
<td>90.68 (59.9-105.3)</td>
<td>274.5 (191.8-326.8)</td>
<td>274.5 (191.8-326.8)</td>
</tr>
<tr>
<td>HF at 720 days</td>
<td>2.3±2.1</td>
<td>184.5 (160.5-192.0)</td>
<td>505.6 (421.7-547.8)</td>
<td>90.68 (59.9-105.3)</td>
<td>274.5 (191.8-326.8)</td>
<td>274.5 (191.8-326.8)</td>
</tr>
<tr>
<td>CRS1 1898 &amp; 2388 days</td>
<td>4.9±2.9</td>
<td>505.6 (421.7-547.8)</td>
<td>90.68 (59.9-105.3)</td>
<td>274.5 (191.8-326.8)</td>
<td>274.5 (191.8-326.8)</td>
<td>274.5 (191.8-326.8)</td>
</tr>
<tr>
<td>CRS1 at 720 days</td>
<td>2.3±2.1</td>
<td>505.6 (421.7-547.8)</td>
<td>90.68 (59.9-105.3)</td>
<td>274.5 (191.8-326.8)</td>
<td>274.5 (191.8-326.8)</td>
<td>274.5 (191.8-326.8)</td>
</tr>
</tbody>
</table>

Conclusions: In the cyclophosphamide group, 46% achieved remission at 1 year, compared with 71% and 54% at 6 months (low dose and high dose group respectively) in the ELNT. This discrepancy in results may be at least partially explained by the different demographics. The remission rate was 52% in our MMF group compared with 46% in our cyclophosphamide group. This suggests that MMF is not inferior to cyclophosphamide with respect to outcome, in keeping with the Cochrane findings. We acknowledge that indication bias may have influenced the results in our cohort.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author/disclosure.
Methods: In this study, we included 4 groups: 5RCIN patients with AKI(RCIN), 14 patients with AKI but no-exposition to CM(AKI_no CM), 5 patients with exposition to CM(RCIN), and 16 healthy controls. Plasma from diabetic mice incubated with RTCs in standard condition for 24h and, subsequently, viability, apoptosis and necrosis was evaluated by flowcytometric assay. Quantitative analysis of NGAL was performed in plasma. The Kruskal–Wallis test for multiple comparisons was applied to compare groups. The Rank Order Correlation Coefficient (rho) was used to test the correlation between variables. A p-value of <0.01 was considered statistically significant.

Results: RCIN groups is characterized by lower viability and higher apoptosis rates compared with other groups (p<0.01). AKI_noCM and CM_noAKI groups have decreased viability and increased apoptosis compared with CTR. AKI_noCM group showed a significantly increased viability rate and a significantly increased level of apoptosis compared with CTR (p<0.01). There is a positive correlation between NGAL levels and apoptosis (0.87) and Necrosis (0.75) and an inverse correlation between NGAL and cell viability (−0.84).

Conclusions: This study clearly demonstrates that CM-induced epithelial tubular renal cells apoptosis represents a key mechanism of RCIN-AKI. In our results, the toxic effect of CM was confirmed and causes renal tubular cells death by apoptosis. These results suggest that AKI and CM may add their effects in RCIN patients and could induce in vivo a strong damage on kidney structures and functions.

SA-PO737

Ribonuclease 6: A Novel Antimicrobial Peptide in the Human and Murine Urinary Tract

Brian Becknell, Kirk M. McHugh, David S. Hains, John David Spencer. Nationwide Children’s Hospital.

Background: Recent studies stress the importance of antimicrobial peptides (AMPs) in preventing urinary tract infections (UTIs). Members of the Ribonuclease A superfamily are potent AMPs that contribute to sterility in other organs. The goal of this study was to determine the expression and antimicrobial activity of Ribonuclease 6 (Rnase6) in the urinary tract.

Methods: Cytis in mice was achieved via transurethral inoculation of 10^6 colony forming units of uropathogenic E.coli (UPEC) into 8-12 week old C57BL/6 females. Organs were harvested for isolation of RNA/protein or fixed in 4% PFA. RNA/protein were also isolated from non-infected human bladder/kidney tissue and tissue with pyelonephritis. Human RNASE6 and mouse Rnase6 mRNA levels were measured by qRT-PCR. Immunohistochemistry localized Rnase6 expression. Immunoblot quantitated protein levels. Antimicrobial kill assays were performed using recombinant human RNASE6 against 10^5 CFU/mL UPEC.

Results: Human RNASE6 and mouse Rnase6 mRNAs are detectable at low levels throughout the uninjured ureteric tract, but their encoded peptides are undetectable by immunoblotting. UPEC infection induces murine Rnase6 bladder mRNA 1-fold at 48 hours (p = 0.001). At this time point, murine Rnase6 protein localizes to myeloid cells infiltrating the bladder urethral epithelium. Similarly, IHC demonstrates that leukocytes express Rnase 6 in kidney tissue with pyelonephritis. Human RNASE6 and mouse Rnase6 are detectable by immunoblotting in kidneys with acute pyelonephritis as well as infected urinary sediment. Reconstituted human RNASE6 protein binds to the bacterial cell wall and demonstrates dose-dependent bactericidal activity toward UPEC. Recombinase Rnase6 6 demonstrates minimal cytotoxicity toward host tissues.

Conclusions: Our study demonstrates that human RNASE6 and mouse Rnase6 proteins are expressed in the urinary tract and implicates human RNASE6 as a novel AMP toward UPEC. Our results suggest that Rnase6 is a leukocyte-derived AMP that may play an important role in innate immunity of the urinary tract. Rnase6 may represent a novel therapeutic target for children with complex UTI.

Funding: Other NIH Support - NIH K08DK09470-02 to JDS

SA-PO738

Single Photon Emission Computed Topography Imaging of Kidney Aminopeptidase N Expression in a Transgenic Mouse Model of Urothelial Transitional Cell Carcinoma

Hariprasad Gali,1 Gopal Pathuri,1 Andria F. Hedrick,2 Venkateshwar Madka,2 Vibhudutta Awasthi,2 Chinthalapally V. Rao,2 David S. Hains,3 Benjamin D. Cowley,3 Kirk M. McHugh,3 Brian Becknell,4 Kirk M. McHugh, David S. Hains, John David Spencer. Nationwide Children’s Hospital.

Background: Several studies have shown that Aminopeptidase N (APN; CD13; EC 3.4.11.2) is a zinc-dependent membrane-bound exopeptidase that catalyzes the removal of N-terminal amino acids from peptides. APN is well known to be highly expressed on renal proximal tubules. APN expression has been demonstrated to be significantly decreased in renal cancer tissues compared to adjacent normal tissues. Thus, molecular imaging of APN expression in the kidney could be a suitable technique to monitor progression of ADPKD in animal models. However, further research is required to validate the results and correlate the PET renogram parameters with the disease status.

Methods: In this study, we included 4 groups: 5RCIN patients with AKI, 14 patients with AKI but no-exposition to CM, 5 patients with exposition to CM, and 16 healthy controls. Plasma from diabetic mice incubated with RTCs in standard condition for 24h and, subsequently, viability, apoptosis and necrosis was evaluated by flowcytometric assay. Quantitative analysis of NGAL was performed in plasma. The Kruskal–Wallis test for multiple comparisons was applied to compare groups. The Rank Order Correlation Coefficient (rho) was used to test the correlation between variables. A p-value of <0.01 was considered statistically significant.

Results: RCIN groups is characterized by lower viability and higher apoptosis rates compared with other groups (p<0.01). AKI_noCM and CM_noAKI groups have decreased viability and increased apoptosis compared with CTR. AKI_noCM group showed a significantly increased viability rate and a significantly increased level of apoptosis compared with CTR (p<0.01). There is a positive correlation between NGAL levels and apoptosis (0.87) and Necrosis (0.75) and an inverse correlation between NGAL and cell viability (−0.84).

Conclusions: This study clearly demonstrates that CM-induced epithelial tubular renal cells apoptosis represents a key mechanism of RCIN-AKI. In our results, the toxic effect of CM was confirmed and causes renal tubular cells death by apoptosis. These results suggest that AKI and CM may add their effects in RCIN patients and could induce in vivo a strong damage on kidney structures and functions.

SA-PO740

Enalapril Treatment Prevents and Reverses Renal Damage in the ZSF1 Obese Rat Model of Diabetic Nephropathy


Background: The prevalence of diabetic nephropathy is on a rise despite medical advancements. Novel therapies to slow the decline in renal function are urgently needed. Accordingly, preclinical models of diabetic nephropathy (DN) are warranted to support the advancement of novel compounds into the clinic. Recent reports suggest that the obese diabetic ZSF1 rat model closely approximates the pathological conditions of human DN, including: hypertension, proteinuria and hyperglycemia. Angiotensinogen Converting Enzyme Inhibitors (ACEi) have been shown to slow the decline in renal function in patients with DN.

Methods: A 15 week time course study was conducted to assess the effect of enalapril initiated at different times on blood pressure, proteinuria and fibrosis. Male ZSF1 obese rats (n=9/group), telemetry instrumented for blood pressure recording, were randomly assigned to six treatment groups. Enalapril administration (3 mg/kg in the drinking water; 10 for a treatment duration of 15, 12, 10, 8 and 5 weeks, respectively. Vehicle treated male ZSF1 obese animals were used as comparators. Weekly urine collections, body weight, water and food consumption recordings, and clinical observations were performed. Blood pressure was continuously recorded. Blood collection, creatinine and pharmacokinetic determinations were performed on select weeks. At termination, renal tissue was assessed for incidence of glomerulosclerosis and interstitial fibrosis.

Results: Enalapril administered in a prophyactic (duration of 15 and 12 weeks) and therapeutic (duration of 10, 8 and 5 weeks) manner significantly decreased mean arterial pressure and urinary protein to creatinine ratio compared to vehicle. Glomerular and interstitial lesions were modestly reduced across all treatment groups.

Conclusions: In summary, the ZSF1 obese rat constitutes a preclinical model of diabetic nephropathy in which an ACEi both prevents and reverses renal damage.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim Pharmaceuticals, Inc.
SA-PO741 Cardiorenal Syndrome Type 5 Mechanism: A New Hypothesis for Organs Damage. Alessandra Brocca, Grazia Maria Virzi, Giacomio Mason, Massimo de Cal, Claudio Ronco. Nephrology Dep-IRIV, Vicenza, Italy.

Background: Cardiorenal Syndrome Type 5 (CRS5) is characterized by the presence of combined cardiac and renal dysfunction due to systemic disorder. Severe sepsis represents the most common condition which can damage both organs. Activation and induction of pro-inflammatory cytokines can cause cardiac and renal dysfunction due to systemic disorder. Severe sepsis represents the most common condition which can damage both organs.

Methods: We enrolled 11 patients with CRS5 (68.4±10.8yrs), and 16 controls (CTR) (52.0±7.7yrs). Plasma from different groups were incubated with RTCs for 24h and subsequently, cell apoptosis was assessed using Annexin-V/Propidium Iodide assay and quantitative real-time PCR analysis showed significantly higher apoptosis and necrosis rates compared to CTR (p<0.001). A significantly lower viability was observed in RTCs incubated with CRS5 plasma compared to CTR (p=0.001).

Results: In CRS5 plasma, a quantitative analysis showed significantly higher apoptosis and necrosis rates compared to CTR (p<0.001). A significantly lower viability was observed in RTCs incubated with CRS5 plasma compared to CTR (p=0.001).

SA-PO742 Tubular Overexpression of Gremlin in Transgene Mice Induces Renal Damage Susceptibility. Sergio A. Mezzana, Alejandra M. Draguet, Daniel Carpio Paniagua, Bredford Kerr, Raquel Rodriguez-Diez, Jesus Egido, Marta Ruiz-Ortega. 1Nephrology, Universidad Austral de Chile, Valdivia, Los Rios, Chile; 2Centro de Estudios Científicos, CECIS, Valdivia, Los Rios, Chile; 3Fundacion Jimenez Diaz, Universidad Autonoma, Madrid, Spain.

Background: Gremlin is an embryonic gene with a key role in nephrogenesis that is reexpressed in many human renal diseases, including diabetic nephropathy, pauci immune glomerulonephritis and chronic allograft nephropathy. Some authors have proposed that gremlin could be involved in renal damage, acting as a downstream mediator of TGF-b.

Methods: To examine the in vivo role of Gremlin in the kidney we generated seven specific proximal tubular epithelial cells human gremlin (GREM1) transgenic mouse lines, presenting 1.2 to 200-fold increase of GREM-1 gene expression levels. These GREM1 transgenic mice developed higher proteinuria after 7 and 14 days than wild type mice. Tubular GREM1 overexpression was associated to renal upregulation of pro-inflammatory factors, such as TGF-b and a-SMA, and increased proliferating cells compared to wild type mice.

Results: Our results suggest that GREM1-overexpressing mice might have an increased susceptibility to develop renal failure supporting the involvement of gremlin in renal damage progression.

SA-PO743 Xylene Induces DNA Methylation Changes in Podocytes and Tubular Epithelial Cells. Zhongxiu Xu, Wei-song Qin, Xianghua Cao, Cai-hong Zeng, Zhi-hong Liu. Research Institute of Nephrology, Jinling Hospital, Nanjing Univ School of Medicine, Nanjing, China.

Background: To determine if there is an epigenetic mechanism underlying organic solvent-induced renal injury, we investigated the change of DNA methylation in conditionally immortalized human podocytes and proximal tubular cell line HK2 treated with xylene.

Methods: DNA methylation changes in cultured human podocytes and proximal tubular cells were identified by comparing DNA methylation profiles of the cells treated with xylene and the untreated control. Illumina human 450k CpG DNA methylation microarray was used to analyze DNA methylation of the cells. Bisulfitel sequen sequencing PCR and pyrosequencing were used to validate the microarray results. Quantitative real-time PCR (qRT-PCR) was carried out to examine the correlation between the mRNA expression and methylation level of a gene.

Results: We identified 52 probes that displayed significant methylation level changes in xylene-treated podocytes compared with untreated control cells, among which 25 were increased, while 26 decreased. mRNA qRT-PCR analyses of the corresponding genes revealed the correlations of IL-20 and p53 expressions with their methylation levels, respectively. For HK2 cells, there were 243 probes that displayed significant methylation change, of which 109 showed increased, while 134 decreased. Methylation level qRT-PCR analyses confirmed the correlation between the mRNA expression and the methylation level of EIF1A1 or KDM5D. The results of pyrosequencing were well consistent with the microarray data.

Conclusions: Xylene can induce DNA methylation change in podocytes and tubular cells, which may be part of the mechanism by which xylene causes injury of these cells.

Funding: Government Support - Non-U.S.

SA-PO744 Inhibition of Cytochrome-2 Does Not Ameliorate Lithium-Induced Renal Microcytosis Injury and Polyuria in Adolescent Rat. Kirsten Madken,1,2 Gitte Kjaersgaard,1 Niels Marcusen,2 Boye Jensen,1 1Dept of Cardiovascular and Renal Research, Univ of Southern Denmark, Odense, Denmark; 2Dept of Pathology, Odense Univ Hospital, Odense, Denmark.

Background: In human patients, chronic treatment with lithium leads to tissue injury with multiple microcytoses that originate in cortical collecting duct and nephrogenic diabetes insipidus (NDI). In this study it was hypothesized that renal COX-2 activity promotes microcyst formation.

Methods: Microcystic kidney injury was induced in male adolescent rats by feeding dams with lithium [50 mmol Li/kg chow] from postnatal days 7 to 34.

Results: Lithium treatment induced cortical microcysts and dilatations in the distal nephron; it increased cortical cell proliferation and increased inactive pGSK-3b. It lowered AQ2 expression and induced polyuria with decreased ability to concentrate the urine and it increased COX-2 protein level in thick ascending limb. Concomitant treatment with lithium and a specific COX-2 inhibitor, parecoxib (5mg/kg/day, P10-P34) did not prevent the induced microcystic injury and polyuria, but improved urine concentrating ability transiently after a dDAVP challenge. COX-2 inhibition did not reduce nore-renal cell-induced cell proliferation or inactivating phosphorylation of GSK-3b. COX-1 protein abundance increased in kidney cortex in response to lithium and was associated with microcysts and dilatations in collecting ducts in both rats and humans.

Conclusions: In summary, COX-2 is marginally stimulated in cortical loop of Henle cells in chronic lithium-treated adolescent rats; COX-2 is not colocalized with microcystic epithelium; mitotic activity and pGSK-3b in collecting duct; a blocker of COX-2 does not prevent cell proliferation, cyst formation or GSK-3b inactivation. It is concluded that COX-2 activity is not the primary cause for microcystic injury and polyuria in a NaCl-substituted rat model of Li-nephropathy while COX-1 is a likely candidate to affect the injured epithelium.

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

SA-PO745 The Effect of Pioglitazone on Mitochondrial Biogenesis in the Kidney of Dahl Salt Sensitive Hypertension Rat. Toshihito Hayashi, Yuuki Kusano, Tatsuyuki Kanzaki, Makoto Kikuchi, Shigeki Hashimoto, Masaaki Nakayama, Tsuyoshi Watanabe. Fukushima Medical Univ, Nephrology and Hypertension, Fukushima, Japan.

Background: Thiazolidinediones (TZDs) improve insulin sensitivity but also appear to have antihypertensive effects in obesity. Increases oxidative stress in renal outer medulla by salt loading is thought to be one of the causes of hypertension and kidney damage. To closely examine the antihypertensive and renoprotective effects of TZDs, we used non-obese salt sensitive hypertension rat with pioglitazone (pio).

Methods: Aged 6week Dahl salt sensitive (DSS) rats were divided into the four groups: LS (0.3% Low salt fed n=10), LSP (LS fed containing pio n=10), HS (4.0% High salt fed n=20) and HSP (HS fed containing pio n=20). The combination of pio in chow is kept at 0.005%. Rats were sacrificed at 12th week. Nitrotyrosine, SOD1 and SOD2 in kidney were observed by immunohistochemistry or western blot. We also determined two subunits (COX-I and SDH-A) of oxidative phosphorylation enzyme complex to elucidate the mitochondrial biogenesis of kidney by western blot. COX-I is mitochondrial DNA-encoded, and SDH-A is nuclear DNA-encoded.

Results: Between HS and HSP groups, significant improvement were observed in systolic blood pressure (171 vs 156 mmHg), creatinine clearance (2.3 vs 3.1 ml/min) in HSP. Significant differences were observed in body weight, serum glucose and insulin levels, and urinary protein excretion. Serum triglyceride levels was decreased (96 vs 67 mg/dl, p<0.01), and adiponectin levels was increased (3.3 vs 5.2 mg/ml, p<0.01) in HSP. Nitrotyrosine was detected in fibrosis area in renal outer medulla and nitrotyrosine levels were significantly reduced compared to HSP (1.0±0.1 vs 0.7±0.3) in HSP. Expression of SOD2 levels (1.0±0.1 vs 1.3±0.2, p<0.05) and ratio COX1/SDH-A (1.0±0.1 vs 1.3±0.4, p<0.05) were increased in HSP.

Conclusions: Pioglitazone suppressed salt sensitive hypertension, renal damage in DSS rats, and apparent changes in serum glucose and insulin levels. Increased adiponectin to induce mitochondrial biogenesis might be involved in these renoprotective effects of pioglitazone.
Poster/Saturday

SA-P0746
Alpha-1-Microglobulin Protects Renal Proximal Tubule Epithelial Cells from Apoptosis and Cell Damage following Hemoglobin-, Heme-, and Oxidative Overload
Magnus Gram, Sara Davidsdottir, Maria Johansson, Bo Akerman.

Methods: Mice fed with Western-type diet or normal diet from 4 weeks of age were used. SCD mice (n=12) were used as a positive control group while the corresponding wild-type mice (n=12) were used as a negative control group. The mice were sacrificed after 4 weeks of treatment.

Results: Exposure to oxyHb, metHb, heme, or ROS led to upregulation of interleukin-1β (IL-1β), heme oxygenase-1 (HO-1), ICAM-1 and p21 mRNA expression at 4 and 24 hours. Furthermore, results showed an increased necrosis (LDH), and apoptosis (caspase activation) in epithelial cells exposed to metHb and heme but not in cells exposed to oxyHb. Treatment with A1M reversed the metHb and heme-induced effects on gene expression as well as necrosis and apoptosis responses.

Conclusions: Following systemic hemolysis, as a result of cardiac surgery or blood transfusions, there is an acute increase of extracellular Hb-metabolites that have potential pathophysiological effects on the kidneys, sometimes rendering irreversible damage to the kidneys. We show that treatment of the Hb-, heme-, and ROS-induced inflammatory and stress response in the kidney cell line HPRTPEC could be inhibited by the heme- and radical scavenger A1M. Our studies therefore present a therapeutic opportunity and a means of decreasing the damage to the kidneys following intravascular hemolysis.


SA-P0747
Podocyte Injury with Hypercholesterolemia Promotes Intraglomerular Lipid Deposition
Satoshi Hara, 1 Kazuo Sakamoto, 2 Yasutoki Takashima, 1 Namiko Kobayashi, 1 Toshifuru Ueno, 1 Noriko Usugi, 1 Taiji Matsusaka, 1 Michio Nagata. 1

Methods: Male Wistar rats (n=5 per group) underwent the 2-stage subtotal nephrectomy (SNx) or a sham procedure. The left kidney was two thirds resected with right total nephrectomy (SNx) or a sham procedure. The left kidney was two thirds resected with right total nephrectomy. After a further 4 weeks, blood was taken for serum analysis, and aorta’s were removed and placed in serum free organ culture for 30min. The resulting conditioned medium was analysed by LC-MS/MS for patterns of cyclooxygenase, lipoxigenase and epoxyeicosatrienoic acid (EET).

Conclusions: Male Wistar rats (n=5 per group) underwent the 2-stage subtotal nephrectomy (SNx) or a sham procedure. The left kidney was two thirds resected with right total nephrectomy. After a further 4 weeks, blood was taken for serum analysis, and aorta’s were removed and placed in serum free organ culture for 30min. The resulting conditioned medium was analysed by LC-MS/MS for patterns of cyclooxygenase, lipoxigenase and epoxyeicosatrienoic acid (EET).

Results: Subtotal nephrectomy resulted in increases in (P<0.05) in serum urea (sham 6.1±0.2; SNx 17.4±1.6 mmol/l), creatinine (sham 42.0±1.5; SNx 85.2±3.0 mmol/l), Ca2+ (sham 2.712±0.019; SNx 2.846±0.020 mmol/l) and mean arterial blood pressure (sham 137±26; SNx 157±19.6) but albumin, Na+ and K- were unchanged. Sham and SNx aorta released an almost identical pattern of eicosanoids with prostacyclin the major EARL produced by both groups (sham 65.12; SNx 58.9±ng/ml). The one exception was a significant increase in the eicosanoids arachidonic acid metabolite 14,15-EET (sham 131±13; SNx 233±104 pg/ml, P<0.02).

Conclusions: 14,15-EET acts as a vasodilator and anti-inflammatory EARL which may represent a novel biomarker and mediator of possibly inadequate compensatory renal response to chronic kidney disease, the same usefulness of the other elevates 14,15-EET levels, e.g: soluble epoxide hydrolase inhibitors, to limit the adverse cardiovascular outcomes associated with CKD remains to be determined.

SA-P0748
Vascular Eicosanoid Generation in Experimental Uremia
David Bishop-Bailey, 1 Julius Edward Kiewisch, 2 Kieran McCafferty, 3 Scott Thompson, 3 Matthew Edin, 1 Darryl Zeldin, 1 Magdi Yaqoob. 2

Results: NOX2. ET-1 mRNA was 269±36% of control while p47phox was 172±15% of control results were recapitulated in the renal cortex of the same animals with the exception of ET-1. NOX2 mRNA was 142±16% of control while p47phox was 112±11% of control. NOX2 expression was elevated in both the glomeruli and the medulla of both SCD and SNx mice when compared to C57 control mice (p<0.01, n=6). Furthermore, we found that SCD mice have significant increases in both NOX2 and p47phox but not NOX4 mRNA in their glomeruli (186±21 and 301±64% of control respectively, p<0.01, n=6). These results were recapitulated in the renal cortex of SCD mice with the exception of NOX2. ET-1 mRNA was 269±36% of control while p47phox was 172±15% of control mice (p<0.01, n=6).

Conclusions: Combined with our previous experiment, these data support the hypothesis that chronically elevated ET-1 leads to the creation of ROS via NADPH oxidase in the glomeruli of sickle animals, contributing to renal damage in the progression of SCD.

Funding: Other NIH Support - NHLBI

SA-P0750
Clinical Assessment of Urine Magnesium Excretion Rate as a Predictor for Tubulo-Interstitial Disorders

Methods: Renal tissues were carefully dissected and glomeruli were harvested from 14-week-old, knock-in Hbs only sickle and C57BL/6j mice and were assessed for relative ET-1, NOX2, and p47phox mRNA. Results: We found that sickle mice have 401:89% more glomerular ET-1 mRNA when compared to C57 control mice (p<0.01, n=6). Furthermore, we found that sickle mice have significant increases in both NOX2 and p47phox but not NOX4 mRNA in their glomeruli (186±21 and 301±64% of control respectively, p<0.01, n=6). These results were recapitulated in the renal cortex of sickle mice with the exception of NOX2. ET-1 mRNA was 269±36% of control while p47phox was 172±15% of control mice (p<0.01, n=6).

Conclusions: Combined with our previous experiment, these data support the hypothesis that chronically elevated ET-1 leads to the creation of ROS via NADPH oxidase in the glomeruli of sickle animals, contributing to renal damage in the progression of SCD.

Funding: Other NIH Support - NHLBI
Evaluation of Various Dendritic Cell Markers in Renal Biopsy Specimens of 48 Patients with Various Renal Diseases


Background: Dendritic cells (DCs) are the most potent antigen-presenting cells, and their participation in the pathogenesis of glomerulonephritis has been suggested. We therefore investigated subtypes of DCs in kidneys of patients with various renal diseases.

Methods: We examined renal biopsy specimens from sixty-five patients with renal diseases or renal specimens of normal controls; 7 with ANCA-associated vasculitis (AAV), 9 with IgA nephropathy (IgAN), 5 with focal segmental glomerulosclerosis (FSGS), 10 with membranoproliferative glomerulonephritis (MPGN), 8 with tubulointerstitial nephritis (TIN) and normal control kidneys. Five distinct markers of DCs (CD1c, CD209, CD208, CD1a and CD303) and T cell subtypes (CD4, CD8) were analyzed immunohistochemically. The clinical data and pathological features of renal biopsy were statistically evaluated for possible relation with immunostaining results.

Results: Among the five markers of DCs, three markers, i.e., CD1c (a marker of conventional DCs), CD209 (DC-specific ICAM3-grabbing nonintegrin; DC-SIGN, a marker of monocyte-derived DCs) and CD208 (DC-lysosome-associated membrane glycoprotein; DC-LAMP, a marker of interdigitating DCs), positive cells significantly increased in interstitium of the kidneys of AAV and TIN. The numbers of these interstitial DCs per area correlated with the number of interstitial CD4 positive cells and the grade of tubulointerstitial inflammation. Generally, DCs are rarely found in the glomeruli of renal diseases, however, a few CD208+ DCs were observed in glomeruli in the patients of AAV and TIN. In addition, DC208+ DCs may induce inflammation not only in interstitium but also in glomeruli of patients with AAV.

Conclusions: These observations suggest that interstitial myeloid DCs may interact with CD4+ T cells and may induce tubulointerstitial injury in the patients of AAV and TIN.

Our study confirms the involvement of DCs in renal diseases and suggests that DCs may contribute to the pathogenesis of renal injuries, including inflammation and fibrosis.

SA-PO754

HIV-Induced Podocyte Ang II Production Sustains Downregulation of Vitamin D Receptor (VDR) through Upregulation of Snail


Background: Ang II plays an important role in the development and progression of HIV-associated nephropathy (HIVAN). Recently, we reported that HIV enhances the activation of renin angiotsin system (RAS) in podocytes through down regulation of VDR (Am J Physiol, 2013). We hypothesize that HIV may be sustaining podocyte Ang II production through up regulation of Snail.

Methods: Protein blots were prepared from renal tissues of age and sex matched control and HIV transgenic mice (Tg26; n=8) and probed for TGF-β, Snail, and VDR, the markers of RAS, upregulated and probed for Ang II. Cells were treated with either buffer or losartan (10-7M, an Ang II blocker) and probed for VDR, renin (RAS) and TGF-β. Ang II content was measured in cellular lysates of EV/CCHIP and HIV/CCHIP by ELISA. To determine the contribution of Ang II, EV/CCHIP and HIV/CCHIP were incubated in media containing either buffer or losartan (10M, an Ang II blocker) for 24h (n=3). Subsequently, protein blots were probed for TGF-β, Snail and Actin.

Additionally, effect of hedge pathway was studied in modulation of podocyte monolayer permeability and expression of Ang II. Hedgehog pathway inhibitors were added and cellular lysates were prepared and probed for TGF-β, Snail, and VDR; the same blots were reprobed for actin. Renal tissue lysates of control and Tg26 mice were also assayed for their Ang II content by ELISA. Conditionally immortalized human podocytes (CIHP) were transduced with either empty vector (EV/CCHIP) or NL-4-3 construct (HIV/ CCHIP). Protein blots of cellular lysates EV/CCHIPs and HIV/CCHIPs were probed for VDR, renin (RAS) and TGF-β. Ang II content was measured in cellular lysates of EV/CCHIP and HIV/CCHIP by ELISA. To determine the contribution of Ang II, EV/CCHIP and HIV/CCHIP were incubated in media containing either buffer or losartan (10M, an Ang II blocker) for 24h (n=3). Subsequently, protein blots were probed for TGF-β, Snail and Actin.

Results: Renal tissues of Tg26 mice displayed increased Ang II content and enhanced expression of TGF-β and Snail, but down regulation of VDR. HIV/CCHIPs displayed down regulation of VDR but up regulation of renin; moreover, HIV/CCHIPs showed enhanced generation of Ang II when compared to EV/CCHIPs. HIV/CCHIPs also exhibited enhanced expression of TGF-β and Snail. Snail/CCHIPs exhibited down regulated expression of VDR. Interestingly, losartan not only attenuated HIV-induced podocyte expression of TGF-β and Snail but also upregulated VDR.

Conclusions: HIV sustains generation of Ang II through down regulation of podocyte VDR and upregulation of Snail.

Funding: NIDDK Support

SA-PO755

Hedgehog Pathway Plays a Vital Role in HIV-Induced Podocyte Epithelial-Mesenchymal Transition (EMT)


Background: HIV-associated nephropathy (HIVAN) is characterized by heavy proteinuria, progressive renal insufficiency, and distinct morphological changes in the form of collapsing glomerulopathy, microcystic dilatation of tubules, and tubulointerstitial fibrosis. HIV-Induced EMT and proliferation of renal cells are important involved mechanisms contributing to the development of HIVAN phenotype. We hypothesized the role of hedgehog pathway in the HIV-induced kidney cell EMT and associated fibrosis.

Methods: Protein blots were prepared and RNAs were extracted from renal tissues of 4 weeks old control and HIVAN (Tg26) mice (n=4) and probed for molecules involved in hedgehog pathway, including sonic hedgehog (SHH), PTCH1, gli1, and gli2. For in vitro studies, human podocytes (HP) were transduced with either empty vector or HIV (NL-43) and treated with either buffer or Grant58 (an inhibitor of gli1 transcription) for 48 hours. Subsequently, protein blots of EV/HP and HIV/HPs were probed for molecules involved in hedgehog pathway, including PTCH1, SHH, gli1, and gli2. Additionally, expression of hedge pathway was studied in modulation of podocyte monolayer permeability by utilizing albumin flux assay.

Results: Western blot and real time PCR analysis showed enhanced expressions of SHH, PTCH1, gli1 and gli2 in renal tissues of Tg26 mice. In vitro studies, HIV not only activated the hedgehog pathway but also enhanced the expression of EMT and proliferation markers in podocytes. On the other hand, the blockade of hedgehog pathway with Ganit58, decreased expression of HIV-induced kidney cell EMT markers. Albumin flux assay showed HIV/CCHIPs increased podocyte monolayer permeability, which could be partially attenuated by Ganit58.

Conclusions: These results indicate that hedgehog pathway plays a vital role in the development of HIVAN; additionally, it provides insight into a new target for HIVAN therapeutic strategy.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
SA-PO756

The Role of MicroRNAs in Podocyte Differentiation and Injury
Christopher P. Carrington,1 Robert H. Jenkins,1 Moin Saleem,2 Timothy Bowen,2 Donald Fraser.1
1Institute of Molecular and Experimental Medicine, Cardiff Univ, Cardiff, United Kingdom; 2Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom.

Background: Wholesale deletion of microRNAs (miRs) within murine podocytes is associated with proteinuria and progressive glomerulosclerosis. However little is known about the role of specific miRs in the maintenance of human podocyte phenotype.

Methods: Using a laser capture microdissection (LCM) based approach we have isolated and array profiled (Taqman Low Density Array (TLDA)) the miR expression patterns in glomeruli from 8 nephritic patients with idiopathic membranous nephropathy (IMN).

Results: Using this approach we identified several miRs that were highly expressed in glomeruli of patients with IMN and altered with TGFβ stimulation.

Conclusions: These are the first measurements of single glomerular permeability in diabetic humans. Glomerular L4/F1 is elevated in early diabetes in humans and rats.

SA-PO759

Podocyte Hypertrophy Is Regulated by Ubiquitin C-Terminal Hydrolase-L1 Induced Cytoplasmic p27kip1 Accumulation in Rat Membranous Nephropathy
Catherine Meyer-Schwesinger, Tobias N. Meyer,1 Maja Lindenneyer, Thorsten Wiech,2 Clemens D. Cohen,2 Rolf A. Stahl,1
1Nephrology, UKE, Germany; 2Nephrology, AKB, Germany.

Background: Podocytes are terminally differentiated and react to injury with hypertrophy and loss of barrier function. p27kip1 is a key regulator of cellular hypertrophy through induction of G1 arrest. Subcellular localization of p27kip1 in tumours is influenced by ubiquitin C-terminal hydrolase L1 (UCH-L1), a key neuronal protease in the ubiquitin-proteasome pathway.

Methods: We recently demonstrated de novo UCH-L1 expression and activation in podocytes of patients with membranous nephropathy (MGN) and in rodent models of MGN. Here, we investigated the role of UCH-L1 in podocyte p27kip1 homeostasis and hypertrophy.

Results: MicroRNAs co-localization studies were performed in human MGN and in the rat model of MGN, the passive Heymann nephritis (PHN). The effects of UCH-L1 overexpression, knockdown and inhibition of hydrolase function on podocyte hypertrophy and p27kip1 homeostasis were evaluated in cultured podocytes and in PHN.

Conclusions: In human and rodent MGN, podocyte hypertrophy correlated with up-regulation of p27kip1 and cytoplasmic p27kip1 levels and cell cycle inhibitors. The expression in human and rodent MGN of p27kip1 resulted in cytoplasmic accumulation of p27kip1 protein in podocytes in vitro and vivo. UCH-L1 activity in podocytes decreased the percentage of cells in G1 arrest, increased cellular turnover, hypertrophy, migration and cytoskeletal rearrangement, which are associated with known oncogenic functions of cytoplasmic p27kip1 in cancer. Inhibition of UCH-L1 activity in rodent models of MGN and in the rat model of MGN, the passive Heymann nephritis (PHN). The effects of UCH-L1 overexpression, knockdown and inhibition of hydrolase function on podocyte hypertrophy and p27kip1 homeostasis were evaluated in cultured podocytes and in PHN.

Conclusions: These are the first measurements of single glomerular permeability in diabetic humans. Glomerular L4/F1 is elevated in early diabetes in humans and rats.

SA-PO757

2-Photon Microscopy Reveals Stationary Podocytes in Living Zebrafish Larvae
1Anatomy and Cell Biology, Univ Medicine Greifswald, Greifswald, Germany; 2Internal Medicine, Div of Nephrology and Immunology, RWTH Aachen Univ Hospital, Aachen, Germany; 3Pharmaceutical Technology, Univ of Regensburg, Regensburg, Germany.

Background: Podocytes are an essential component of the glomerular filtration barrier and cover the outer aspect of glomerular capillaries. They form a complex actin-based cytoskeleton in vivo and show a prominent look in vitro. Since a long time it has been speculated whether podocytes are stationary or mobile in vivo.

Methods: To address this question we performed two-photon microscopy (2PM) of the pronephros of translucent zebrafish larva (casper) expressing eGFP specifically in podocytes and determined the expression periods of time.

Results: By intravital 2PM, podocyte cell bodies as well as the interdigitating branching pattern of major processes could be resolved in zebrafish larva at 5-7 dpf (days post fertilization) with a resolution of about 1 μm in the xy-plane. Time-lapse imaging demonstrated that podocytes neither migrated nor changed their branching pattern of major processes over a time period of up to 18 h. Podocyte motility was neither detected by recording at low rates (2-5 images per h) nor at high rates (up to 5 images per s). By contrast, weakly GFP-positive cells close to the pronephric glomerulus that were probably of neural crest origin exhibited vigorous motility in 2PM time-lapse recordings.

Conclusions: In summary, we have generated a translucent zebrafish with fluorescently labeled podocytes for intravital 2PM revealing that podocytes are stationary cells in the intact glomerulus.

Funding: Government Support - Non-U.S.

SA-PO758

Increased Glomerular Water Permeability in Human and Streptozotocin-Induced Diabetes Mellititus
Amy Russell, Yan Qiu, Kenton Arkill, Andy Salmon.
Microvascular Research Laboratories, Physiology & Pharmacology, Univ of Bristol, Bristol, United Kingdom.

Background: Diabetic nephropathy patients show endothelial dysfunction, albuminuria and increased glomerular filtration rate. We hypothesized that glomeruli from humans and animals with diabetes would have increased water permeability.

Methods: Male Sprague Dawley rats were injected intravenously with streptozotocin (45 mg/kg) or citrate buffer alone. 7 days later, streptozotocin-injected rats were hyperglycemic (before: 6.0±0.13 mmol/L; after: 27.1±7.7 mmol/L, p<0.001) and proteinuric (sham: 11.6±0.9 mg/day; diabetic: 25.3±6.7 mg/day, p=0.005). Kidneys were perfused via the abdominal aorta with 4% bovine serum albumin (BSA) under anaesthesia (sodium pentobarbital). Glomeruli were isolated via a sieving procedure. Human glomeruli were isolated from kidneys not suitable for transplantation, from donors with and without diabetes. Glomeruli were aspirated onto a micropipette and equilibrated in 1/5% BSA. The perfusate was exchanged to 8% BSA causing fluid efflux. The resultant glomerular volume decrease was used to calculate volume-corrected glomerular volume permeability (L4/F1 = μm/min).

Results: L4/F1 was significantly elevated in diabetic animals (sham: 1.00±0.09 (90/9); streptozotocin: 1.54±0.16 (74/9)) (mean±sem (glomeruli/animals)) p<0.01). Human glomerular L4/F1 was also increased in diabetes (healthy: 1.0±0.1 (25/3); diabetic donors 2.3±0.4 (16/3)) (p<0.001).

Conclusions: These are the first measurements of single glomerular permeability in diabetic humans. Glomerular L4/F1 is elevated in early diabetes in humans and rats.

SA-PO760

Regulation of Apolipoprotein-L1 Splicing by Wilms Tumor-1 Protein
Hidefumi Waskush, Jeffrey B. Kopp. NIDDK, NIH, Bethesda, MD.

Background: Apolipoprotein L1 (APOL1) genetic variants are associated with increased glomerular disease risk. Apol1 has several RNA splice variants, producing distinct protein isoforms: APOL1-A is encoded by exons 1, 3-7; APOL1-B is encoded by exon 1-7; and APOL1-C is encoded by exons 1, 3, 5-7. Wilms tumor-1 (WT1) protein participates in kidney development and podocyte differentiation.

Methods: We raised a rabbit antisera against APOL1-B exon 2 peptide, which is specific for this isoform. We examined the expression of APOL1 splicing variants, using by TA cloning, RT-PCR and WT1 knockdown, and subcellular localization, using immunofluorescence (IF), Flag tagged vector transfection, in cultured human podocytes, WT1 inducible human osteosarcoma cells, and human kidney.

Results: Seven APOL1 splicing variants (classed as V1-V4) were cloned from immortalized human podocytes. These include three splicing variants that contain exon2: APOL1-V1-2, V2-2 and V2-3, which encode APOL1-B-1, B-2 and B-3 respectively. APOL1-V1-2 consists of exon 1-7. V2-2 is distinguished by having a longer exon 3. V2-3 lacks exon3, which contains a signal sequence. Human kidney expressed 5 APOL1 splicing variants. Using IF, we found that APOL1-B was expressed by podocytes in normal human kidney and was decreased in FSGS kidney. Transfected C-terminal Flag-tagged APOL1-B-3 was detected by both APOL1-B-1 and Flag ab, and co-localized with F-actin in immortalized human podocytes. APOL1-B-1 and B-2 were not detected by APOL1-B-1 but were detected by Flag ab. In WT1-expressing UB27 human osteosarcoma cells, the APOL1-V2-3 RNA level was increased compared to control cells lacking WT1. WT1 expression dramatically increased APOL1-B protein expression, assessed by WB and IF. Further, WT1 knockdown reduced the expression of APOL1-V2-3 in immortalized human podocytes while other APOL1 variant RNAs were reduced or unchanged.

Conclusions: APOL1-V2-3 is a key regulator of cellular hypertrophy and loss in cultured human podocytes, WT1 induces human osteosarcoma cell and human kidney.

Funding: NIDDK Support
Podocyte Slit-Diaphragm Protein Nephrin Associates with the Actin Cytoskeleton through Interacting with IQGAP1

Sanjoy K. Sen,*1 Pravin K. Sinha,*1 Prachi K. Sinha,*1 Apurba De,2 and Anamika Chaudhury,2

1Department of Biochemistry, IIT Delhi, India; 2Department of Anatomy, IIT Delhi, India.

Background: The slit diaphragm (SD) is an ion selectivity barrier that plays a crucial role in the maintenance of the glomerular filtration barrier. Podocin is an essential component of the SD, required for proper assembly and integrity of the glomerular filtration barrier. Podocin is known to interact with actin, which is essential for maintaining the integrity of the actin cytoskeleton in podocytes. However, the identity of other actin-interacting proteins in podocytes that contribute to the unique podocyte architecture is not known.

Methods: Podocin was shown to interact with actin by co-immunoprecipitation experiments. Podocin was also shown to interact with another actin-interacting protein, Pdlim2, in vitro and in vivo co-immunoprecipitation studies. These interactions were further confirmed by in vivo and in vitro immunofluorescence and electron microscopy studies.

Results: In vivo and in vitro immunofluorescence and electron microscopy studies showed that podocin and actin co-localize in close proximity with each other in podocytes. In vitro co-immunoprecipitation experiments showed that podocin co-immunoprecipitated with actin and Pdlim2, indicating the presence of a podocin-actin-Pdlim2 complex.

Conclusions: Podocin interacts with both actin and Pdlim2, suggesting that podocin is an important component of the actin cytoskeleton in podocytes.

Funding: This work was supported by grants from the Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT), India.

SA-PO764

Mechanism of CLIC5A-Mediated Ezrin Phosphorylation

Abass Almomany, Lajii Li, Barbara J. Ballermann.

University of Alberta, Edmonton, Canada.

Background: CLIC5A deficiency in mice potentiates hypertension and adriamycin-induced glomerular injury. CLIC5A is highly and uniquely expressed at the apical plasma membrane (PM) of podocyte foot processes as part of the Ezrin-Podocalyxin complex (Am. J. Physiol. Cell Physiol. 298: F1492, 2010). Phosphorylated ezrin (Ezrin) links podocalyxin to the cortical actin. In podocytes of CLIC5A deficient mice, Ezrin abundance is reduced. This study explored the molecular mechanisms by which CLIC5A regulates ezrin function.

Methods: CLIC5A cDNA or vector (control) were introduced into Cos-7 cells, which expresses CLIC5A but not CLIC5A at baseline. Protein abundance was evaluated by immunoblot (IB) and protein localization by immunofluorescence (IF) confocal microscopy (CF).

Results: Since ezrin phosphorylation requires its binding to phosphatidylinositol 4,5-bisphosphate (PIP2), the distribution of the PIP2 reporter RFP-PH-PLC was evaluated with live-cell CF. CLIC5A expression induced surface ruffles (Scanning EM) and actin polymerization. The ratio of Ezrin - Total Ezrin in Cos-7 cells expressing CLIC5A than in control cells (0.84±0.06 vs. 0.38±0.06, mean±SE, n=3, p<0.01), indicating increased apical PM PIP2 content. Activation of phospholipase C (with PMA) increased ezrin phosphorylation to 1.56±0.06 (mean±SE, n=8, p<0.01), and PIP2 depletion with PIP2 losses to 3.46±0.62 (mean±SE, n=8, p<0.01), indicating increased apical PM PIP2 content. Activation of phospholipase C (with PMA) increased ezrin phosphorylation to 1.56±0.06 (mean±SE, n=8, p<0.01), and PIP2 depletion with PIP2 losses to 3.46±0.62 (mean±SE, n=8, p<0.01), indicating increased apical PM PIP2 content.

Conclusions: Hence, CLIC5A may activate and/or recruit PI3K/Akt, resulting in localized PI2 generation, ezrin phosphorylation and cell-surface re-organization. We postulate that in podocytes, where it is highly expressed, CLIC5A maintains high, apical PIP2 and Ezrin concentrations, in turn contributing to the unique podocyte architecture and podocyte-dependent integrity of apical capillary.

Funding: Government Support - Non-U.S.
shown by western blotting and immunofluorescence. Also albumin and Cav-1 expression in HRGECs transfected with Cav-1 SiRNA were significantly decreased in comparison to normal HRGECs.

Conclusions: These findings indicate that albumin enters HRGECs through the caveole. Caveole on HRGEC play an important role in the pathogenesis of albuminuria by providing a new pathway through which albumin can enter glomerular endothelial cells.

Funding: Government Support - Non-U.S.


Background: The cytokine vascular endothelial growth factor A (VEGF-A) is a key regulator in the maintenance of the glomerular filtration barrier by promoting survival of podocytes and endothelial cells. There are seven proangiogenic VEGF-A splice variants. Longer isoforms containing heparin and neuropilin binding sites, such as VEGF-A 165 and 189, have a more prolonged and more effective mode of action than shorter isoforms, such as VEGF-A 121. In various kidney diseases quantitative changes in VEGF-A expression play an important role. In this study, we set out to investigate the renal splicing pattern of VEGF-A in various kidney disease entities in humans and mice.

Methods: Kidney biopsies from patients with acute rejection after kidney transplantation, patients with diabetic nephropathy, and from healthy controls were collected. Also kidney samples from mice with graft versus host disease and controls were collected. Lung, lymph node, spleen and thymus tissue samples from healthy mice were obtained. The relative expression of each individual splice variant was measured by RT-PCR followed by quantitative fragment analysis with capillary electrophoresis.

Results: In the healthy human kidney VEGF-A 121 was the dominant isoform with a relative expression of 75.08, VEGF-A 165 and 189 showed relative expression levels of 21.66% and 3.26%. The splicing pattern in diabetic nephropathy and in transplanted kidneys with acute rejection and in graft versus host disease did not differ from that in control kidneys.

In rodent kidneys VEGF-A 164 was the dominant isoform with a relative expression of 48.84%. VEGF-A 120 and 188 showed relative a expression of 43.24% and 7.74%, respectively. Different splicing patterns of VEGF-A were detected in samples from different organs.

Conclusions: VEGF-A splicing in the glomeruli is different between humans and rodents. Although it has been shown that there are quantitative changes of VEGF-A in transplanted kidneys with acute rejection and in diabetic nephropathy, the splicing pattern does not change in these disorders. Apparently quantitative rather than qualitative changes of VEGF-A mRNA levels play an important role in renal diseases.

SA-PO767 Molecular Mechanism of Steroid-Induced Thrombus Formation in Kidney Disease Noritaka Kawada, Toshiki Moriyama, Harumi Kitamura, Hiromi Rakugi, Yoshitaka Isaka. Osaka Univ, Health Care Center, Toyonaka, Osaka, Japan; 2Dept of Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

Background: The use of exogenous steroid positively associates with the risk of thromboembolism (Johannesdottir-SA et. al. J Am Soc Nephrol 24: 2013, 1-10). Plasminogen activator inhibitor-1 (PAI-1) inhibits plasminogen activator (IPA), plasmin and matrix metalloproteinase (MMP) and is known as an established risk marker for cardiovascular disease and thrombus formation. We tested the effects of exogenous steroid on the PAI-1 expression in cultured cells originated from rat kidney.

Methods: Rat primary cultured mesangial cells (rMSC), renal fibroblast cells (rRF), renal tubular cells (rNTK52), were exposed to dexamethasone (Dex) and/or TGFi. The mRNAs were quantitated and the collected cultured mediums were processed to test the induction of PAI-1 protein and MMP activity.

Results: rMSCs exposed to Dex (10-6M) or TGFi (2ng/ml) 6 hours for mRNA and 16 hours for protein, induced both mRNA and protein for PAI-1 (mRNA: Dex ×130%, p<0.01; TGFi ×190%, p<0.01; n=6 each). At the same experiment, the mRNA for IPA were reduced only in Dex (Dex ×36%, p<0.01; TGFi ×20%, p<0.01), n=6 each. The rMSCs exposed to both Dex and TGFi further induced PAI-1 protein and mRNA (PAI-1 mRNA: +640%, p<0.001; IPA mRNA: -40%, p<0.01; n=6). This was accompanied by the inhibition of MMP activity (p<0.01, n=6). The induction in PAI-1 and the reduction in IPA were also observed in NTK-49F and 52E cells exposed to Dex and/or TGFi. The effects of Dex and TGFi on PAI-1 and IPA expression in rMSCs were blunted by enhanced cAMP production with adenylate cyclase activator (Forskolin) or β2 antagonist (Betaxolol).

Conclusions: Steroid may promote thrombus formation in kidney disease through the induction of PAI-1 and the inhibition of IPA and MMP activity. Enhanced cAMP production has potential to moderate these unwiling side effects.

SA-PO768 PDGF Launches Mesangial Cell Proliferation via a Positive Feed-Back Loop Involving Erk5 and Akt Downstream of PI 3 Kinase Falguni Das, Amit Bera, Nandini Ghosh-choudhury, Balakantumala S. Kasiathan, Hana E. Abdou, Goutam Ghosh-Choudhury. 1Medicine, UTHSCSA, San Antonio, TX; 2Pathology, UTHSCSA.

Background: PDGF-forced proliferation of mesangial cells is an ominous feature of mesangiospliferative glomerulonephritis. The mechanistic underpinning of MC proliferation is not clear. We probed the role of most recently identified MAPK, Erk5.

Methods: Glomerular mesangial cells (MCs) were used.

Results: PDGF increased activating phosphorylation of Erk5 concomitant with enhanced tyrosine phosphorylation of several proteins including PDGF receptor in a time-dependent manner. XMD-8-92, an inhibitor of Erk5, attenuated PDGF-stimulated Erk5 phosphorylation. DNA synthesis and MC proliferation in the absence of any effect on Erk1/2 phosphorylation. Similarly, expression of dominant negative (DN) Erk5 or siRNA-mediated downregulation of Erk5 significantly inhibited PDGF-induced DNA synthesis and proliferation. Inhibition of Erk5 markedly blocked cyclin D1 mRNA and protein expression induced by PDGF, resulting in inhibition of its target cyclin-dependent kinase 4 (CDK4) phosphorylation and its substrate pRB inactivating phosphorylation. Interestingly, exogenous expression of wild type cyclin D1 or CDK4 reversed DN Erk5- and siErk5-mediated suppression of DNA synthesis and proliferation of mesangial cells induced by PDGF. As we have shown previously that PI3 kinase/Akt axis regulates PDGF-induced MC proliferation, we interrogated its role. Inhibition of PI3 kinase significantly blocked Erk5 phosphorylation. Since Akt is a downstream target of PI3 kinase, we examined the contribution of Erk5 in its activation. XMD-8-92, DN Erk5 and siErk5 inhibited PDGF-stimulated Akt phosphorylation. Interestingly, ME2206, a specific inhibitor of Akt kinase and DN Akt abrogated Erk5 phosphorylation by PDGF.

Conclusions: Together our results provide the first evidence demonstrating the presence of a micro-circuitry mechanism involving Erk5 and Akt to instruct cyclin D1/CDK4 to drive cell cycle progression and proliferation of MC in response to PDGF.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO769 Vitamin D Receptor Participate in the High Glucose-Induced Epithelial-Mesenchymal Transition of Mouse Podocytes through Wnt/GSK-3β/Catenin Signaling Pathway Guo Jia, Navin Lin; 1Nephrology, The First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China; 2Key-Disciplines Laboratory Clinical-Medicine Henan, Zhengzhou, Henan, China.

Background: Proteinuria, closely related with the disease development, is the main clinical symptoms of diabetic nephropathy. Previous studies and our previous results were all confirmed that epithelial-mesenchymal transition (EMT) of mouse podocyte cells was the major pathophysiological mechanism of proteinuria in diabetic nephropathy. It has been reported that the Wnt/GSK-3β/b-catenin signaling pathway involved in the EMT process of renal tubular epithelial cell induced by high glucose. Vitamin D receptor was reported involving in the EMT of renal tubular epithelial cells of end-stage renal diseases. And decreased expression of \VDR could lead the expression of b-catenin increased. The purpose of this study is to testing whether VDR participate in the EMT process of mouse podocytes caused by high glucose through Wnt/GSK-3β/b-catenin pathway.

Methods: The expressions of key molecules in Wnt/GSK-3β/b-catenin signaling pathway were detected in mouse podocytes with high glucose treatment and the normal control group by western blot and RT-PCR. Co-localization of the key molecules of Wnt/GSK-3β/b-catenin signaling pathway and VDR were observed by immunofluorescence.

Results: High glucose cultured mouse podocytes had obvious EMT phenomenon. The activity and expression of GSK-3β were significantly increased compared with the normal control group (P<0.05). The expressions of b-catenin and its downstream snail were also up-regulated compared with normal control group (P<0.05), while the VDR expression declined. By using the immunofluorescence assay, b-catenin in high glucose cultured mouse podocyte was found translocation to nuclear, showing less co-localization with GSK-3β and more co-localization with the VDR compared with the normal group.

Conclusions: Decreased expression of VDR may be involved in the EMT process caused by high glucose of mouse podocytes through Wnt/GSK-3β/b-catenin signaling pathway.

Funding: Government Support - Non-U.S.

SA-PO770 The Role of Dynamin in the Development of Proteinuria Ramzi Khalil, Reshma Lalai, Rosalie Bor, Reinhold Kreutz, Emile De Heer, Jan A. Bruijn, Hans J. Baelde. 1Pathology, Leiden Univer Medical Center, Leiden, Netherlands; 2Institute of Clinical Pharmacology and Toxicology, Charité - Univ Medicine, Berlin, Germany.

Background: Dynamin has been established as a protein essential in membrane scission, vesicular transport and fusion with action in cytoskeleton regulation. Rats with a podocyte-selective knock out of Dynamin showed proteinuria, renal failure and foot process effacement. In a previous microarray experiment, we identified dynamin mRNA as differentially expressed in spontaneously proteinuric Dahl SS rats. This study aims to investigate the role of dynamin in the time course of the development of proteinuria and the direct relationship between dynamin deficiency and loss of glomerular permselectivity.
SA-PO773
Effect of Rho Kinase (ROK) Inhibition on Rho A Induced Podocyte Injury
Linning Wang,1 William Eissner,12 Robert F. Spurney,12 1Medicine, Duke Univ, Durham, NC; 2Medicine, Durham VA Medical Center, Durham, NC.

Background: We previously created transgenic (TG) mice that expressed a constitutively active Rho A construct (V14Rho) specifically in glomerular podocytes in a doxycycline inducible fashion. In these TG mice, induction of V14Rho caused albuminuria and foot process (FP) effacement (Kidney Int 81:1075, 2012). In this same study, V14Rho promoted apoptosis of cultured podocytes and this apoptotic effect was attenuated by treatment with the ROK inhibitor Y27632.

Methods: To determine if Y27632 attenuated V14Rho induced podocyte injury in vivo, we treated V14Rho TG mice with doxycycline for 2 wks followed by doxycycline and either Y27632 or saline for an additional 2 wks.

Results: Treatment with doxycycline alone caused albuminuria (43±3 vs 10±2; P=0.01). The addition of saline vehicle to doxycycline treatment had little effect on albuminuria (38±10 μg/ml; P=NS) but Y27632 increased the albuminuric response (142±26 μg/ml; P=0.05). Because abnormal podocyte motility may be associated with albuminuria and FP effacement, we determined the effect of Y27632 on podocyte motility using a wound-healing assay. We found that V14 Rho alone had little effect on wound closure. In contrast, Y27632 enhanced wound closure in either the presence or absence of V14Rho suggesting that Y27632 increased podocyte motility. We next determined the molecular signature of Y27632 induced motility by investigating the effects of V14Rho and Y27632 on the actin and microtubule cytoskeleton. In cultured podocytes, V14Rho promoted formation of actin stress fibers and endogenous tubulin as well as phosphorylation of both myosin light chain (MLC) and coflin. Incubation with Y27632 inhibited V14Rho induced MLC phosphorylation, coflin phosphorylation and tubulin deacetylation but not formation of detyrosinated tubulin. With the exception of coflin, the effects of Y27632 were similar in V14Rho-expressing TG mice treated with Y27632.

Conclusions: The molecular signature of a motile podocyte in vitro was largely recapitulated in vivo. These data suggest that ROK inhibition promotes podocyte motility which, in turn, may diminish the beneficial effects of ROK inhibitors in glomerular diseases.

Funding: Veterans Affairs Support

SA-PO774
Urinary Microvesicles Differentiate Patients with Diabetic Nephropathy from Those with Active Glomerulonephritis

Background: Microvesicles (MVs) are small membrane-enclosed sacs that are shed from activated or injured cells and have been identified in different body fluids including urine. They contribute to a variety of pathophysiological processes involving cell-cell interaction. We hypothesized that urinary MVs may serve as a diagnostic marker in differentiating between glomerulonephritis (GN) and diabetic nephropathy.

Methods: Digital flow cytometry was used to characterize urinary MVs expressing podocyte markers in patients with type 2 diabetes mellitus (DM) (n=31, male=19, female=12) and biopsy-proven GN (n=9, male=6, female=3) including focal segmental glomerulosclerosis (n=4) and membranous nephropathy (n=5). Of 31 patients with DM, 23 had urine albumin <300mg/L (Group I) and 8 had urine albumin >300 mg/L (Group II). For diabetic patients, other etiologies causing proteinuria including autoimmune diseases, hepatitis B, C, or monoclonal gammopathy were excluded. Data were analyzed by non-parametric Kruskal-Wallis test. Results are shown as median. Units for urinary MVs are expressed as MVs/μL of urine.

Results: Median age in GN group was 52 vs. 64.5 years in Group II (P=0.03) and protein to creatinine was 3.5 vs. 1.4 mg/mg (P=0.05). There was no difference in the GFR between the two groups (43±4 vs. 64±1 mg/min/1.73m²). GN patients compared to Group II had significantly higher number of urinary MVs expressing podocyte markers such as nephrin (618 ± 335 P=0.03), & podocalyxin (1376 ± 587, P=0.04). There were also significantly greater number of parietal cell specific markers, claudin-1 plus CK-8 positive MVs (761 ± 310, P=0.04). There were no differences in the number of urinary MVs expressing podocyte markers between GN group and Group I. There was no association between degree of proteinuria or GFR and presence of urinary MVs (data not shown).

Conclusions: The high number of urinary MVs found in GN patients is suggestive of active ongoing injury to the podocyte in contrast to patients with advanced diabetic nephropathy. Urinary MVs may be used as a novel biomarker in distinguishing GN from DM with macroalbuminuria.

Funding: Other NIH Support - NICHD
SA-PO775
Transforming Growth Factor Beta Signalling Impairment in PLCE1 Mutant Podocytes
Carl James May, Gavin Iain Welsh, Moin Saleem.
Academic Renal Unit, Univ of Bristol, Bristol, Avon, United Kingdom.

Background: PLCE1 is a gene mutated in inherited nephrotic syndrome, causing diffuse mesangial sclerosis. It is unusual in not having a known role at the podocyte slit diaphragm or in actin regulation. We generated a conditionally immortalised cell line from a child with a PLCE1 mutation, and studied its biology.

Methods: Wild type and PLCE1 mutant human podocytes were treated with 2ng/ml recombinant TGF-B1. Podocyte markers and TGF signalling activity were measured by western blot and IF. Podocyte motility and barrier function were assessed by scratch assays and Electric Cell-substrate Impedence Sensing (ECIS) respectively.

Results: The mutant podocytes expressed typical podocyte markers at similar levels to wild type cells. Interestingly, the mutant cell line appeared mesenchymal in culture, and significantly upexpressed mesenchymal markers such as fibronectin and α-SMA. Despite expressing TGFBR1 and TGFBR2 there was no phosphorylation of SMAD2 in the mutant cell line. Non-canonical TGF-B1 signalling pathways were similarly impaired. This lack of SMAD2 signalling in response to TGF-B1 treatment also had functional consequences. Wild type podocytes became significantly more motile in response to 2ng/ml TGF-B: the mutant podocytes were unresponsive. This has clear implications for TGF-B signalling in vivo.

Conclusions: Sypl2 has no direct intermolecular contact with any known slit diaphragm molecules but is prone to develop the Finnish-type nephrotic syndrome. Sypl2-null mice with intact slit diaphragm genes still develop pathogenic footprocess deformation and hyperlipidemia instead of the Finnish-type nephrotic syndrome. It provides an animal model to study the metabolic-mediated nephrotic syndrome.

SA-PO777
Pathophysiology of Reductions in Renal Blood Flow (RBF) and Glomerular Filtrate Rate (GFR) in Sepsis
Ruben M. Sandoval,1 George Rhodes,1 Silvia B. Campos-bilderback,2 Sarah E. Wean,1 Bruce A. Mollitoris.1,2 Medicine/Nephrology, IU School of Medicine, Indianapolis, IN; 2Roudebush VAMC Indianapolis, IN.

Background: It is well known that the reduction in GFR in sepsis far exceeds the fall in RBF yet the mechanism(s) remain unknown.

Methods: We used the cecal ligation and puncture (CLP) sepsis model in Munich Wistar Fröntr rats with surface glomeruli to evaluate glomerular vascular alterations during ongoing sepsis at 24 hours.

Results: Serum creatinine increased from 0.3 to 0.8 mg/dl at 24 hours and was associated with a marked reduction in glomerular capillary RBF flow rates from 1.771 ± 0.467μm/sec in untreated rats to 0.576±0.327μm/sec (P=0.01). At 24 hour post injury, WBC adherence increased from 0.42 ± 0.33/25μm volume in untreated rats to 7.25 ± 0.82/25μm 24Hrs post CLP (p=0.05). Most noticeable was the heterogeneous nature of RBF flow and RBC density within the capillary lumens. Areas of markedly reduced or stagnant flow were observed with channeling of flow into adjacent areas. We quantified capillary branch point densities, which we determined to occur at approximately 48 ± 18.8 points per glomerular volume. Shunting of RBC flow was measured using changes in RBC density within the capillary lumens showing a decrease in RBC density within occluded loops. Untreated rats had a visual RBC density of 80.8 ± 3.5% while rats imaged 24HR post CLP had a decreased RBC density of 56.2 ±15.8% (p=0.01). Glomerular permeability was measured using a 150kDa Rhodamine dextran which increased from 0.007 ± 0.003 in untreated rats to 0.096 ± 0.046 (p=0.05) 24HR post CLP.

Conclusions: These data imply the marked dissociation between GFR and RBF during sepsis is due to a reduction in the glomerular surface area available for filtration and shunting of blood flow around the glomerulus via intraglomerular capillary branch points allowing for small decreases in RBF resulting from marked reductions in GFR.

Funding: Other NIH Support - NIH P-30 to Bruce A Mollitoris

SA-PO778
Sypl2-Robo2 Signaling Decreases Non-Muscle Myosin IIA Activity in the Podocyte
Xueping Fan, Anna Pisarek-Horowitz, Hila Milo Rasouly, Stefanie Chan, David J. Salant, Weining Lu. Renal Section, Dept of Medicine, Boston Univ Med Center, Boston, MA.

Background: We have recently discovered that Robo2 is a novel podocyte protein localized to the basolateral cell surface of the podocyte. Sypl2-Robo2 signaling inhibits neprin-induced actin polymerization and regulates podocyte foot process structure. However, the downstream signaling components of this Sypl2-Robo2 pathway in podocytes are unknown.

Methods: Yeast two-hybrid screen and protein precipitation assays were performed to identify novel downstream signaling components of Sypl2-Robo2 pathway in podocytes. Immunocytochemistry was used to verify protein expression of novel components in podocytes. We also performed genetic interaction studies in podocyte-specific knockout mice of Robo2 and the newly identified gene.

Results: Using yeast two-hybrid screen, we find that the myosin II regulatory light chain (MRLC), a subunit of non-muscle myosin IIA heavy chain (NM IIA, encoded by MYH9 gene), interacts directly with Sypl2-Robo2 GTPase activating proteins (sGAPs). Protein precipitation assays show that NM II A, MRLC, sGAPs, and Robo2 receptor form a protein complex that is enhanced by Sypl2 ligand. Immunocytochemistry indicates that NM IIA, MRLC and sGAPs are expressed in podocytes. In vivo functional study demonstrates that Sypl2-Robo2 signaling decreases NM IIA activity in podocytes. In vivo studies show that Myh9 and Robo2 podocyte-specific double knockout mice have fewer podocyte numbers compared with Robo2 single knockout mice.

Conclusions: We have identified sGAPs, MRLC and NM IIA (Myh9) as novel downstream signaling components of the Sypl2-Robo2 signaling in podocytes. NM IIA activity is down-regulated by Sypl2-Robo2 signaling, which may play a role in regulating podocyte cell adhesion and dynamics.

Funding: NIDDK Support, Private Foundation Support

SA-PO779
ERK1/2 Are Dispensable for Normal Podocyte Function and Initial Response to Injury In Vivo
Johannes S. Schindlendorf, Eliyahu V. Khankan.
Div of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background: The Erk pathway is one of the canonical mitogen activated protein kinase signaling pathways and plays a central role in critical cellular functions, including survival and differentiation. Erk activation is a common manifestation in multiple human glomerular diseases and mouse models. However, it remains unclear whether its role is as a mediator or mitigator of disease, with conflicting results from in vitro studies. Here we present data that deletion of Erk1/2 in podocytes is dispensable for normal glomerular function.
Methods: Mice with a germline deletion of ERK1 (ERK1-/-), a f-allele of ERK2 (ERK2 f-fox/fox), and podocyte specific Cre expression were generated. These podocyte ERK1-/- mice and ERK2-/- mice were crossed with wild-type (Cre +/-) mice to produce podocyte-specific Cre reporter animals. Urinary microalbumin-to-creatinine ratios in male C57BL/6J mice were measured in 24-hour urine samples. The results showed that male C57BL/6J mice demonstrated no gross or historic renal abnormalities at 6 weeks of age and have no significant albuminuria at that time. At 8 months of age, male mice showed a trend toward mildly elevated microalbumin/Cr ratios. Podocyte ERK1-/- deficient males did not differ from their littermates with regard to peak proteinuria after NTS injection, nor with initial recovery at 11 days post-NTS. However, one month after NTS injection, podocyte ERK1-/- deficient males showed approximately two fold higher residual albuminuria.

Conclusions: Podocyte development and function is not dependent upon ERK1/-/- in vivo. ERK2-/- mice may show a similar initial response to acute, transient podocyte injury in the NTS model, though there is evidence that they do not recover as well from the injury. In summary, these findings suggest that ERK1/-/- do not play an essential role in baseline podocyte function and likely has only a minor role in podocyte response to injury or stress.

Funding: NIDDK Support, Private Foundation Support

SA-PO780

Cyclosporine A Protects Podocyte via Upregulating the Expression of Calb-1 in Podocytes

Xiaoyan Zhang,1 Xiaoyan Li,1 Youfei Guan,2 Jie Ding.1

1Pediatric, Beijing Univ First Hospital, 2Physiology and Pathophysiology, Beijing Univ Health Science Center.

Background: Podocyte foot process is dysregulated in nephrotic syndrome. The effacement of podocyte foot processes typically arises owing to perturbations in the actin cytoskeleton. Calcineurin inhibitor Cyclosporine A (CsA) is currently used in the treatment of nephrotic syndrome. Recent data suggest that the effects of CsA on nephrotic syndrome are independent of its effects on the immune system. They identified that CsA can stabilize the actin cytoskeleton through stabilizing synaptopodin in podocytes and thereby reduce proteinuria directly. Other studies also showed that CsA induced collagen phosphorylation and promoted stress fiber generation in proximal tubular cells. However, whether the antiproteinuric role of CsA is played by regulating calbindin-1 in podocyte has not been studied.

Methods: Acute podocyte injury and nephrotic syndrome were induced by puromycin aminonucleoside (PAN) injection in rats with or without CsA. Cultured podocytes were exposed to PAN with or without CsA treatment. Calbin-1, nephrin, synaptopodin expression were detected by western blot or immunofluorescence. The calbin-1 specific effect was determined using calbin-1 siRNA.

Results: CsA reduced proteinuria, restored expression of calbin-1, nephrin, synaptopodin and repaired foot process effacement of PAN induced nephropathy in vivo. In vitro studies showed that exposure of CsA restored the expression of calbin-1 and nephrin which decreased by PAN. CsA also reduced actin cytoskeleton impaired by PAN. The protective effect of CsA was disappeared partially when cultured podocytes were exposed to calbin-1 siRNA.

Conclusions: The antiproteinuric effect of CsA is derived from the stabilization of the podocyte actin cytoskeleton by upregulating expression of calbin-binding protein calbin-1.

Funding: Government Support - Non-U.S.

SA-PO781

Calbin-1 (28kDa) Inactivation Leads to Proteinuria: Studies in Zebrafish (Danio rerio)

Laura L. Beverly-Staggss, Patricia Ann Schroer, Konstantin Deutsch, Michelle P. Winn, Gentzon Hall, Ron Korstanj, Christoph Kornauth, Hermann G. Haller, Mario Schiffr.1

1Div of Nephrology, Hanover Medical School, Hanover, Germany; 2Mount Desert Island Biological Laboratory, Salisbury Cove, ME; 3The Jackson Laboratory, Bar Harbor, ME; 4Dept of Pathology, Medical Univ of Vienna, Vienna, Austria; 5Div of Nephrology, Duke Univ Medical Center, Durham, NC.

Background: Calbin-1 (Calb-1) is an intracellular calcium-binding protein containing four active calcium binding domains. As calcium homeostasis is important for podocyte function and maintenance. The scores, reflecting the negative logarithms of the significant p values, for the top 3 networks included functional categories of: a) Cell cycle, cell development, cell signaling; b) RNA post-translational modification, cell morphology, cellular assembly and organization; c) Cell-to-cell signaling and interaction, cellular compromise, cellular function and maintenance. The scores, reflecting the negative logarithms of the significant p values, for the top 3 networks included functional categories of: a) Cell cycle, cell development, cell signaling; b) RNA post-translational modification, cell morphology, cellular assembly and organization; c) Cell-to-cell signaling and interaction, cellular compromise, cellular function and maintenance. The expression levels, reflecting the negative logarithms of the significant p values, for the top 3 networks included functional categories of: a) Cell cycle, cell development, cell signaling; b) RNA post-translational modification, cell morphology, cellular assembly and organization; c) Cell-to-cell signaling and interaction, cellular compromise, cellular function and maintenance.

Conclusions: In summary we found that Calb-1 knockdown results in a podocyte phenotype in zebrafish. In contrast in a rodent model the knockdown did not lead to proteinuria but to an upregulation of calreticulin indicating a delicate balance of calcium binding proteins in the podocyte.

Funding: Private Foundation Support

SA-PO782

Prostaglandin E2 Upregulates Olfactory Genes in Podocytes with Recovery from Nephrotic Syndrome Induced Injury

Nino Kvirkvelia, Maggie McNemamin, Afu Abdul, Michael P. Madaio. Medicine, Georgia Regents Univ, Augusta, GA.

Background: PGE, promotes resolution of Nephrotic Syndrome in mice, and this was due, at least in part, to promoting glomerular cell recovery. In cell culture, PGE, reduced nephrotic serum (NTS) induced apoptosis of glomerular cells and promoted cell repoliferation after NTS-mediated injury.

Methods: To define the pathways involved, microarray analysis (Affymetrix oligonucleotide chips) was used to investigate PGE; regulated gene expression profiles in mouse glomerular epithelial cells after NTS treatment. Genes with a minimal 1.5-fold change and p<0.05 were selected for network generation and pathway analyses by Ingenuity Systems. GenBank IDs of the selected genes were then mapped to the functional networks available in the Ingenuity Pathway Knowledge Base.

Results: A total of 237 genes with 3.5-1.5 changes (p<0.05) were identified, and the top 3 networks included functional categories of: a) Cell cycle, cell development, cell signaling; b) RNA post-translational modification, cell morphology, cellular assembly and organization; c) Cell-to-cell signaling and interaction, cellular compromise, cellular function and maintenance. The scores, reflecting the negative logarithms of the significant p values, for the top 3 networks included functional categories of: a) Cell cycle, cell development, cell signaling; b) RNA post-translational modification, cell morphology, cellular assembly and organization; c) Cell-to-cell signaling and interaction, cellular compromise, cellular function and maintenance. The expression values of: 2.807; 2.681; 2.464; 2.229; 2.208; 2.110; 2.052; 1.951; 1.901; 1.893 respectively.

Conclusions: We found edema, proteinuria and foot process effacement in zebrafish sh embryos injected with pan overexpressing wt TRPC6 or TRPC6M131T, and decreased by ~70% in mouse TRPC6-/- mice showing a 2.4 fold increase in TRPC6 membrane expression suggesting synpo limits cell surface expression of TRPC6. Moreover, synpo was upregulated by ~2 fold in podocytes overexpressing wt TRPC6 and expression of FS-GS-FS-Ca++/sodium-mutant TRPC6 in cultured and primary mouse podocytes were achieved by lentiviral system.

Results: Close co-localization of TRPC6 and synpo was observed in podocyte FPs by immunogold double labeling in mouse kidney sections. Interaction between TRPC6 and synpo was observed by co-IP in HEK293, cultured podocytes and mouse glomeruli. This interaction is significant because surface TRPC6 in synpo down-regulated podocytes showed a 2.4 fold increase in TRPC6 membrane expression suggesting synpo limits cell surface expression of TRPC6. Moreover, synpo was upregulated by ~2 fold in podocytes overexpressing wt TRPC6 or TRPC6(Ca++/Sodium) in cultured and primary mouse podocytes were achieved by lentiviral system.

Funding: NIDDK Support

SA-PO783

Synaptopodin Limits Cell Surface Expression of TRPC6 in Podocytes

Andreas D. Kistler, Stuart E. Dryer, Jochen Reuss.1 Nephrology, Univ of Miami, Miami, FL; 2Biology and Biochemistry, Univ of Houston, Houston, TX; 3Medicine, Rush Univ, Chicago, IL.

Background: TRPC6 mutations have been shown to cause familial FSGS and increased TRPC6 in podocytes is found in acquired glomerular diseases. Synaptopodin (synpo) is a stabilizer of actin cytoskeleton in podocytes and it can be preserved by Cyclosporine A (CsA). We show that synpo interacts with TRPC6 and this interaction is functionally important and may have a role in regulating membrane localization of TRPC6.

Methods: Immunogold labeling and co-immunoprecipitation (co-IP) were performed to examine co-localization and interaction of TRPC6 and synpo, respectively. Cell surface biotinylation assay in synpo knock-down mouse podocytes was carried out to measure TRPC6 cell surface levels. Knockdown of synpo in podocytes and overexpression of TRPC6. Moreover, synpo was upregulated by ~2 fold in podocytes overexpressing wt TRPC6 or TRPC6(Ca++/Sodium) in cultured and primary mouse podocytes were achieved by lentiviral system.

Results: Close co-localization of TRPC6 and synpo was observed in podocyte FPs by immunogold double labeling in mouse kidney sections. Interaction between TRPC6 and synpo was observed by co-IP in HEK293, cultured podocytes and mouse glomeruli. This interaction is significant because surface TRPC6 in synpo down-regulated podocytes showed a 2.4 fold increase in TRPC6 membrane expression suggesting synpo limits cell surface expression of TRPC6. Moreover, synpo was upregulated by ~2 fold in podocytes overexpressing wt TRPC6 or TRPC6(Ca++/Sodium) and decreased by ~70% in mouse TRPC6-/- glomeruli and TRPC6 primary podocytes. Reduction of synpo was rescued by expressing wt TRPC6 in TRPC6-/- primary podocytes. These data may reflect a feedback mechanism for podocytes to counteract the effect of malfunctioning or excessive TRPC6.

Conclusions: We demonstrate that synpo negatively regulates TRPC6 expression on cell membrane, presumably by direct binding. CsA, a drug that has been used to treat FSGS, was shown to stabilize synpo in podocytes. We propose a mechanism that CsA protects podocytes from excessive TRPC6 or FSGS-causing TRPC6 mutants by lowering cell surface expression of TRPC6 through stabilization of synpo.

Funding: NIDDK Support
SA-PO784

Dynamin1 Regulates Actin Cytoskeleton in Podocytes in a Phosphorylation Dependent Manner
Changyu Gu, Sanja Sever.
Nephrology, Massachusetts General Hospital, Charlestown, MA.

Background: Dynamin is an essential actin regulatory protein in podocytes, and loss of its function is closely connected to podocytes damage and proteinuria. Recently, our data has shown that dynamin directly regulates actin cytoskeleton via its oligomerization state. This dynamin oligomerization can be regulated through interaction with diverse cellular proteins, and it is reported that dynamin1 can differentially alter the affinity for its protein binding partners via phosphorylation by two different serine/threonine kinases, GSK3b and CDK5, in neurons. Based on these data, we hypothesize that phosphorylation-dependent dynamin1 oligomerization is an important molecular mechanism that regulates actin dynamics in podocytes.

Methods: Various phospho-dynamin1 mutants were generated by site-directed mutagenesis, and adenoviruses carrying these mutants were produced using Adenoviral Expression System (Invitrogen). Actin and paxillin in podocytes were stained to observe actin stress fibers and focal adhesions, respectively. Western blotting was done to detect oligomerization state of different phospho-dynamin1 mutants in podocytes.

Results: 1. Inhibition of GSK3b or CDK5 alters actin structures in podocytes.
2. Dynamin1 is phosphorylated by GSK3b and CDK5 in podocytes.
3. Dynamin1 mutants lacking PRD domain inhibited the effects of GSK3b inhibitor on actin structures in podocytes.
4. Dynamin1 mutants which cannot be phosphorylated by GSK3b stimulate the formation of actin stress fiber and focal adhesions in podocytes.
5. FLIM assay showed that ablation of the GSK3b-specific phosphorylation site on dynamin1 induces dynamin1 oligomerization in podocytes.

Conclusions: The role of dynamin in actin cytoskeleton is essential to maintain the filtration barrier function of podocytes. Dynamin directly regulates actin structures via its oligomerization state. Our data show that dynamin1 oligomerization can be modulated by its phosphorylation state, and phosphorylation-dependent dynamin1 oligomerization contributes to regulation of actin dynamics in podocytes.

Funding: NIDDK Support

SA-PO785

Paricalcitol Ameliorates TGF-β Induced Glomerulopathy via Notch Pathway Activation
Taiichi Murakami, Koji Okamoto, Shashi Shivastav, Hidefuni Wakashita, Jeffrey B. Kopp.
NIDDK, NIH, Bethesda, MD.

Background: Vitamin D (VitD) is a promising approach to renoprotection. TGF-β1 and VEGFa as they both regulate glomerulosclerosis.

Methods: Notch-related gene regulation was determined by qRT-PCR and protein expression confirmed by immunoblot (WB) and immunofluorescence (IF)

Results: Direct TGF-β1 stimulation of the ligand, Jag1, was detected (WB, mRNA) by 1-8h. We detected TGF-β/Jag1-induced Notch1, but not Notch2, cleavage by WB at 4-24h. Interestingly, we observed a second wave (24-48 hr) of Jag1 gene expression that was positive for Notch cleavage dependent. 

Conclusions: Notch1 is engaged in cross-talk with Notch-dependent pathways in podocytes. To understand this specificity in podocytes, we investigated Notch signaling in response to growth factors TGF-β1 and VEGFa as they both regulate glomerulosclerosis.

Funding: NIDDK Support

SA-PO786

Effect of Angiotensin II on Podocyte Autophagy
Imane Benchabla, 1,2 Carole Hénique-Gréciet, 1,2 Pierre-Louis F. Tharaux.
Paris Cardiovascular Research Centre - PARCC, INSERM, Paris, France; 1'univ Paris Descartes, Sorbonne Paris Cité.

Background: Injury and loss of podocytes are leading factors of glomerular diseases and renal failure. Angiotensin II (AngII) promotes albuminuria, aggravates non hypertensive glomerulosclerosis and severe hypertension nephropathy (HTN). Recently, autophagy has been identified as a major mechanism that delivers damaged proteins and organelles to lysosomes in order to maintain cellular homeostasis. Podocytes exhibit an unusually high level of constitutive autophagy.

Methods: The aim of this study was to evaluate the role of AngII on autophagy in podocytes. Expression of LC3 II, an autophagosome membrane protein, was measured in kidney homogenates and in podocytes from HTN mice after chronic infusion of AngII or its inverse, in primary cultures of podocytes from mice with normal or constitutive activation of the AT1 receptor.

Results: Mice with chronic HTN presented decreased autophagy activity in podocytes. Furthermore, podocyte culture from mice with constitutively active AT1 mutant (CAM) displayed lower autophagy flux than wild type mice. Chronic activation of the AT1 receptor induced significant podocyte loss, as demonstrated by WT1 and podocin staining in aged mice. In primary podocyte culture, autophagy regulation is independent of the PI3-kinase-mTOR pathway, as shown after rapamycin treatment. To further investigate the importance of autophagy in podocyte survival, we used a mouse model with podocyte specific deletion of Atg5 alleles, that is required for autophagosome formation and maturation (Pod-Atg5 mice). Pod-Atg5 mice developed more severe glomerular injury than wild type counterparts upon chronic AngII infusion, with severe albuminuria and glomerulosclerosis.

Conclusions: In conclusion, chronic activation of the AT1 receptor promotes decrease in autophagy activity and unravel a protective function for podocyte autophagy in AngII-mediated glomerulosclerosis.

Funding: NIDDK Support

SA-PO787

TGF–β1 and VEGFa Differentially Regulate Notch Signaling in Podocytes
Mariva T. Sweetwyne, Katalin Sustak.
Renal, Electrolyte and Hypertension Div, Univ of Pennsylvania, Philadelphia, PA.

Background: The Notch family is comprised of receptors (N1-4) and the Jagged (Jag1-3) and Delta-Like (DLL1, 3, 4) ligands. The regulation of these receptors and ligands suggests that they are not functionally redundant in podocytes. We previously showed that loss of N1 from podocytes (via floxed Notch1/podocin Cre) protects glomeruli from diabetic injury in vivo. Conversely, expression of Notch2 is critical for podocyte development. To understand this specificity in podocytes, we investigated Notch signaling in response to growth factors TGF-β1 and VEGFa as they both regulate glomerulosclerosis.

Methods: Murine podocytes were transfected with plasmids containing either a constitutively active Notch1- or a constitutively active VEGF165 receptor (VEGF receptor expression was confirmed by immunoblot (WB) and immunofluorescence (IF)).

Results: Direct TGF-β1 stimulation of the ligand, Jag1, was detected (WB, mRNA) by 1-8h. We detected TGF-β/Jag1-induced Notch1, but not Notch2, cleavage by WB at 4-24h. Interestingly, we observed a second wave (24-48 hr) of Jag1 gene expression that was positive for Notch cleavage dependent. TGF-β1 suppressed expression of the Notch ligand Dll1 while inducing expression of Jag1 and Dll4. Jagged1 and Jag1 (IF) was induced heterogeneously, with cells expressing either Jagged1 or Dll4. Furthermore, TGF-β1 also induced Notch dependent VEGFa expression in podocytes. Direct stimulation of podocytes with VEGFa induced Notch dependent expression of Dll4 but not other ligands, suggesting that TGF-β1-induced Dll4 expression is downstream of Jagged1 and VEGFa.

Conclusions: TGF-β1 directly induces Jagged1 expression and Notch1 activation in podocytes after time point 4h. Stimulation of podocytes with VEGFa is sufficient to induce Dll4. Our results reveal an important ligand-specific response to TGF-β1/VEGFa cross-talk converging on the Notch signaling pathway.

Funding: NIDDK Support

SA-PO788

Melanocortin 1 Receptor Protects against Puromycin Induced Attenuated Stress-Fiber Rearrangement
Johannes Elvin, 1 Annika Lindskog Jonsson, 1 Lisa Maria Buval, 1 Anna Granqvist, 1 Jenny C. Nystrom, 1 Borje Haraldsson. 1 Dept of Nephrology, Massachusetts General Hospital & Harvard Medical School, 2Dept of Physiology, Institute of Neuroscience and Physiology, Univ of Gothenburg, Sweden.

Background: Drugs targeting the melanocortin 1 receptor (MC1R) have shown to possess beneficial properties in treatment of patients with nephrotic syndrome. We have earlier demonstrated reduced proteinuria in combination with improvement in glomerular morphology following MC1R treatment in a nephrotic rat model. We are currently investigating the mechanisms behind the beneficial effects of MC1R stimulation, with focus on actin dynamic regulatory pathways in podocytes.

Methods: Conditionally immortalized mouse podocytes over-expressing human MC1R were subjected to the nephrotic agent puromycin aminonucleoside (PAN) and simultaneously treated with a selective synthetic MC1R agonist (SA) or a non-selective MC1R agonist (α-MSH). Following PAN and MC1R agonist treatment, F-actin was visualized with Rhodamine-Phallodin and stress fiber content in cells was calculated and compared between treatment groups.

Results: The MC1R agonist SA or α-MSH were both able to restore stress fibers in podocytes with disrupted actin cytoskeleton due to PAN treatment. Stress fiber analysis following MC1R agonist treatment, revealed restoration of up to 40% of the actin stress-fibers in cells compared to PAN treatment alone.

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

808A
Conclusions: MCIR stimulation hereby demonstrates the ability to restore stress fibers in podocytes when exposed to nephrotoxic agents such as PAN. Adding to previous work, we know that MCIR signals through a cyclic AMP-dependent (cAMP) pathway. These data could propose that MCIR protects glomerular podocytes by reactivating the actin cytoskeleton through a cAMP dependent pathway.

Funding: Government Support - Non-U.S.

SA-PO791

Tumor Necrosis Factor-α, Interleukin-6 and High Insulin Disrupt Podocyte Insulin Responses In Vitro Abigail Charlotte Lay, Gavin Iain Welsch, Moin Saleem, Peter W. Mathieson, Richard Coward. Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom

Background: We have previously demonstrated that podocytes are insulin-responsive cells in vitro and the podocyte-specific depletion of the insulin receptor (IR) in vivo results in glomerular dysfunction. It is recognised that insulin resistance is associated with albuminuria and type 1 and type 2 diabetic patients with insulin resistance are more at risk of developing nephropathy. Hyperinsulinaemia and increased circulating levels of the pro-inflammatory cytokines TNF-α and IL-6 are factors associated with insulin resistance. Here, the effects of Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6) and high insulin concentrations on podocyte insulin responses in vitro were examined.

Methods: Conditionally immortalised mouse podocytes were grown in the presence of insulin, TNF-α and IL-6, and the effects on podocyte insulin responses investigated. Insulin-stimulated glucose uptake was assessed via a 2-deoxyglucose uptake assay, western blotting was performed to determine changes in protein expression and insulin-stimulated phosphorylation cascades and focused insulin signalling PCRs were performed to determine any changes at the mRNA level.

Results: Exposure to TNF-α and IL-6 reduces insulin-stimulated glucose uptake in podocytes. Western blotting demonstrated no significant reduction in IR protein levels and insulin-stimulated phosphorylation of IGF-IR (Tyr1131)/IR (Tyr1146) and Akt (Ser473, Thr308). Other aspects of the insulin signalling cascade are currently being investigated in a focused insulin signalling PCR array. Preliminary data suggests podocyte exposure to high concentrations of insulin in vitro reduces IR protein expression and phosphorylation of IGF-IR (Tyr1131)/IR (Tyr1146). Furthermore, Akt phosphorylation (Ser473, Thr308) also appears depressed.

Conclusions: Prolonged exposure of mouse podocytes to insulin and the pro-inflammatory cytokines TNF-α and IL-6 in vitro disrupts podocyte insulin responses. Investigating factors contributing to podocyte insulin insensitivity will enhance our understanding of the causes of glomerular disease in settings of insulin resistance.

SA-PO790

HIV Induces Podocyte Epithelial Mesenchymal Transition (EMT) through Modulation of Tumor E최 Transcription Factor (Tert) Tejinder Singh, Nirupama Chandel, Partab Rai, Gautam Kishore Valecha, Pravin C. Singhal. Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY

Background: HIV-associated nephropathy (HIVAN) is characterized by podocyte proliferation and loss of foot process formation of collapsing glomerulopathy. HIV induces podocyte proliferative phenotype through podocyte expression of TERT in a HIV transgenic mouse model. We earlier reported that proliferative phenotype of kidney cells in HIVAN was the consequence of HIV-induced epithelial mesenchymal transition (EMT). In the present study, we hypothesized that HIV induces EMT in podocytes through the modulation of kidney cell Tert expression.

Methods: Renal cortical sections of control and HIVAN mice (Tg26) were immunolabeled for Tert, and EMT markers. In vitro studies, conditionally immortalized human podocytes (CHP; these podocytes constitutively Tert) were transduced with either HIV (NL4-3, HIV/CHP) or empty vector (EV/CHP). CHP proliferated at 33°C and differentiates at 37°C. To determine the effect of HIV on Tert expression and occurrence of EMT, EV/CHPs and HIV/CHPs were incubated in media at 33°C for 72h, followed by differentiation at 37°C for 72h (CIDHDP). Cellular lysates of control and experimental cells were probed for Tert, vimentin, α-SMA, p-cadherin, and FSP-1. To probe relationship between Tert and podocyte EMT, HIV/CHDP were silenced for Tert and evaluated for vimentin, SMA and FSP-1.

Results: Tert expression of Tg26 mice displayed enhanced Tert expression by podocytes. In vitro studies, HIV/CHP exhibited enhanced expression of Tert and robust expression of vimentin, α-SMA and FSP-1 when compared to EV/CHPs. HIV/CIDHP displayed moderate expression of Tert, vimentin, α-SMA, and FSP-1 but decreased expression of p-Smad2/3 and p-Smad4 and synaptopodin. HIV/CIDHDP displayed robust expression of Tert, α-SMA, and FSP-1 and decreased expression of nephrin, synaptopodin and WT1. siRNA/α-TERT and siRNA/α-CIDHDP demonstrated attenuated expression of vimentin, α-SMA, and FSP-1.

Conclusions: These findings indicate that induced podocyte EMT is mediated through HIV-induced Tert expression.

Funding: NIDDK Support
type 2 diabetes/advanced DKD. Notably, SAA3 was prominently expressed in glomerular podocytes. The aim of this study was to evaluate direct effects of SAA on podocyte inflammatory responses that may contribute to podocyte dysfunction. 

Methods: Mouse podocytes were treated with SAA (human SAA isoform 1), advanced glycation end products (pro-inflammatory control), or normal control conditions for 6, 24 and 48 hours. Nuclear Factor kappa B (NF-kB) activity was measured in cell lysates. Podocyte death was also assessed with SAA for 1 day and mRNA measured (quantitative real-time PCR) using pathway arrays featuring NF-kB and inflammation-related genes. Mouse SAA3 protein was also measured from conditioned media (ELISA).

Results: Mouse podocytes exposed to SAA or AGE increased NF-kB activity. SAA protein expression increased in response to the DNA at around 63-65 °C targets to numerous inflammatory alpha and beta chemokines including ENA-78, RANTES, and MCP-1. Inflammatory cytokines were also induced, including IL-6, G-CSF, and SAA3 itself. SAA3 protein production was also augmented in podocytes exposed to SAA.

Conclusions: SAA induces a wide-ranging inflammatory response in podocytes, making it a likely candidate to instigate inflammatory mechanisms in diabetic glomerular disease. Increased expression of an SAA gene, and consequent mRNA translation, in response to exposure to an SAA isoform suggests up-regulation via an autocrine positive feedback loop in podocytes.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO794

Blockade of AT1 Receptor Upregulates Vitamin D Receptors in Podocytes through Downregulation of CYP24A1

Tejinder Singh, Nirupama Chandel, Rivka Lederman, Partab Rai, Ashwami Malhotra, Pravin C. Singhal, Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

Background: Blockade of AT1R leads to the slow down in the progression of renal lesions in several kidney disease models. We hypothesized that blockade of AT1R would provide protection against podocyte injury by de novo up regulation of vitamin D receptor (VDR).

Methods: Control and HIV transgenic mice (Tg26) were evaluated under control and Telimisartan treatment (2 wks, Tg/Tel) for renal tissues expression of VDR and CYP24A1. Human podocytes (HPT) incubated in media containing either buffer, losartan (10 μM) + Ang II (100 μM), or Ang II-stimulating mitogens (HIV, high glucose,30 mM) (n=3). To determine the role of AT1, CBHs transfected with siRNA-AT1R or scrambled siRNA (SCR) in the presence/absence of losartan.To determine the role of tyrosine kinase, HPTs were treated with either buffer or genistein (10 μM) ± Ang II. To determine the role of Vat D3; CBHs were incubated in serum free media (SFM) containing either buffer, vit D3 (10 pM) or losartan for 24h (n=3). All Protein blots were probed for VDR and CYP24A1 expression.

Results: Renal tissues in Tg/Tel mice displayed attenuated VDR but enhanced CYP24A1 expression. In vitro studies Ang II, glucose and HIV down regulated podocyte VDR expression; whereas, losartan enhanced podocyte VDR expression under basal as well as Ang II-, glucose-, and HIV-stimulated conditions. HPT-siRNA-AT1 also displayed enhanced VDR but attenuated CYP24A1 expression. Ang II, HIV and glucose stimulated podocyte expression of CYP24A1. Interestingly, losartan enhanced VDR expression only enhanced VDR but attenuated CYP24A1 expression. Ang II, HIV and glucose stimulated AT1R blockade.

Conclusions: AT1 blockade upregulates VDR through down regulation of CYP24A1 and the former provides protection against HIV-induced podocyte injury.

Funding: NIDDK Support

SA-PO795

Rapid Multiplex Detection of E. coli and K. pneumoniae by Loop Mediated Isothermal Amplification in Urine

Ashish Yeri,1 Ishwad Chandra,1 Abhay N. Vats.1 1Nephrology, Children's Hospital of Pittsburgh; 2Chemical and Petroleum Engineering, Univ of Pittsburgh.

Background: The need for rapid point-of-care diagnostics for infectious diseases has been steadily increasing globally, especially in low resource settings. E. Coli and K. pneumoniae are responsible for a large proportion of urinary tract infections (UTI) as well as other infections. Detection of these organisms is generally done by bacterial culture which usually takes 48 hours or more. Recently, a loop mediated isothermal amplification (LAMP) technique has been developed which amplifies a DNA sequence in a reaction mixture at temperatures between 60-65 °C with high specificity in 30-60 minutes or less. We utilized LAMP protocols and lateral flow display to detect these two common UTI associated organisms in a multiplex reaction. Methods: The LAP procedure utilizes 6 primers and can be performed on a regular wall or heating block maintained at a constant temperature of 60-65 °C. The detection of the LAMP E. Coli and K. pneumoniae amplification product was performed on lateral flow display (LFD) strips LFD primarily consists of a nitrocellulose membrane with antibodies immobilized at specified locations. Labeled primers, namely biotin, digoxigenin (K. pneumoniae) and fluorescent (E. Coli) labeled (E. Coli) products were mixed to form tetramers which were then determined by performing a sandwich type immunoassay. We analyzed 8 identified human urine samples from patients with suspected UTI with LAMP and LFD and compared results with culture and PCR.

Results: LAMP amplification took about 30 minutes or less which was followed by LFD detection in 5 minutes or less. LFDs showed a clear visible lines for E. Coli and K. pneumoniae. Exposure to an SAA isoform suggests up-regulation via an autocrine positive feedback loop in podocytes.

Funding: Private Foundation Support

SA-PO796

Pseudoperphosphatemia during Exposure to Liposomal Amphotericin B Therapy

Nicole Bohm,1 Katherine Hoover,1 Amy E. Wahlgquist,2 Juan Carlos Q. Velez,2 1Dept of Pharmacy, Medical Univ of South Carolina; 2Div of Nephrology, Medical Univ of South Carolina; 2Dept of Public Health Sciences, Medical Univ of South Carolina.

Background: Reports have emerged linking exposure to liposomal amphotericin B therapy with factually elevated serum phosphorus (sPhos) levels (pseudoperphosphatemia) caused by interference of the phospholipid component of L-AmB with the kinetic-based clinical assay. However, this phenomenon remains under-recognized.

Methods: We reviewed records of adult hospitalized patients treated with L-AmB or fluconazole (Fcz, control) at our institution in the last 5 years, excluding those with estimated glomerular filtration rate (eGFR) < 20 ml/min.

Results: Among those without chronic kidney disease (CKD) [eGFR > 59] and no concomitant infection or kidney injury (AKI) [50% rise in serum creatinine], de novo high sPhos [>5.0 mg/dl] occurred more often during L-AmB therapy compared to Fcz therapy [36% (12/33) vs 13% (63/491), respectively, p<0.01]. Very high sPhos [>7.0 mg/dl] was also more common during L-AmB therapy [6% (2/33) vs 1% (2/249), respectively, p<0.01]. Among those with CKD [eGFR 20-59] and no concomitant AKI, high sPhos also occurred more often during L-AmB therapy [60% (12/20) vs 24% (45/184), p<0.01]. Similarly, very high sPhos was more common during L-AmB therapy [15% (3/20) vs 3% (6/184), p<0.02]. None of the L-AmB-treated subjects with high sPhos received phosphorus supplements. An unexpected drop in serum calcium, use of phosphorus binders and baseline eGFR, L-AmB-treated patients remained more likely to have high sPhos than the Fcz group [4.0 (95% CI: 1.9 to 8.6) times in non-CKD and 4.3 (95% CI: 1.6 to 11.7) times in CKD, p<0.01]. In the presence of concomitant AKI, no differences were observed. In addition, we identified 6 cases where unexpectedly high sPhos levels during L-AmB therapy prompted a re-run of the sera utilizing a confirmatory endpoint-based assay. In all 6 cases, re-run values were normal [median spurious rise in sPhos: 1.7 (0.6 - 3.6) mg/dl].

Conclusions: We conclude that pseudoperphosphatemia may not be uncommon during L-AmB therapy. Awareness of this phenomenon should be raised.

Funding: Private Foundation Support

SA-PO797

Utility of the Urinalysis in the Diagnosis of Primary Glomerular Disease: Report of the NEPTUNE Collaborative Study

Howard Trachtman,1 Richard A. Gomes,2 Geoffrey T. Groop,3 Debbie S. Gispert,3 Matthias Ketteler,4 Peter J. Nelson,4 Marie C. Hogan,5 John C. Lieske,5 Sharon G. Adler,6 Heather N. Reich,7 Kevin E.C. Meyers.3 1NYU Langone Medical Center, New York, NY; 2Stanford Univ, Stanford, CA; 3Univ of Michigan, Ann Arbor, MI; 4Univ of Washington, Seattle, WA; 5Mayo Clinic, Rochester, MN; 6Harbor-UCLA Medical Center, Torrance, CA; 7Toronto General Hospital, Toronto, Canada; 8Children’s Hospital of Phila., Philadelphia, PA.

Background: Urinalysis (UA) is a key screening test in patients with primary glomerular disease (PGD) and proteinuria. Although differences in UA findings have been reported in patients with the various forms of PGD, there is little information about the utility of the UA in the diagnosis of PGD in a large unbiased disease population. Therefore, we assessed the value of the UA in making the diagnosis of minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranoproliferative GN (MN) in patients enrolled in the NEPTUNE cohort study with a confirmed histopathological diagnosis (n=376).

Methods: Dipstick testing results were recorded for hematuria (n=189) and leukocyturia (n=167). All patients had proteinuria (> 500 mg/d) and required a diagnostic kidney biopsy. Hematuria or leukocyturia above trace was considered positive. UA results were compared between patients in the three categories of PGD and those with other diseases, predominantly IgA nephropathy, immune complex glomerular disease, and diabetic nephropathy.

Results: There were 56 cases of MCD, 47 of FSGS, 34 of MN, and 52 with other glomerular disease with UA testing. Hematuria was less frequent in those with MCD/ FSGS (32%) vs MN (59%) or other glomerular diseases (67%) (P<0.01). Leukocyturia was generally absent in patients with MCD, FSGS, and MN but low-grade leukocyturia was more common (15%) in those with other glomerular diseases (P<0.05).

Conclusions: Patients with MCD and FSGS are less likely to have hematuria compared with MN. Although hematuria can be used to assess the probability of MN vs. MCD or FSGS, it is not a discriminating factor. The presence of leukocyturia was indicative of other PGD.

Funding: NIDDK Support, Private Foundation Support

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

Underline represents presenting author/disclosure.
SA-PO798  
Short Synacthen Test: Outcome in Patients with Glomerulonephritis on Long Term Steroids  
Rosshi Rathore, Michael Venning. Dept of Renal Medicine, Central Manchester Univ Hospitals NHS Trust, Manchester, United Kingdom.

Background: Although potency, dose and duration of steroid use are important predictors of presence of hypothalamic-pituitary axis suppression, the preferred method to assess adrenocortical function is the response to synthetic ACTH. Short synacthen test is widely used for assessing adrenocortical function prior to weaning off long term steroids.

In our regional renal vasculitis clinic, we see a large population of renal patients with glomerulonephritides requiring long term immunosuppression. We specifically looked at our practice of performing short synacthen test before completely stopping steroids in this population.

Methods: We retrospectively analysed data obtained from biochemistry database at University Hospitals of South Manchester along with patients’ case notes. We gathered data on 50 patients who had one or subsequent short synacthen test between 1993 and 2007. The patients were in remission and had been maintained at 5 mg daily or less of Prednisolone for some weeks or months. We divided them into those that had been successfully weaned, those that are still on steroids and those that were back on steroids after complete withdrawal.

Results: Time taken to completely off steroids ranges from 3 months to 30 months. Three different regimens are being used for tapersing the dose- 1) Reduction by 1 mg every month 2) Missing dose a day and subsequently longer in a week 3) Alternate day dosing and reduction. Relapse or presence of active disease has been the main reason for prolongation of cessation of steroids. There was no documented evidence of major complication in the form of addisonian crisis when steroids were weaned after adequate cortisol response to synacthen. Most patients have required 60 min test to confirm adequate response.

Conclusions: 1. A 60 minute cortisol rise of > 250 nmol/l can adequately predict safe steroid withdrawal if undertaken over several months. 2. An adequate cortisol rise of > 550 nmol/l is not necessary for subsequent safe steroid withdrawal if undertaken over several months; 2. An adequate cortisol rise of > 250 nmol/l at 30 min is not necessary for subsequent safe steroid withdrawal; 3. With this protocol, a peak rise in cortisol to >550 nmol/l is not necessary for subsequent safe steroid withdrawal as traditionally described.

SA-PO799  
Exosomal mRNA for Biomarkers of Renal Injury Is Not Increased after Renal Transplantation  
Zoltan H. Endre, Philip Peake, Timothy J. Pianta, Lena McViecar. Dept of Nephrology, Prince of Wales Hospital, Randwick, NSW, Australia.

Background: mRNA extracted from urinary exosomes may provide a snapshot of altered renal cell metabolism after injury, preceding or paralleling changes in urinary biomarker protein concentrations.

Methods: Exosomes were isolated using nanomembrane concentrators from urine obtained immediately following renal transplantation, from patients with stable kidney transplant function, from healthy volunteers, and from patients with CKD complicated by proteinuria. The expression of exosomal mRNA for neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), cystatin C and kidney injury molecule-1 (KIM-1) was compared with the levels of the corresponding urinary protein and18S RNA.

Results: Exosomal mRNA concentrations of all biomarkers of injury increased after kidney transplantation, and exosomal 18S RNA increased after transplantation and in CKD. Exosomal mRNA for NGAL, IL-18 and cystatin C was detected in all subjects with CKD and in some subjects in all groups, except in patients with stable transplant function. However, mRNA for KIM-1 was mostly undetectable. mRNA expression did not correlate with urinary protein concentrations. NGAL mRNA was found after following acute transplantation, but not in normal subjects and those with CKD, although urine NGAL had risen by 4h post transplantation, and was high in CKD. IL-18 mRNA in CKD was higher than after transplantation, while urinary IL-18 levels in CKD were normal.

Conclusions: mRNA for NGAL, IL-18 and cystatin C is present in urinary exosomes, but levels do not reflect urinary protein concentration or acute injury. This may result from selective sorting of mRNA to exosomes by the parent cell, or by immunosuppression acting on these cells.

SA-PO800  
Induction of Chitotriosidase in Human Macrophages by Incubation with Cystine Crystals: Clinical Utility in Nephropathic Cystinosis  
Mohamed A. Elmenom, 1 Lambert Van den Heuvel, 2 Neveen Soliman, 3 Elena N. Levchenko. 2,3 *Clinical and Chemical Pathology, Inherited Metabolic Disorder Laboratory (IMDL), Faculty of Medicine, Cairo Univ, Cairo, Egypt; 1Pediatric Nephrology, Growth and Retardation, Univ Hospital Leuven, KU Leuven, Leuven, Belgium; 2Pediatrics, Center for Pediatric Nephrology and Transplantation (CPNT), Faculty of Medicine, Cairo Univ, Cairo, Egypt.

Background: Nephropathic Cystinosis (NC) is an inherited autosomal recessive disorder. Mutations of the CTNS gene, coding for cystinosin, lead to accumulation and crystallization of cystine inside different cells. The aminothiol cysteine is the only specific treatment for cystinosis, and so far, cystine content in white blood cells (WBC) is the main diagnostic tool and the only therapeutic monitor. Chitotriosidase enzyme is a human lysosomal enzyme produced by myeloid lineages whose level elevation was shown in many lysosomal disorders, and is used as a therapeutic monitor for enzyme replacement in Gaucher disease.

Methods: Different concentrations of cystine crystals were incubated with control human macrophages in-vitro to detect macrophage activation by assaying TNF-α in supernatant and chitotriosidase activity by measuring enzyme mRNA expression in the cell lysate. Chitotriosidase activity was also measured in the plasma of 45 NC patients, and compared with matched 34 normal controls and 24 renal disease patients. Chitotriosidase levels were also correlated with cystine in WBC for 33 patients on enzyme therapy.

Results: TNF-α, released in supernatant, increased up to ten folds after cystine crystal incubation and correlated with crystal concentration. Chitotriosidase activity and mRNA expression were also significantly increased. Enzyme activity (mmol/mh) in NC patients (0-3800, median 163) was significantly elevated compared to normal controls (0-72, median 14) and renal patients (2-144, median 39), P<0.001 for both groups. Chitotriosidase activity also correlated with cystine content in WBC (r = 0.8).

Conclusions: Chitotriosidase enzyme is a promising screening marker for NC patients among the clinically suspected and a probable therapeutic monitor for cysteine therapy.

SA-PO801  
Urinary microRNAs Are Stabilised by Association with Argonaute 2 Protein  
Donald Fraser, Cristina Beltrami, Timothy Bowen. Section of Nephrology, Cardiff Univ School of Medicine, Cardiff, United Kingdom.

Background: microRNAs (miRs) are endogenous, short, non-coding single-stranded RNA transcripts that regulate gene expression at the post-transcriptional level. Recent work has shown that miRs found in serum and plasma are present in microvesicle-free and microvesicle-associated form, in each case showing a resistance to RNase activity that enhances their disease biomarker utility. Urinary miRs represent a potentially novel source of biomarkers for chronic kidney disease (CKD); however, the stability of miRs in urine and their interaction with microvesicles and sensitivity to degradation remain poorly characterized. The purpose of this study was to identify the location of miRs in urine, and to investigate their stability.

Methods: Microvesicle-free and microvesicle urinary fractions were prepared by sucrose gradient ultracentrifugation prior to analysis by flow cytometry, immunoblotting and RT-qPCR. Endogenous urinary miRNA stability was then compared with that of spiked-in, exogenous, C. elegans-specific cel-miR-39 using RNase or proteinase K digestion followed by RT-qPCR. Protein:miR associations were analysed by RNA-immunoprecipitation (RNA-IP).

Results: Over 95% of urinary miRs were present in microvesicle-free urine, with the majority of the remainder associated with exosomes. Endogenous miRs had significantly greater resistance to RNase degradation than cel-miR-39 in urine samples from both control subjects and proteinic diabetic nephropathies. Proteinase K digestion significantly decreased circulating miR stability, suggesting protection by protein binding partners. Investigation of putative partners using RNA-IP showed association between urinary miRs and Argonaute 2, a protein component of the RNA-induced silencing complex, but not albumin.

Conclusions: Our data demonstrate that the majority of urinary miRs are not associated with microvesicles, provide a mechanism by which their stability is enhanced, and suggest that miRs do not freely cross the glomerular filtration barrier. These findings have important implications for the use of urinary miRs as a novel class of CKD biomarkers.

SA-PO802  
Phospholipase A2 Receptor Staining in Biopsies of Stage I Primary Membranous Glomerulonephritis  
Margarita Ryan, Gyorgyi Nadasy, Anjali A. Satoskar, Sergey V. Brodsky, Tibor Nadasy. Pathology, The Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: Phospholipase A2 receptor (PLA2R) is a protein component of the RNA-induced silencing complex, but not albumin. Investigation of putative partners using RNA-IP showed association between urinary miRs and Argonaute 2, a protein component of the RNA-induced silencing complex, but not albumin.

Conclusions: Over 95% of urinary miRs were present in microvesicle-free urine, with the majority of the remainder associated with exosomes. Endogenous miRs had significantly greater resistance to RNase degradation than cel-miR-39 in urine samples from both control subjects and proteinic diabetic nephropathies. Proteinase K digestion significantly decreased circulating miR stability, suggesting protection by protein binding partners. Investigation of putative partners using RNA-IP showed association between urinary miRs and Argonaute 2, a protein component of the RNA-induced silencing complex, but not albumin.

Conclusions: Our data demonstrate that the majority of urinary miRs are not associated with microvesicles, provide a mechanism by which their stability is enhanced, and suggest that miRs do not freely cross the glomerular filtration barrier. These findings have important implications for the use of urinary miRs as a novel class of CKD biomarkers.

Methods: From our biopsy archives, we identified fifteen cases of primary (by clinical history) glomerular stage I MGN. We stained the biopsies for the IgG subclasses by direct immunofluorescence on frozen sections and for PLAR2 by indirect immunofluorescence on paraffin-embedded sections.

Results: The majority (n=11) of these cases were IgG1 dominant or codominant. Six cases were IgG1 dominant, four codominant for IgG1/IgG4, one codominant for IgG1/IgG2, one for IgG2/IgG4 and one for IgG2 for IgG4 dominant. Two of the cases (one IgG1 dominant and one IgG1/IgG4 dominant) did not have glomeruli available for evaluation for PLAR2 staining. All cases with IgG1 dominant glomerular deposits (n=5) were negative for PLAR2. One of these cases had serum PLAR2 testing, which was also negative. Because of the retrospective nature of the study, we were unable to compare serum PLAR2 antibodies with the histologic findings for the other cases. Three of the four cases with dominant glomerular IgG4 and the three cases with codominant IgG1/IgG4 staining were positive for PLAR2. The biopsy with IgG1/IgG2 codominant glomerular staining was negative for PLAR2.

Conclusions: The lack of PLAR2 staining in all cases of IgG1-dominant early stage MGN suggests that in very early stage primary MGN antigens other than the PLAR2 may be the target antigens. Alternately, it is possible the PLAR2 initially evokes an IgG1 response which later may switch into an IgG4 response, but serial biopsies to prove this are unavailable.
SA-PO803

Biomarkers of Interstitial Kidney Pathology in Lupus Nephritis – The CKD Biomarker Consortium
Brad H. Rovin,1 Huijuan Song,2 Cassandra L. Hines,2 Haifeng M. Wu,3 Vasan S. Ramachandran,4 Paul L. Kimmel,1 John W. Kusek,5 Harold I. Feldman,6 Michael Merchant,7 Jon B. Klein.1 1University of Louisville; 2Ohio State Univ; 3NIDDK; 4Boston Univ; 5University of Pennsylvania.

Background: Interstitial inflammation (INF) correlates with long-term renal outcomes in lupus nephritis (LN). Monitoring the interstitium during therapy to determine if INF is resolving or interstitial fibrosis (FIB) is increasing could improve outcomes.

Methods: Discriminant analysis was used to design non-invasive biomarker panels that could distinguish INF and FIB in > 25% of interstitial tissue. Urine biomarkers tested were chosen as plausible candidates from literature, or from differentially-expressed urine proteins identified by mass spectrometry followed by ELISA from LN patients with varying levels of INF and FIB. Combinations of MCP-1, hemopexin (HPX), endostatin, protein C receptor (EPCR), serum creatinine (SCr), and proteinuria were tested for the ability to discriminate between levels of INF and FIB ≤ 25% involvement.

Results: The function that best discriminated ≥25% INF from <25% INF was Y = 3.7*log (uMCP-1) – 2.1*log (HPX) + 1.1*log (uHPX) – 3.6, where Y ≥ 25% INF with 82% accuracy and an area under the ROC curve of 0.89. The discriminant function Y ≥ 25% INF from <25% INF was Y = 2.2*log (EPCR) + 1.3*log (uHPX) + 0.2, where Y ≥ 25% INF had 63% accuracy and an area under the ROC curve of 0.79. The INF equation had only 63% accuracy identifying glomerular necrosis or cellular crescents in ≥ 25% of glomeruli. The FIB equation had ≥ 60% accuracy in identifying glomerulosclerosis or fibrous crescents in > 25% of glomeruli, respectively.

Conclusions: These data demonstrate the potential value of combining biomarkers into diagnostic panels that discriminate between levels of interstitial pathology in LN with good accuracy and specificity. If validated, these panels can be of potential use to follow interstitial injury prospectively, and guide therapy.

Funding: NIDDK Support

SA-PO804

Urine Podocyte Specific mRNA in Alport Syndrome
Laraya T. Wickman,1 Farsad Afshininia,2 Shiqi Wang,3 Mahboub A. Chowdhury,4 Ryuzoh Nishizono,5 Jocelyn E. Wiggins,6 David B. Kershaw,6 Roger C. Wiggins.7 1Univ of Michigan.

Background: There is increasing evidence that podocytes may play an important role in pathophysiologic mechanism leading to progression in Alport syndrome. It was shown that type IV collagen originates solely from podocytes. Studying urinary expression profile of podocyte specific mRNA podocin may help to understand pathophysiologic mechanisms of disease progression, guide treatment and lead to biomarker discovery that can aid assessment of novel therapies.

Methods: Urine pellet RNA is isolated and reverse-transcribed to cDNA using High-Capacity cDNA Reverse Transcription Kits. Quantification of podocin mRNA was performed using the 7900 HT Fast Real-Time PCR System. All assays were performed against cDNA standards to allow data to be expressed in moles per gram of creatinine. Normal range was derived from single samples of urine from individuals without kidney disease and compared to average values for each clinic patient with Alport.

Results: We have collected and analyzed 20 urine samples from 10 patients with Alport syndrome and 291 urine samples from controls. This included 6 patients with biopsy proven Alport, 3 patients with hematuria/proteinuria and family history of Alport and 1 patient with hematuria/proteinuria and thin GBM on biopsy. Majority of the patients (80%) were treated with Ramipril-Angiotensin System (RAS) inhibitors. Urine samples from Alport patients contained 23 fold elevated amounts of podocin mRNA when compared to controls (P<0.001).

Conclusions: We have shown that podocin mRNA levels are significantly higher in representative subset of patients with Alport compared to normal controls. We need to extend the observation to examine whether this methodology can be used to identify Alport disease progression at an early stage before development of significant proteinuria and to determine whether initiation of RAS inhibition on early stages can slow the rate of podocyte detachment.

Funding: NIDDK Support, Other NIH Support - NIH T32DK065517 training grant and by a NEUTONE Career Development Award U54 DK083912 from the NIDDK and the NIH Office of Rare Diseases Research (ORDR)/NCATS

SA-PO805

Urineary Podocalyxin Excretion Levels and Podocyte Damage
Masahide Hashigwa,1 Akira Hiwatashi,2 Hirayasu Kai,3 Joichi Ushi,4 Naoki Morito,4 Chie Saito,5 Keigyou Yoh,6 Hiroyuki Kurosawa,6 Kunihiro Yamagata.1 1Pediatrics, Yoshida Hospital, Tsubame, Niigata, Japan; 2Research and Development, Denka Seiken Co., Ltd., Gosen, Niigata, Japan.

Background: Podocalyxin (PCX), the major sialoglycoprotein of glomerular epithelial cells (podocytes) is expressed on apical membrane, and helps maintain the architecture of the foot process and the patency of the filtration slits. PCX was excrated in urine as vesicle form in various glomerular diseases and this vesicle was originated from microvilli of podocyte membrane by shedding.

Methods: We examined urinary level of PCX and ultrastructural podocyte changes in rat animal models of membranous nephropathy (active Heymann nephritis (AHN)), minor chain nephrotic syndrome (early phase of purinomycin aminonucleoside nephritis (PAN)) and focal segmental glomerulosclerosis (late phase of PAN). AHN was induced by ip injection of Freund’s complete adjuvant and renal cortex homogenate. PAN was induced by 4 times (day 1, 28, 35, 42) ip injection of PA, and early phase (day 10) and late phase (day 52) were studied.

Results: Urinary PCX levels were higher in AHN and early phase PAN rats than normal control rats and late phase PAN rats.

SA-PO806

Light Microscopic Identification of Urinary Podocytes Using Light Particles Bound with Anti-Podocalyxin Antibody
Masanori Haru,1 Hirokui Kurosawa.2 1Pediatrics, Yoshida Hospital, Tsubame, Niigata, Japan; 2Research and Development, Denka Seiken Co., Ltd., Gosen, Niigata, Japan.

Background: One of the causes for podocyteonia is detachment of podocytes from the GBM and leakage into the urine. While urinary podocytes are usually detected using immunofluorescence (IF), in the current study we developed a reliable light microscopic procedure using light particles bound with an anti-podocalyxin (PCX) antibody.

Methods: An anti-PCX monoclonal antibody was coupled with latex particles (0.4-3.0 um) with various latex colors, and the particles checked for binding to PCX using an ELISA plate coated with purified PCX from isolated glomeruli. These particles were then further examined using for binding to PCX-transfected HEK cells, as well as urine samples from patients with glomerulonephritis. Optimal conditions for light microscopic identification were determined by comparing various factors, such as the types of anti-PCX antibodies, particle sizes, color, pretreatment of the samples and incubation conditions. Quantitation of urinary podocytes counted by this new procedure was then directly compared with that by IF.

Results: The best conditions for the identification of urinary podocytes were as follows; 1) the antibody which reacts with sugar components of PCX, 2) 1 um of particle size, 3) blue color for particles, 4) 30 minutes for incubation period with two-way shaking, 5) pretreatment of urine samples by EDTA buffer. When 60 urine samples containing various densities of urinary podocytes were compared using these two detection methods, a significant positive correlation (r=0.85 by Spearman; P<0.001) was found, which had both good specificity and sensitivity (0.90 and 0.80, respectively). The time needed for the entire new procedure, including microscopic examination, was ~60 min., compared to ~150 min. for the IF procedure.

Conclusions: We have developed a new method to detect urinary podocytes using antibody-bound latex beads that is faster, simpler, and equally reliable to the historical IF-based method. This new approach thus offers great advantages for the expansion of the use of semi quantitative podocyturia measurement as a practical biomarker for podocyte injury.

SA-PO807

Cytokines Profile in ICU Patients with Sepsis and AKI
Anna Clementi,1 Grazia Maria Virzi,2 Massimo de Cal,2 Claudio Ronco,3 Antonio Granata.4 1Nephrology Dept, Agrigento; 2Nephrology Dept-IRRIV, Vicenza, Italy.

Background: Sepsis, defined as systemic inflammatory response syndrome associated with an infectious disease, is a primary cause of morbidity and mortality in ICU patients (pts) with mortality rates 20-60% for septic shock. Sepsis is also a contributing factor for AKI, with cases requiring renal replacement therapy (RRT). Several mechanisms contribute to AKI development.

We examined the inflammatory profile in ICU pts and investigated the possible correlation between cytokines and the development of sepsis and AKI requiring RRT(AKI_RRT) as well as the outcomes (out) in these pts.

Methods: 56pts (37Male, 63±15yrs) were recruited for the study at admission in ICU. 38/56pts had Endotoxin value higher than 40 units, used as cut-off value, 25/56pts had AKI_RRT. 40/56pts had negative out during ICU stay. We measured TNFα, IL6, IL18 in ICU pts sera. Mann-Whitney test was used for cohort comparisons. Statistical significance was set at p<.05.

Results:

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Mean (SD)</th>
<th>AKI_RRT</th>
<th>NoAKI_RRT</th>
<th>Positive_out</th>
<th>Negative_out</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα pg/ml</td>
<td>8.6±1.83</td>
<td>69.4±57.3</td>
<td>131-908</td>
<td>41-218</td>
<td>4-125</td>
</tr>
<tr>
<td>IL6 pg/ml</td>
<td>201±269</td>
<td>1472±574</td>
<td>1455-2465</td>
<td>258±158</td>
<td>119-505</td>
</tr>
<tr>
<td>IL18 pg/ml</td>
<td>2597±1211</td>
<td>461±1586</td>
<td>439.7±933.5</td>
<td>2409±1567</td>
<td>1221-259</td>
</tr>
</tbody>
</table>

There was no significant difference in TNFα and IL6 levels between septic and non septic pts, while IL18 resulted to be significantly higher (p<.01) in septic pts. TNFα and IL18 levels were significantly higher in AKI_RRT pts compared with NoAKI pts (p<.01),
while IL-6 did not differ significantly. TNFα and IL18 levels were significantly higher (p=0.012 and p=0.017, respectively) in pts with poor out, while there was no significant difference in IL6 levels.

Conclusions: Our study suggests that IL6 may be considered an unspecific inflammatory index, whose levels may increase in critically ill pts, independently on the development of sepsis or AKI. TNFα and IL18 levels seem to correlate sepsis and AKI in ICU pts and their increase is associated to poor out.

**SA-PO808**

**Evaluation of Endogenous Insulin Secretory Capacity in Patients with Advanced Chronic Kidney Disease**

Yukinari Yamaguchi, 1 Koji Harada, Juri Tukahara, Yuto Kasahara, Kouichi Sumida, Yasuhiro Akai. 1 Department of Nephrology and Rheumatology, Rakukawaki Otoha Hospital, Yamashina, Kyoto, Japan; 2 Center for Diabetes Care and Research, Nara Medical University, Kashihara, Japan.

Background: Diabetes is one of the major causes of ESRD, and adequate glycemic control is important to prevent the progression of diabetic nephropathy. Accurate evaluation of endogenous insulin secretory capacity (EISC) is important in choosing proper diabetic medications because the efficacy of these medications in lowering blood glucose could be dependent on the degree of EISC. There were few reports regarding EISC in advanced CKD patients. We conducted this study to investigate the methods to evaluate EISC in advanced CKD patients.

Methods: Thirty-four non-dialysis CKD patients were divided into 2 groups as follows, DM group (DM), patients with 2-h plasma glucose ≥ 200 mg/dl during the 75-g oral glucose tolerance test (OGTT); non-DM group (non-DM), 2-h plasma glucose < 200 mg/dl. To assess the EISC, we evaluated fasting serum insulin, plasma C-peptide, 24-urinary C-peptide, and glucagon stimulation test (GST). Furthermore the insulinogenic index (IHG) or insulin secretion area under the curve of insulin [IAAUC] was divided by the incremental area under the curve of glucose [GA/AUC] was calculated during the 0- to 30-min and 0- to 120-min time period of OGTT.

Results: Twenty-three patients were in DM and 11 in non-DM. There was no significant difference in the eGFR, HbA1c, and 24h-urinary C-peptide between DM and non-DM (22.0±9.7 vs 24.1±11.2 ml/min/1.73 m², p=0.64, 7.2±1.7 vs 6.2±0.9%, p=0.0255, 20.9±12.6 vs 25.9±24.6 µg/day, p=0.10). In 75-g OGTT, fasting serum insulin and C-peptide were not significantly different between 2 groups (7.1±6.1 vs 6.4±3.1 µU/ml, p=0.94, 3.4±1.7 vs 2.9±1.2 ng/ml, p=0.57). However, IA(IAAU)/GA(AUC) and the difference of C-peptide after GST were significantly lower in DM than in non-DM (0.46±1.50 vs 0.70±0.68, p=0.0016, 0.12±0.11 vs 0.31±0.17, p=0.0010, 1.74±0.96 vs 3.41±1.99, p=0.0194).

Conclusions: Whereas the estimation of EISC using fasting blood sample is inappropriate, OGTT and/or GST should be performed to properly evaluate EISC in advanced CKD patients.

**SA-PO809**

**A National Survey of the Availability and Use of Urine Microscopy in the UK**

Shafi Malik. 1 Nephrology, Toronto General Hospital, Toronto, Canada; 2Nephrology, Wrexham Macer Hospital, Wrexham, North Wales, United Kingdom.

Background: Urine microscopy has been used as a diagnostic tool since the 17th century, its use has been steadily declining. Studies have shown its use in differentiating between the causes of Acute Kidney Injury. Urine microscopy findings are found to correlate to renal histology. Urine microscopy is considered a basic and essential skill for a Nephrologist. We conducted a national survey of all the renal centers both adult & pediatric in the UK, aiming to study the availability and use of urine microscopy by Nephrologists. We also aimed to study whether its use helped in management decisions and the importance in the UK.

Methods: A web based survey was created. A link to the survey was sent by email to all the clinical directors of renal units and to Nephrology trainees in the country. All answers were anonymously collected.

Results: Of 70 Renal units, 26 responded (37%). 42% of respondents were from district general hospitals and 58% from University teaching hospitals. 52% of the 26 respondents performs urine microscopy in their unit. Where Nephrologists did not perform urine microscopy, urine specimens were sent to Microbiology for microscopy. In centers where urine microscopy was done, 63% said it helped in management decisions. In 80% of the hospitals that responded Nephrology trainees were not encouraged to learn and do urine microscopy. 53% of Renal clinical directors thought that urine microscopy should be part of the renal training curriculum. 78% of trainees who responded said that urine microscopy helped in management decisions and 57% said it should be included in the training curriculum.

Conclusions: This is the first national survey studying the use of urine microscopy in the UK. Only 20% of the hospitals that responded currently use urine microscopy. When performed, majority felt it helped in management decisions and more than 50% of trainees and Nephrology leads want it included in the Nephrology training curriculum.
SA-PO813
Preservation of HIF-1 and ERK Phosphorylation Are Involved in Hypothermic Protection of Renal Ischemia-Reperfusion Injury
Dae Jun Chei,1 Jin Young Jeong,1 Sarah Chung,2 Yoon-Kyung Chang,2 Ki Ryang Na,3 Kang Wook Lee,4 Young Tai Shin.5 1Internal Medicine, Changgung National University Hospital, 2Nephrology, Daemyung St Mary Hospital, 3Daejeon, Republic of Korea.

Background: Although hypothermia attenuates renal injury induced by ischemia-reperfusion (IR), precise molecular pathways have not been known yet. Our previous study showed ERK phosphorylation plays an important role in hypothermic protection in renal IR injury. Hyposxia-inducible factor-1 (HIF-1) has been known as one of the potent protective proteins in IR injury. We evaluated the role of HIF-1 and interaction with ERK phosphorylation in hypothermic protection of renal IR injury.

Methods: C57Bl/6 mice were divided into four groups; sham operated mice, cold IR mice(30℃), warmIR mice(37℃) and PD98059 (MAP kinase inhibitor) treated cold IR mice(IR injury; reperfusion 27 minutes after clamping of both renal artery and vein). Kidneys were harvested at 10min and 27min after both renal artery ischemia and reperfusion.

Results: s-Cr, and tissue injury score, 8-OHdG and TUNEL positive cells in kidneys of PD98059 treated cold IR mice were significantly lower than those of warm IR mice(all, p<0.01). s-Cr, and tissue injury score, 8-OHdG and TUNEL positive cells in kidneys of PD98059 treated cold IR mice were significantly higher than those of untreated cold IR mice(all, p<0.05). Renal HIF-1, PGC-1 alpha, and AMPK expression were significantly increased when kidneys of cold ischemic mice at 10min and 27min after both renal artery ischemia and reperfusion compared to sham operated mice. PD98059 treatment in cold IR mice decreased renal HIF-1 significantly (p<0.01). However, PGC-1 alpha and AMPK were not changed.

Conclusions: In conclusion, HIF-1 preservation induced by ERK phosphorylation may be involved in hypothermic protection of renal ischemia-reperfusion injury.

SA-PO814
Multigene Involvement and Detection of Tissue Gadolinium in a Rodent Model of Nephrogenic Systemic Fibrosis
Tareq Issa Nassar,1 Brent Wagner.2 1Internal Medicine Dept, Univ of Texas Health Science Center at San Antonio; 2Neurology, Univ of Texas Health Science Center at San Antonio.

Background: Nephrogenic systemic fibrosis (NSF) is an irreversible systemic disorder that is characterized with exposure to gadolinium-based magnetic resonance imaging (MRI) contrast in patients with compromised renal function. Gadolinium (Gd) has been detected on the surface of fibroblasts and keratinocytes, suggesting that the extracellular space of cells is Gd transport organelles. We would like to investigate whether the Gd is present in the interstitium, or the perivascular spaces in kidneys of rats treated with MRI contrast agents. Gadolinium deposits may be harmful to renal and cardiac function.

Methods: Rats were treated with MRI contrast agents and sacrificed at different intervals after treatment. Kidneys were harvested and examined for Gd deposits with immunofluorescence analysis. Tissue sections were stained with an antibody against Gd. Tissue sections were also stained with an antibody against CD31, a marker for blood vessels, and for SMA, a marker for smooth muscle cells.

Results: Gd deposits were observed in the extracellular matrix of kidneys of rats treated with MRI contrast agents. Gd deposits were also observed in the perivascular spaces of kidneys of rats treated with MRI contrast agents. Gd deposits were not observed in the extracellular matrix of kidneys of rats treated with saline solution.

Conclusions: Gd deposits in kidneys of rats treated with MRI contrast agents may contribute to the development of NSF. Further studies are needed to determine the mechanism of Gd deposition in kidneys of rats treated with MRI contrast agents.

SA-PO815
Hydrostatic Distalysis: A New Method to Enhance Urinary Vesicles for Clinical Analytics
Luca Musante,1 Dorota Ewa Tataruch,1 Alberto Benito Martin,2 Dongfeng Gu,3 Giulio Calzaferri,4 Harry B. Holthofer.5 1Centre for Bioanalytical Sciences, Dublin City Univ, Dublin, Ireland; 2Hematology/Oncology Dept, TWeill Medical College of Cornell Univ, New York; 3The Third Affiliated Hospital of Southern Medical University, Guangzhou, China.

Background: Secreted vesicles in urine are released from all nephron segments and the epithelial lining the urinomtral tract and have been proposed as valuable source of disease biomarker. Typically the vesicles contain specific signature proteins reflecting their cellular origin as well as DNA, and a variety of RNA species which suggest of important regulatory and communication functions. Despite their proposed importance, there are still significant challenges to overcome for successful clinical application, starting from simple method which allow to process large volumes of urine to enrich material for both proteomic and transcriptomic analysis. Here we show the full characterization of a novel easy method to simplify and enrich urinary vesicles and extract its transcript content.

Methods: In the enrichment method urinary vesicles are first concentrated and dialysed by a simple hydrostatic dialysis system which offers the following advantages: First, handling of large volumes of urine (~400ml) within a working day. Second, concentration of vesicle fraction up to 100 times. This easily meets the needs for the biobanking storage of urine sample material in smaller volumes Thrél, introduction of dialysis step necessary to equalise the physical-chemical properties of vesicles and specific pH optimization of the concentration of the samples and thus to reduce the technical-individual variability.

Results: Application of this method mimicking a clinical pilot study has revealed that the minimum volume of urine necessary to perform a proteomic analysis for a discovery phase is not less than 200ml and at least 100ml for a transcriptomic profiling. About 50ml of urine is needed for a validation analysis. Finally, 10ml of urine routinely collected may be utilised for specific targeted approaches including Western blots.

Conclusions: Our protocol for vesicle isolation paves the way to utilization of full diagnostic potential of urinary vesicles.

SA-PO816
Intraoperative Cell-Saver Blood Product: In Vitro Effect on Renal Tubular Cells
Grazia Maria Virzi,1 Tommaso Hina Dossi,2 Alessandra Brocca,1 Massimo de Cal,1 Lori Salvador,2 Claudio Romeo.1 1Nephrology Dept-IRBI, Italy; 2Cardiosurgery Dep, Italy.

Background: The hazards of transfusions has led to an emphasis on blood conservation in cardiac surgery. Mediastinal shed blood has high inflammatory properties, so it must be carefully managed with regard to the development of post-operative complications as AKI and renal failure. Many modalities including intraoperative cell-saver (CS) have emerged as alternatives to avoid transfusion. The aim of this study was to investigate the effect of CS product on renal tubular cells (RTC).

Methods: 14 patients (46±14yrs) underwent on-pump cardiac surgery were enrolled. An intraoperative CS device was used in each patient. We collected 2 blood samples for each patient: one at the end of cardiopulmonary by-pass (CPB) from the venous reservoir and one from the CS treated blood pack. For each patient, CPB and CS product were incubated with RTCs for 24h and, subsequently, apoptosis and necrosis was evaluated by cytometer.

Results: A quantitative analysis of cell viability showed significantly higher apoptosis and necrosis rates in RTCs incubated with CS group compared to CPB(both, p<.01) with a median increase of oxidative stress was observed in CS(p<.05). An increase of oxidative stress was observed in CS(p<.05).

Conclusions: Cell viability analysis indicated that CS product induces RTCs death by apoptosis and necrosis. CS product was able to induce a damage on RTCs and systemic disequilibrium caused by oxidative stress. In these patients, there could be injury to nephrons, which may lead to subclinical or recognized AKI with post-operative complications and poor outcomes.
Metal-Ion Complexation to Serum Carnosinase Is Increased upon Hemodialysis

Sibylle Jenny Hauske, Shiqi Zhang, Sarah Kabini, Emmanouil Ntasis, Elein Stamellou, Bernhard K. Krämer, Benito Yard. Vith Medical Dept, Medical Faculty Mannheim, Univ. of Heidelberg, Mannheim, Germany.

Background: We have previously shown that in serum the carnosinase (CN1) protein is only partly complexed with metal ions and that the relative proportion of not complexed (nc) CN1 negatively correlates with CN1 activity. ncCN1 can be detected by ELISA using RYSK173 (monoclonal IgG) antibody which we have raised against recombinant CN1.

Methods: In the present study we evaluated the relevance of Zinc binding to CN1 for detection by RYSK173. Since changes in divalent metal concentrations (conc.) have been reported to occur during hemodialysis (HD) we also assessed if HD affects the quality of CN1 by measuring total CN1 and ncCN1 conc. before and after HD.

Results: By making use of myc-tagged CN1 fragments we were able to narrow-down the RYSK173 epitope to a stretch of 40 amino acids in close vicinity to the metal binding region of CN1. While in serum ncCN1 constituted only 5% of total CN1, for recombinant CN1 expressed in Cos-7 cells approximately 50% of total CN1 was recognized by RYSK173. When recombinant CN1 was spiked into human serum, it was poorly detected by RYSK173. Similarly, addition of ZnCl₂ to either serum or recombinant CN1 strongly diminished its detection by RYSK173. In HD patients (N=30) we measured both total CN1 and ncCN1 conc. before and after HD. While total CN1 conc. were significantly increased after HD, ncCN1 conc. were decreased. The increased total CN1 conc. positively correlated with the percentage of plasma fluid depletion during HD.

Conclusions: In conclusion our data further demonstrate the presence of different qualities of CN1 in human serum. These qualities are due to the extent of metal-ion complexation to CN1. Since the RYSK173 epitope is in close vicinity to the metal binding region of CN1 our data indicate that occupation of this region by metal-ion prevents RYSK173 binding. Interestingly, ncCN1 conc. as detected by RYSK173 significantly decreased after HD supporting the suggested role of divalent metal ions (such as Zn²⁺) that have complexed to CN1 after HD. The identity of the metal ions as well as the consequence for CN1 activity remains to be assessed.

Funding: Government Support - Non-U.S.

SA-PO818

Osteoprotegerin in Exosome-Like Vesicles from Human Cultured Tubular Cells and Urine

Alberto Benito Martín,1 Alvaro C. Ucero,1 Irene Zubiri,1 Maria Posada Ayala,1 Beatriz Fernández,1 María Concepción Izquierdo,1 Marta Ruiz-Ortega,1 Jesús Esgido,2 Gloria Alvarez Llamas,1 Alberto Ortiz.1 INS- Fundación Jimenez Diaz; 2IDIP AZ; 3Universidad Autonoma de Madrid.

Background: Urinary exosomes have been proposed as a potential diagnostic tool. TNF superfamily cytokines and receptors may be present in exosomes and are expressed by proximal tubular cells. We have now studied the expression of selected TNF superfamily proteins in exosome-like vesicles from cultured human proximal tubular cells and have identified additional proteins in these vesicles by LC/MS/MS proteomics.

Results: Human proximal tubular cells constitutively released exosome-like vesicles that did not contain the TNF superfamily cytokines TRAIL or TWEAK. However, exosome-like vesicles contained osteoprotegerin (OPG), a TNF receptor superfamily protein, as assessed by Western blot, ELISA or selected reaction monitoring by nLC-(QQQ)MS/MS. Twenty-nine additional proteins were identified in these exosome-like vesicles, including basement membrane proteins type IV collagen, nidogen-1, agrin and fibulin-1. Urine from chronic kidney disease patients contained a higher amount of exosomal protein and exosomal OPG than urine from healthy volunteers. Specifically OPG was increased in autosomal dominant polycystic kidney disease urinary exosome-like vesicles and expressed by cystic epithelium in vivo.

Conclusions: OPG is a novel in urine exosome-like vesicles secreted by proximal tubular epithelial cells and isolated from Chronic Kidney Disease urine.

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

SA-PO819

Laser Capture Microdissection Enables mRNA and microRNA Quantification of Parietal Epithelial Cells (PECs) and Cellular Crescents from Paraffin Embedded Renal Biopsy Tissue

Clemens L. Bockmeyer, Karen Säuberlich, Stephanie Zell, Philip Zeuschner, Jan U. Becker. Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 'Div of Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan.

Background: The risk assessment for developing end-stage kidney disease (ESKD) remains limited in patients with IgA nephropathy (IgAN). The aim of our study was to develop and validate a prediction rule for estimating the individual risk of ESKD in patients with IgAN.

Methods: We followed retrospectively 698 patients with IgAN diagnosed by renal biopsy at Kyushu University Hospital (derivation cohort). The Oxford classification was used to evaluate the pathologic lesions. The risk factors for developing ESKD were evaluated using a Cox proportional hazard model. Furthermore, we verified the prediction rule using the data of 702 patients diagnosed at Japanese Red Cross Fukuoka Hospital (validation cohort).

Results: There were 221 (44.2%), 135 (27.0%), 96 (19.2%), and 48 patients (9.6%) with TA-P of <0.5, 0.5-0.99, 1.0-1.99, and ≥2.0 g/g, respectively. During a median follow-up duration of 65 (12-154) months, D-sCr was observed in 1 (0.5%), 3 (2.2%), 18 (18.8%), and 30 patients (30.0%) of each group (P=0.001). There was no difference in the development of D-sCr between patients with TA-P of <0.5 g/g and those with TA-P of 0.5-0.99 g/g. ESRD did not occur in these two groups, while 11 (11.5%) and 23 patients (47%) with TA-P of 1.0-1.99 and ≥2.0 g/g, respectively, progressed to ESRD. In a multivariable Cox model after adjustment for age, estimated glomerular filtration rate, blood pressure, pathological findings, and treatment, the risk of D-sCr did not differ between patients with TA-P of <0.5 g/g and those with 0.5-0.99 g/g (HR, 3.67; 95% CI, 3.34-36.2; P=0.281), whereas it was significantly higher in patients with TA-P of 1.0-1.99 g/g (HR, 27.6; 95% CI, 3.30-230.5; P=0.002) and those with TA-P of ≥2.0 g/g (HR, 140.6; 95% CI, 16.4-1209.1; P<0.001).

Conclusions: The results of our study suggest that the optimal proteinuria levels are <1.0 g/g in patients with IgAN. Further studies are required to clarify whether reduction of proteinuria of <0.5 g/g may confer a more prognostic advantage.

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

SA-PO821

Development and Validation of a Prediction Rule Using the Oxford Classification in IgA Nephropathy

Shigeru Tanaka,1 Toshiharu Ninomiya,1 Ritsuko Katafuchi,1 Kosuke Masutani,1 Akihiro Tsuchimoto,1 Hideki N. Yoo,1 Shin-Wook Kang,1,2 Seung Hyok Han.1 'Div of Nephrology, College of Medicine, 'Brain Korea 21; Yonsei Univ, Seoul, Korea.

Background: Investigation of Parietal Epithelial Cells (PECs) and Cellular Crescents not only in patients with Schoenlein-Henoch purpura.

Methods: We have previously shown that in serum the carnosinase (CN1) protein interacts with a stretch of 40 amino acids in close vicinity to the metal binding region of CN1 which we have raised against recombinant CN1. When recombinant CN1 was spiked into human serum, it was poorly detected by RYSK173. Similarly, addition of ZnCl₂ to either serum or recombinant CN1 strongly diminished its detection by RYSK173. In HD patients (N=30) we measured both total CN1 and ncCN1 conc. before and after HD. While total CN1 conc. were significantly increased after HD, ncCN1 conc. were decreased. The increased total CN1 conc. positively correlated with the percentage of plasma fluid depletion during HD.

Conclusions: In conclusion our data further demonstrate the presence of different qualities of CN1 in human serum. These qualities are due to the extent of metal-ion complexation to CN1. Since the RYSK173 epitope is in close vicinity to the metal binding region of CN1 our data indicate that occupation of this region by metal-ion prevents RYSK173 binding. Interestingly, ncCN1 conc. as detected by RYSK173 significantly decreased after HD supporting the suggested role of divalent metal ions (such as Zn²⁺) that have complexed to CN1 after HD. The identity of the metal ions as well as the consequence for CN1 activity remains to be assessed.

Funding: Government Support - Non-U.S.
Clinical Implication of Crescentic Lesion in Patients with IgA Nephropathy

Background: Early case series showed that the presence of crescents was associated with proteinuria and rapid deterioration of renal function in patients with IgA nephropathy (IgAN). To date, however, there has been much controversy about the role of crescentic lesions as a significant prognostic factor. In this study, we elucidated whether crescentic lesions predicted adverse renal outcomes in IgAN patients.

Methods: A total of 430 patients with biopsy-proven IgAN diagnosed between January 2001 and December 2010 were included. Histologic variables of the Oxford classification (Oxford-MEST) and the presence of crescents were assessed. The primary endpoint was a 50% decline in estimated glomerular filtration rate (eGFR).

Results: Among 430 patients, 81 (18.8%) had crescentic lesions. During a mean follow-up duration of 61 months, the primary outcome was significantly more observed in patients with crescents (19%, 23.5%) compared to patients without crescents (40 patients, 11.5%) (P = 0.01). A Kaplan-Meier plot showed that the 10-year renal survival rates were significantly lower in patients with crescents than without crescents (P = 0.01). However, in a multivariable Cox regression analysis including clinical factors and the Oxford-MEST score, crescents were not significantly associated with an increased risk of the primary outcome (HR, 0.78; 95% CI, 0.40-1.51; P = 0.35). Conclusion: Crescentic lesions were not an independent prognostic factor in patients with IgAN, suggesting that crescents had limited value in predicting renal outcome in these patients. Further studies are required to clarify the clinical implication of crescentic lesions in patients with severe IgAN or IgAN with rapidly progressive nature.

Funding: Government Support - Non-U.S.

Microbiota in Patients with Immunoglobulin A Nephropathy

Background: Immunoglobulin A nephropathy (IgAN) is one of the most common forms of primary glomerular disease. Along structural IgA abnormalities, hyperproduction of poorly galactosylated IgA1 is thought to play a role in the pathogenesis of primary IgAN. The downstream effector mechanisms triggered by mesangial IgA1 deposition and its etiology are poorly understood. Recently, it was shown a possible role of the enteric microbiota in educating the immune system and disease development. This study aimed at comparing the differences of the fecal microbiota between IgAN pts and Healthy Controls (HC).

Methods: Based on clinical data, IgAN pts were grouped into “non-progressors” (NP) and “progressors” (P). Each group was composed by 16 volunteers. The total active faecal microbiota was characterized through an integrative approach of culture-dependent and -independent methods and metabolomic analyses. Bacterial tag-encoded FLX-titanium amplicon pyrosequencing (BTEFAP) and Biochip 30 series Amino Acid Analyzer were carried out for general bacterial and phenotype analyses.

Results: The main bacterial phyla (Firmicutes and Bacteroidetes) significantly (P = 0.05) changed between the fecal microbiota of NP, P and HC. Overall, a decreased level of metabolically active and cultivable bacteria was found in NP and, especially, in P compared to HC. In addition, the composition of some genera mainly changed among NP, P and HC. Metabolites produced by intestinal microbes play a direct role in health and disease. According to the differences in the composition of the microbiota, the metabolome also differed in NP and P patients compared to HC. As shown by multivariate statistical analyses, the levels of free amino acids and volatile organic compounds of fecal and urine samples were markedly affected in NP and, especially, P pts.

Conclusions: The microbiota differences among NP, P and HC pointed out in this study, may have implications regarding specific diagnostic test, and/or for treatment and prevention.

Kidney Transplant following Crescentic IgA Nephropathy

Background: Crescentic IgA nephropathy (Cres-IgAN) is a severe form of IgAN that often leads to ESRD. Little is known about the clinical course of patients (pts) with crescentic IgAN who undergo kidney transplantation.

Methods: We reviewed the charts of 153 IgAN pts who underwent kidney transplantation at CUMC between Jan-2000 and Jan-2013. Native kidney biopsy reports were available for n=70. Crescentic IgAN was defined as ≥30% glomeruli with cellular, fibrous, or fibrocellular crescents.

Results: Crescentic IgAN was found in 15 pts (21%), of whom 8 were male. Race/ethnicity included white (n=8), AA (n=4), Asian (n=2), and Hispanic (n=1). Two pts had received a second transplant. Of 17 transplants, 7 were living-related, 6 were living-unrelated, and 4 were deceased-donor. Mean ±SD age at first transplant was 36±11 yrs (range 22-55 yrs).

Conclusions: Crescentic IgAN is an aggressive form of IgAN that often leads to ESRD. Little is known of the clinical course of patients (pts) with crescentic IgAN who undergo kidney transplant.

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

Underline represents presenting author/disclosure.

816A
Results: During a mean follow-up duration of 68 months, D-SCr occurred in 52 patients (10.4%), and 35 patients (7.0%) progressed to ESRD. There was a significant stepwise increase in the development of D-SCr as the Haas classes increased (P < 0.001). In addition, the primary endpoint of D-SCr occurred significantly more in patients with the Oxford M and T lesions than those without such lesions (P < 0.001). In multivariable Cox regression analyses adjusted for age, blood pressure, proteinuria, and eGFR, the Haas class V (HR, 12.19; 95% CI, 2.61-63.8; P = 0.002) and the Oxford T1 (HR, 6.68; 95% CI, 2.86-15.6; P = 0.001) and T2 (HR, 12.16; 95% CI, 4.78-30.9; P < 0.001) lesions were independently associated with a higher risk for reaching D-SCr. Harrell’s C indices of each multivariable model with the Haas and the Oxford classifications were 0.867 (P = 0.015) and 0.881 (P = 0.001), respectively, which was significantly higher compared with clinical factors only (c-statistic = 0.819). However, there was no difference in c-statistics between the two models with the Haas and the Oxford classifications (P = 0.348).

Conclusions: Both pathologic classifications were comparable in predicting the progression of IgAN. Further studies are required to delineate relationship between pathologic features and treatment responsiveness in patients with IgAN.

SA-PO830
Urinary Angiotensinogen, a New Biomarker in Primary IgA Nephropathy Patients? Dunxia Zhang, Yinru Zheng. The Renal Dept, Peking Union Med College Hospital, Beijing, China.

Background: Urinary angiotensinogen (AGT) was supposed as a useful local marker of intrarenal Renin Angiotensin System (RAS) activity in renal injury. To investigate the inapporated increased AGT in IgA nephropathy, urinary AGT was measured, and its correlation with clinical and pathological injury index was investigated.

Methods: Patients: 73 IgA nephropathy patients (16-69 years old, 44 male) were recruited. All the patients were diagnosed by pathologist from renal biopsy, and any known secondary IgA nephropathy was excluded. The controls are 19 age-matched healthy volunteers. Urinary AGT (normalized by urine creatinine) levels on the biopsy day were measured by ELISA method.

Results: Urinary AGT was significantly higher in IgA nephropathy patients than in controls (162±234 vs 6.6±6.5μg/g, p<0.05). Urinary AGT was significantly lower in patients treated with RAS inhibitors compared with patients not treated with RAS inhibitors (87±105 vs 217±238 μg/g, p=0.018). Even with the treatment of RAS inhibitors, urinary AGT level was still higher in IgA nephropathy than in the controls (87±105 vs 6.6±6.5μg/g, p<0.05). Urinary AGT was correlated positively with 24-hour urinary protein(=0.703, p=0.000) and renal crescent percent (r=0.428, p=0.000). This correlation was confirmed by multiple regression analysis. Urinary AGT was not correlated with gender, age, blood pressure, serum creatinine, serum albumin, or glomerulosclerosis percent. Taking hypertension and if RAS inhibitors being used before biopsy day into account, these IgA patients were divided into 4 subgroups.

Conclusions: Our data support intrarenal RAS is elevated in IgA nephropathy, and correlated with renal injury activity. Earlier RAS inhibitors may never mean early in IgA nephropathy.

SA-PO831
Serum Under-Ö-Glycosylated IgA Level Does Not Correlate with Glomerular IgA Deposition Based upon Heterogeneity in the Composition of Immune Complexes in IgA Nephropathy Yoshio Shimizu, Hitoshi Suzuki, Yusuke Suzuki, Yasuhiro Tomino. Juntendo Univ Faculity of Medicine, Tokyo, Japan.

Background: Although serum under-O-glycosylated IgA1 in IgA nephropathy (IgAN) patients may deposit more preferentially in glomeruli than normal IgA1, through self-aggregation and the formation of immune-complexes with autoantibodies, the relationship between glomerular IgA deposition level and O-glycan profiles of serum IgA1 remains obscure.

Methods: Serum total under-O-glycosylated IgA was quantified in 32 IgA nephropathy patients (11 males/22 females) by ELISA with Helix aspersa (HAA) lectin. Serum under-O-glycosylated polymeric IgA (pIgA) was selectively measured by a method that was developed by our group (plgA trap). Immunofluorescence of biopsy specimens and image analyses were used to quantify the percentage area of IgA deposition in the whole glomeruli (Area-IgA). Correlations were assessed between the Area-IgA and data from HAA-ELISA or plgA trap.

Results: While the under-O-glycosylated IgA levels were significantly higher in IgAN patients than in healthy controls, when measured by HAA-ELISA (p<0.05), there was no significant difference in under-O-glycosylated IgA. There was no linear correlation between Area-IgA and data from HAA-ELISA or the plgA trap.

Conclusions: Our data suggest that under-O-glycosylated IgA in IgA nephropathy (IgAN) patients may deposit more preferentially in glomeruli than normal IgA1, through self-aggregation and the formation of immune-complexes with autoantibodies, the relationship between glomerular IgA deposition level and O-glycan profiles of serum IgA1 remains obscure.

Methods: Serum total under-O-glycosylated IgA was quantified in 32 IgA nephropathy patients (11 males/22 females) by ELISA with Helix aspersa (HAA) lectin. Serum under-O-glycosylated polymeric IgA (pIgA) was selectively measured by a method that was developed by our group (plgA trap). Immunofluorescence of biopsy specimens and image analyses were used to quantify the percentage area of IgA deposition in the whole glomeruli (Area-IgA). Correlations were assessed between the Area-IgA and data from HAA-ELISA or the plgA trap.

Results: While the under-O-glycosylated IgA levels were significantly higher in IgAN patients than in healthy controls, when measured by HAA-ELISA (p<0.05), there was no significant difference in under-O-glycosylated IgA. There was no linear correlation between Area-IgA and data from HAA-ELISA or the plgA trap.

Conclusions: Our data suggest that under-O-glycosylated IgA in IgA nephropathy (IgAN) patients may deposit more preferentially in glomeruli than normal IgA1, through self-aggregation and the formation of immune-complexes with autoantibodies, the relationship between glomerular IgA deposition level and O-glycan profiles of serum IgA1 remains obscure.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
in each group suggested that dominant immune complexes in the glomeruli consisted of 1. IgA-IgG and complement in groups A and B, 2. pIgA and complement in groups C1 and C2, and 3. monomeric IgA-IgG or aggregated monomeric IgA in group D.

**Conclusions:** Serum under-O-glycosylated IgA levels do not correlate with glomerular IgA deposition based upon heterogeneity in the composition of glomerular immune complexes in IgAN patients.

**Funding:** Pharmaceutical Company Support - Novartis, Tanabe-Mitsubishi, Kowa, Kyowa-Kirin.

**SA-PO832**

**Endothelial Nitric Oxide Synthase (eNOS) Gene Polymorphism and Risk for Progression in IgA Nephropathy**

**Dimitrios Xydas** 1 | Georgios Goulieimos, 2 | Kostas Stylianou, 2 | Antonia N. Papadaki, 2 | Apostolos Papadogiannaklis, 2 | Eugenios Daphnis. 2
1 Nephrology, Venizeleio Hospital, Greece; 2 Univ Hospital of Crete, Greece; 3 Nephrology, Hospital of Chania, Greece.

**Background:** Several studies have shown the influence of eNOS gene polymorphism on the progression of kidney disease. IgA nephropathy has a variable natural history. The aim of this study is to investigate any association between eNOS gene intron 4a/b polymorphism and clinical presentation and progression of IgA nephropathy patients in a geographical region.

**Methods:** We included in our study 103 patients with biopsy-proven IgA glomerulonephritis and a median follow up period of 5.1±2.8 years. All subjects were genotyped for the intron 4a/b polymorphism. The end-points were doubling in baseline serum creatinine and/or initiation of dialysis.

**Results:** At baseline, M/F 68/35, age was 41.5±13.5 years, creatinine 1.21±0.74 mg/dl, proteinuria 1094±1201 mg/24H, 78% of the patients had a baseline creatinine of ≤1.3 mg/dl, 57% had a proteinuria of <1000mg/24H. During follow up time, 12 patients (11.6%) have doubled serum creatinine and 7 of them (6.8%) started dialysis in a period of 1.5±4.2 years. 40.39% patients presented eNOS intron 4 polymorphism a (6 aa,34 ab) and 63 (64%) polymorphism b. Patients reaching the outcome exhibited higher systolic blood pressure (144±20 vs 130±20 mmHg, p=0.02), diastolic blood pressure (82.1±13 vs 72.3±15 mmHg, p<0.028), higher baseline creatinine (2.18±2.7 vs 1.34±0.8 mg/dl, p<0.0005) and more extended tubulointerstitial fibrosis (21% vs 13%, p=0.1).

In a multivariate Cox proportional hazard analysis, the presence of (a) allele of eNOS gene, showed an 8-fold hazard to reach the outcome (HR=8.69, p=0.04) after adjusting for age, sex, presence of hypertension, proteinuria and ACE inhibitors treatment.

**Conclusions:** A significant proportion of patients, present impaired renal function at baseline. The classical risk factors for progression of renal disease also apply to our population. Additionally, the genotype (a) of eNOS gene appears to be associated with a worse outcome. The early detection of (a) allele could indicate those patients at increased risk of renal impairment.

**SA-PO833**

**Association between Low Plasma Renin Activity and Renal Interstitial Fibrosis in Patients with IgA Nephropathy**

Hitomi Nishimoto, Hirofumi Ikeda, Yoriko Ura, Masaru Nakayama. Div of Nephrology and Clinical Research Institute, Dept of Internal Medicine, National Kyushu Medical Center Hospital, Fukuoka City; Fukuoka Pref., Japan.

**Background:** IgA nephropathy (IgAN) is the most common cause of glomerulonephritis. Renal interstitial fibrosis (RIF) is a poor prognostic factor in IgAN. An association between the renin-angiotensin system and RIF has been suggested, with low plasma renin activity (PRA) reflecting increased renal renin-angiotensin system activity.

To date, no studies have evaluated the relationship between RIF and PRA in IgAN patients. To our knowledge, few studies have evaluated the relationship between the renin-angiotensin system and RIF in IgAN patients. The presence of RIF was significantly correlated with the glomerular filtration rate (GFR) in the literature (r=0.58, P=0.0001; r=0.44, P=0.0005, respectively) and also with SCr and eGFR at the time of the end of follow-up (r=0.58, P=0.001; r=0.46, P=0.0003, respectively). Double stainings for plasmin activity and C608 macrophages and neutrophils in ti space with upregulated plasmin activity.

**Conclusions:** These data suggest that TI plasmin activity may promote renal fibrosis by influencing inflammatory cells infiltration in human IgAN as well as in experimental models. Targeting to antagonize plasmin activity in situ may be a promising therapeutic approach to slow renal fibrogenesis and improve renal function.

**SA-PO835**

**Crescentic IgA Nephropathy (C-IgAN) in Children**

Yuko Shima,1 Koichi Nakashima,1 Taketsugu Hama,1 Hironobu Mukaiyama,1 Hiroko Togawa,1 Masashi Sato,1 Kandai Nozu,2 Royjiro Tanaka,3 Kazumoto Iijima,2 Norishige Yoshikawa,1 1Pediatrics, Wakayama Medical Univ, Wakayama, Japan; 2Pediatrics, Kobe Univ, Kobe, Hyogo, Japan; 3Pediatric Nephrology, Hyogo Prefectural Children’s Hospital, Kobe, Hyogo, Japan.

**Background:** Crescentic glomerulonephritis (CN) is defined as nephritis with more than 50% of glomeruli presenting crescents. IgAN is one of CNs of cause.

**Methods:** We analyzed retrospectively consecutive 515 children newly diagnosed as having biopsy-proven IgAN from June 1976 to May 2010. There were 25 children (4.9%) with C-IgAN. We compared clinical and pathological findings between cases with C-IgAN and the remained 490 cases.

**Results:** Among 25 C-IgAN, 16 children (64%) were referred to hospitals by annual school screening program for urinary abnormalities, 7 children for gross hematuria, a child for proteinuria and the remained 490 cases.

**Conclusions:** We confirmed the importance of school screening program to early detection of C-IgAN. We compared clinical and pathological findings between cases with C-IgAN and the remained 490 cases.

**SA-PO836**

**Tonsillectomy in a Pan-European Cohort of 1147 Patients with IgA Nephropathy**


**Background:** The beneficial effect of tonsillectomy in patients with IgA nephropathy (IgAN) is controversial.

While in Asia benefits have been claimed, in Europe small studies failed to show benefits.

**Methods:** The 1147 patients with IgAN enrolled in the European validation study of the Oxford Classification of IgAN (VALIGA), from 55 Centers of 13 Countries, offered a unique opportunity to investigate the effect of tonsillectomy in histologically and clinically well characterized IgAN patients followed in mean for 5 years.

**Conclusions:** The Role of Plasmin in the Development of Tubulointerstitial Change in IgA Nephropathy


**Background:** Plasmin activity has recently been reported to be associated with renal fibrosis in experimental models. However, the role of plasmin in human renal diseases is unclear. We therefore examined the renal plasmin activity in IgA nephropathy (IgAN).

**Methods:** Fifty seven patients with IgAN who were diagnosed by renal biopsy were retrospectively evaluated. Plasmin activity was assessed by in situ zymography with the use of plasmin sensitive synthetic peptide, and the percentage of positively stained area was calculated with image analysis software (LuminaVision Ver. 2.04). The relationships between the results of plasmin activity and the renal histological or clinical parameters were evaluated.

**Results:** Plasmin activity was observed only in tubulointerstitial (TI) space (and mainly in interstitium). Regarding the correlation with histological features, plasmin activity was significantly stronger in patients with TI change than those without TI change (P<0.05). It was significantly correlated with the global glomerulosclerosis rate (r=0.45, P=0.0004). Regarding the correlation with clinical parameters, plasmin activity at the time of renal biopsy was significantly correlated not only with serum creatinine concentration (SCr) or estimated glomerular filtration rate (eGFR) at the time of renal biopsy (r=0.58, P=0.0001; r=0.44, P=0.0005, respectively) but also with SCr and eGFR at the time of the end of follow-up (r=0.58, P=0.0001; r=0.46, P=0.0003, respectively). Double stainings for plasmin activity and CD68, and plasmin activity and neutrophil elastase in selected patients revealed the infiltration of CD68 macrophages and neutrophils in TI space with upregulated plasmin activity.

**Conclusions:** These data suggest that TI plasmin activity may promote renal fibrosis by influencing inflammatory cells infiltration in human IgAN as well as in experimental models. Targeting to antagonize plasmin activity in situ may be a promising therapeutic approach to slow renal fibrogenesis and improve renal function.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Background: Immunoglobulin A nephropathy (IgAN) is one of the most common primary glomerular disorders in the world. Pathogenesis of IgAN is still unclear. We recently established a method to isolate glomeruli from renal samples obtained by micro-sieving from patients with IgAN and MCNS. Fifteen out of the 34 spots were successfully identified proteins would help understanding of the pathogenesis of IgAN as well as MCNS.

Methods: Glomeruli were obtained by micro-sieving from renal biopsy samples of five patients with IgAN and five patients with minimal change nephrotic syndrome (MCNS). Then proteins, extracted from the isolated glomeruli, were separated by two dimensional gel electrophoresis (2-DE) and identified by mass spectrometry (MALDI-TOF/MS). Some of the identified proteins were evaluated by immunohistochemistry.

Results: By 2-DE, we detected in total 1170 protein spots matched among the samples. We found that intensity of 22 out of the 1170 spots was significantly higher in the patients with IgAN than in those with MCNS. Similarly, we found that intensity of 12 out of the 1170 spots was significantly lower in the patients with IgAN than in those with MCNS. Fifteen out of the 34 spots were successfully identified by MALDI-TOF/MS. Among them, we focused on two proteins, α-actinin-4 and glycine amidinotransferase, which intensity was significantly higher in IgAN. Also in immunohistochemistry, the expression of α-actinin-4 was significantly increased in the patients with IgAN than in those with MCNS.

Conclusions: Use of micro-sieving enabled us to obtain only glomerular proteins from renal biopsy samples and thus to analyze protein profiles of glomeruli. Future analysis of the identified proteins would help understanding of the pathogenesis of IgAN as well as MCNS.

SA-PO384

Predicting End-Stage Renal Disease or Death in Henoch Schönlein Purpura Patients Using Predictive Model Absolute Renal Risk Developed for IgA Nephropathy

Background: Patients fulfilling the 1992 revised WHO/ISN criteria for HSP (renal involvement) were considered to have HSPN. We identified a cohort of HSP patients diagnosed with kidney biopsy in the Nationwide Retrospective Cohort Study. The UAGT levels in HSPN 3 (11.74±3.14ug/gCr) were signifi- cantly increased compared with HSPN 1 (3.59±2.34ug/gCr, p<0.01) and HSPN 2 (5.76±1.84ug/gCr, p<0.01). The levels of urinary Cyst(C) and beta2-MG were also enhanced in HSPN 3, compared with other groups. However, the concentration of plasma Cyst(C) had no difference among groups. In HSPN 3, there were the significant positive correlation between UAGT and UCr (r=0.794, p<0.01), also between UAGT and beta2-MG (r=0.757, p<0.01). But, the UAGT levels did not correlate with UALB (r=0.303, p=0.05) in HSPN 3.

Conclusions: These results suggest that the higher levels of UAGT in severe HSPN may mainly reason from the impaired reabsorption capability of proximal tubular cells, while the molecular barrier function of the glomerular capillary wall is injured, and massive AGT is leaked into the tubular lumen. Upregulation of UAGT may lead to the elevated generation of intrarenal angiotensin II and the nephrin.

SA-PO385

Enhanced Urinary Angiotensinogen Is Correlated with the Impaired Reabsorption Capacity of Proximal Tubular Cells in Children with the Severe Henoch-Schönlein Purpura Nephritis

Background: The mechanism of enhanced urinary angiotensinogen (UAGT) in hypertension and some kidney diseases remains to be clarified. The aim of this study was to investigate the levels of UAGT in children with Henoch-Schönlein purpura nephritis (HSPN), and the correlations of UAGT with urinary albumin (ALB), Cystatin C (CysC), and beta2-microglobulin (beta2-MG). Urinary CysC and beta2-MG have been recognized as the markers of the reabsorption capacity of proximal tubular cells. Patients: Patients were classified into three groups, according to the initial clinical presentation. 1) HSPN 1, n=20, hematuria, 5 or more red blood cells in per high power field in a centrifuged specimen, urine protein/creatinine ratio (UPCR)>2000mg/g; 2) HSPN 2, n=30, 200mg/g<UPCR<1000mg/g, with hematuria; 3) HSPN 3, n=30, UPCR>1000mg/g, with hematuria. We measured urinary creatinine (Cr), ALB, AGT, CysC, beta2-MG, plasma CysC levels. The urinary levels of these parameters were expressed in ratios to Cr.

Results: The UAGT levels in HSPN 3 (11.74±3.14ug/gCr) were significantly increased compared with HSPN 1 (3.59±2.34ug/gCr, p<0.01) and HSPN 2 (5.76±1.84ug/gCr, p<0.01). The levels of urinary Cyst(C) and beta2-MG were also enhanced in HSPN 3, compared with other groups. However, the concentration of plasma Cyst(C) had no difference among groups. In HSPN 3, there were the significant positive correlation between UAGT and UCr (r=0.794, p<0.01), also between UAGT and beta2-MG (r=0.757, p<0.01). But, the UAGT levels did not correlate with UALB (r=0.303, p=0.05) in HSPN 3.

Conclusions: These results suggest that the higher levels of UAGT in severe HSPN may mainly reason from the impaired reabsorption capability of proximal tubular cells, while the molecular barrier function of the glomerular capillary wall is injured, and massive AGT is leaked into the tubular lumen. Upregulation of UAGT may lead to the elevated generation of intrarenal angiotensin II and the nephrin.
Attenuated Megalin Expression in Proximal Renal Tubules Is Associated with Tubular Atrophy/Interstitial Fibrosis by Oxford Classification in IgA Nephropathy  
Ikebaya Y,1 Ishimura E,2 Inaba Masaaki,1

1Department of Nephrology, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan.

Background: Although the role of megalin in the proximal tubule is still not well defined. Megalin, a multiligand endocytic receptor involving in the reabsorption of 25-hydroxyvitamin D in renal proximal tubules, plays an important role in VD metabolism. To elucidate the role of megalin in IgAN, its interstitial expression was examined in IgAN kidneys and was compared to Oxford classification of IgAN.

Methods: Renal biopsy specimens were collected from histologically proven 43 IgAN patients (serum creatinine 1.13 ± 0.74 mg/dl, urinary protein 1.24 ± 1.19 g/day) with informed consent. Intestinal megalin expression was determined by immunohistochemistry using ScanScope Aperio Slide Scanner.

Results: In tubular atrophy and interstitial fibrosis (T) by Oxford classification, the megalin expression in T1/2 significantly decreased compared to T0 (P=0.03 by Mann-Whitney U test). Other Oxford categories such as mesangial hypercellularity, endocapillary hypercellularity or segmental sclerosis did not make any difference in the interstitial megalin expression. No significant relationship was observed between interstitial megalin expression and biochemical parameters such as serum creatinine, eGFR, urinary protein, or urinary 02-microglobulin.

Conclusions: Advanced T classification, one of determinants for worse renal prognosis in IgAN, suppressed intestinal megalin expression in IgAN. The suppression of intrinsic VD activation may contribute to the progression of IgAN possibly via renin-angiotensin system.

SA-PO842
Different Impact of Proteinuria on Renal Outcomes in IgA Nephropathy and Membranous Nephropathy

Background: Reduction in proteinuria in chronic glomerular diseases is considered to be a critical therapeutic objective. However, a clear proteinuria target (mean proteinuria during follow-up below which no renal outcomes will develop) has not been established for all glomerular diseases. Some studies have shown a high number of negative renal outcomes in IgA nephropathy (IgAN) with proteinuria persistently > 1 g/24h, but if the same target could be applied to other diseases like idiopathic membranous nephropathy (IMN) is unknown.

Methods: Retrospective, multicenter study performed in 14 Spanish Hospitals that collected two cohorts of patients: biopsy-proven IgAN (n=77) and biopsy-proven IMN (n=129), with a long follow-up (129 and 96 months, respectively). All patients with IMN had achieved remission of nephrotic syndrome (proteinuria >3.5 g/day) spontaneously. Time-average proteinuria (TAP) throughout follow-up was determined in every patient along with clinical, biochemical and histologic parameters. Main outcomes were progression of renal insufficiency measured by a ~50% increase of baseline serum creatinine and the annual rate of GFR loss (GFRR).

Results: Both IgAN and IMN patients were divided in two groups, according to TAP > or < 1 g/24h during follow-up. Whereas a clear difference in renal outcomes between both groups was observed in IgAN, there were no differences in IMN.

Conclusions: TAP >1 g/day is associated with a poor renal prognosis in IgAN, but IMN patients exhibit a significantly better tolerance to similar values of proteinuria. Pathogenic mechanisms explaining this different proteinuria impact are unknown.

SA-PO843
Quantitative Evaluation of Renal Cortical Fibrosis and Renal Prognosis in IgA Nephropathy and Focal Segmental Glomerulosclerosis
Hidetaka Yasui,1 Masayuki Tanaka,2 Atsushi Tanaka,1 Takaaki Moriyama,1 Chihirou Iwasaki,1 Yasuko Oshima,1 Koosuke Nitta.

Background: attenuation of fibrosis area to the area of renal cortex in Azan staining section was defined as fibrosis area ratio (FAR) and evaluated by digital image analysis in IgAN and compared to FSGS patients. We then evaluated its association with renal prognosis during 20 years follow up.

Methods: The ratio of fibrosis area to the area of renal cortex was evaluated quantitatively by an image analyzer software (Image Pro Plus®) in Azan staining section of IgAN and FSGS patients. Immunohistochemistry for CD105 in 159 IgA nephropathy patients was performed by the University of Tokyo. Induction of hemodialysis or doubling of serum creatinine was used as a combined end point, renal prognosis was evaluated with the Kaplan-Meier method, and risk factors were examined by Cox’s proportional hazards model.

Results: After correction with age, sex, and blood pressure at renal biopsy, the fibrosis area ratio was found to be an independent risk factor for renal survival in both IgA nephropathy and FSGS patients by Cox’s proportional hazards analysis. The cut off values of the fibrosis area ratio, determined from the ROC curve using the least-square method, were 0.5% for IgA nephropathy and 15.8% for FSGS. The 20-year rate of renal survival in patients with a cortical fibrosis area ratio lower than 14.5% was significantly longer than those with a ratio higher than 14.5% (23.1 vs. 12.5 years, p<0.0001) in IgA nephropathy. Likewise, it was longer in patients with a cortical fibrosis area ratio lower than 15.8% (20.4 vs. 8.2 years, p=0.0001) in FSGS.

Conclusions: The renal cortical fibrosis area ratio calculated by computer image software is an objective index that enables estimation of long-term renal survival in IgA nephropathy and FSGS patients.

SA-PO844
Long-Term Prognosis of Clinically Early IgA Nephropathy Is Not Always Favorable
Haieong Lee, Dong Ki Kim, Ho Jun Chin, Yun Su Kim, Chuns Woo Lim, Jung Pyo Lee.

Background: Long-term prognosis of clinically early IgA nephropathy (IgAN) patients remains to be clarified. In this study, investigated long-term outcome of IgAN patients with apparently benign presentation and evaluated the prognostic factor for renal survival.

Methods: We included biopsy proven IgAN patients with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m2, normal blood pressure, and proteinuria (PU) ≤0.5 g/day at the time of biopsy. Patients who were younger than 15 years old or with other systemic diseases were excluded. The primary outcome was defined as end-stage renal disease (ESRD) progression. Secondary outcome was defined as 50% increase of serum creatinine or increased amount PU >1 g/day. During the follow-up, cases with loss of microscopic hematuria, PU < 0.2 g/day and stable renal function were categorized to remission group.

Results: A total of 142 patients met these criteria and analyzed. Median systolic blood pressure was 119 (110-121) mmHg, initial eGFR was 85.1 (74.9 – 100.4) mL/min/1.73 m2 and proteinuria was 0.25 (0.13 – 0.38) g/day at diagnosis. More than 13% of patients showed moderate or severe tubular atrophy or interstitial fibrosis. Among them, 4 patients were died, 5 reached to ESRD. Twenty-year renal survival rate was 88.6% during 92 (46 – 204) months of follow up. Increase of serum creatinine levels was found in 3 patients, and development of PU in 11 patients. Remission was demonstrated in 35 patients. No patients were treated by immunosuppressive agents and 61 (43%) of patients were taken renin-angiotensin-aldosterone. Moderate or severe degree of interstitial fibrosis (adjusted odd ratio (OR) 6.828, 95% confidence interval (CI) 1.512 – 30.801, P = 0.013) and mild renal insufficiency (eGFR < 90mL/min/1.73m2) (adjusted OR 3.866, 95% CI 1.004 – 14.933, P = 0.049) were independent predictors for elevation of serum creatinine or increased amount of PU.

Conclusions: This study demonstrated that the prognosis of early IgAN was not always favorable. Besides mild renal insufficiency, pathologic changes including interstitial fibrosis also should be considered as an important prognostic factor for clinically early IgAN patients.

SA-PO845
Effect of Hematuria on the Outcome of IgA Nephropathy with Mild Proteinuria
Kayu Tanaka, Takahito Moriyama, Chihirou Iwasaki, Yasuko Oshima, Kosaku Nitta.

Background: heavy proteinuria has been widely recognized as the risk factor for progression of IgA nephropathy (IgAN), and hematuria recently has been frequently recognized to be exerted from the active inflammatory lesion of glomerular capillaries in IgAN. However the effect of hematuria on the outcome for IgAN remains unknown and the treatment of IgAN with severe hematuria is still controversial.

Methods: We retrospectively examined 88 IgAN patients with proteinuria less than 0.5g/day and were not treated with corticosteroid, immunosuppressive agents or tonsillectomy. We divided them into two groups: the low urinary red blood cells (U-RBC) group (L group, n=48); U-RBC was less than 20 counts/HPF, and the high U-RBC group (H group, n=40); U-RBC was greater than 20 counts/HPF. We analyzed the clinical and historical findings and renal survival rate until progression to end-stage renal disease.

Results: Median U-RBC in H group was significantly higher than L group (L group: 5 vs. H group: 30 counts/HPF, P<0.0001), and the other laboratory data were similar between both groups [estimated glomerular filtration rate (L: 77.1 vs. H: 81.9 mL/min) and proteinuria (0.26 vs. 0.27 g/day)], though some clinical findings were significantly different between both groups [eGFR (L: 81.4 vs. H: 70.2 mL/min), systolic blood pressure (122.8/76.5 vs. 116.1/69.4 mmHg), P=0.017]. Histological findings were not significantly different between both groups. During the 5 years after renal biopsy, median amount of proteinuria remained less than 0.5g/day in both groups, and median amount of U-RBC was decreased from 9 to 5 in H group and 10 to 5 in H group without any intensive therapy. 25 years renal survival rate by the Kaplan-Meier method was 100% in H group, but it was decreased to 85.5% in L group, though it was not significant.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
SA-PO847
The Nationwide Retrospective Cohort Study in IgA Nephropathy in Japan
Takashi Yasuda, Yoshinari Yasuda, Sachiko Ohide, Osamu Takahashi, Tetsuya Kawamura, Seichi Matsuo. Nephrology & Hypertension, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan; Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi, Japan; Center for Clinical Epidemiology, St. Luke’s Life Science Institute, St. Luke’s International Hospital, Tokyo, Japan; Kidney & Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan.

Background: We have started the Nationwide Retrospective Cohort Study in IgA nephropathy in Japan since Sep. 1, 2012. The main purpose is to clarify the choice of therapy, including tonsillectomy in combination with intravenous pulse methylprednisolone followed by oral prednisone (tonsillectomy with pulse), in patients with IgA nephropathy under various clinical presentations. In this interim analysis, we evaluated the therapeutic efficiency on renal outcome defined as 50 percent increase in the serum creatinine concentration from baseline between conservative therapy without steroids, oral steroids, pulse methylprednisolone followed by oral prednisone (pulse methylprednisolone), and tonsillectomy with pulse.

Methods: Adult patients with IgA nephropathy diagnosed by the first renal biopsy during the three years from 2002 to 2004 were eligible. Data at the time of renal biopsy were analyzed. Data at the time of renal biopsy; conservative therapy 475, oral steroids 174, pulse methylprednisolone 121, and tonsillectomy with pulse 106. Among them, we analyzed 931 cases which have sufficient data on renal function. In patients with NS, 392 cases (66.9%) were IgAN with minimal change disease. Corticosteroid achieved high complete remission (CR) rate (86.2%) with a considerable relapse rate (28.1%). In the other 440 patients with NS and mesangial proliferation, corticosteroids and immunosuppressants achieved 57% CR, 31% partial remission (PR) and 12% no response (NR). In patient with proteinuria between 1-3g/d with or without renal dysfunction, immunosuppressive treatment achieved 28% CR, 37% PR, and 35% NR. RAS inhibitors (RAASI) were prescribed in most patients. However, significant effect could only be observed in patients with hypertension. Renal function remained normal in every patient with normal renal function and proteinuria <1g/d during following up. Treatment of RAASI or immunosuppressants did not show any benefit regarding as decreasing of proteinuria or protecting of renal function in these patients.

Conclusions: Renal function decline was observed in 6% of IgAN patients during following up. The prognostic factor of renal survivor were eGFR<90 ml/min, uncontrolled hypertension, NS, severe pathological lesions. Corticosteroids and immunosuppressant was effective in most patients. RAASI only had a limited effect in Chinese patients.

SA-PO848
Efficacy and Safety of Telmasartan, Clopidogrel and Lefunomide in Patients with IgA Nephropathy — A Multicentre, Prospective, Randomized, Double-Blind, Double-Dummy Controlled Clinical Trial
Xiang-Mei Chen, Jie Wu, Shuwei Duan, Ying Zheng. Dept of Nephrology, State Key Laboratory of Kidney Disease, Chinese PLA General Hospital, Beijing, China.

Background: To evaluate the efficacy and safety of telmasartan combined with clopidogrel and/or lefunomide for patients with IgA nephropathy and whether the combination therapy surpass telmasartan in decreasing proteinuria and protecting renal function.

Methods: We enrolled 400 patients aged 18–55 years from 13 centres in Beijing who had proteinuria 0.5–3.5 g/d, baseline serum creatinine (SCr) <3mg/dl. All patients were eluted by taking telmasartan 80mg/d for 4 weeks and then randomly assigned to receive 24 weeks of treatment with telmasartan 80mg/d + clopidogrel placebo + lefunomide placebo (group A), telmasartan 80mg/d + clopidogrel 50mg/d + lefunomide placebo (group B), telmasartan 80mg/d + clopidogrel placebo + lefunomide 20mg/d (group C), telmasartan 80mg/d + clopidogrel 50mg/d + lefunomide 20mg/d (group D). Comparison of 24h urinary protein excretion, the serum creatinine, eGFR, albumin, cholesterol and uric acid after the therapy were assessed.

Results: After treatment for 24 weeks, proteinuria declined significantly in the four groups (P<0.05), while those in group C (1.20±0.76 vs 0.77±0.42 g/d) and group D (1.16±0.63 vs 0.74±0.49 g/d) were decreased more significantly than in group A (1.15±0.87 vs 0.92±0.58 g/d) and group B (1.11±0.83 vs 0.89±0.42 g/d) (P<0.05). Mixed effects model analysis showed that telmasartan, lefunomide and telmasartan combine lefunomide decreased proteinuria (P<0.01). The SCR declined in group C and group D more significantly than that in group A and group B (P<0.05). The level of eGFR in group C and group D were increased more than that in group A and group B. The serum uric acid in group C and group D decreased more significantly than group A and group B (P<0.05). There were no significant differences in the results of albumin and cholesterol among the four groups. No obvious adverse reactions were found in the four groups.

Conclusions: Telmasartan combined with lefunomide was safe and effective in decreasing proteinuria and protecting short-term renal function.

Funding: Government Support - Non-U.S.

SA-PO849
Eculizumab (ECU) Inhibits Thrombotic Microangiopathy (TMA) and Improves Renal Function in Pediatric Atypical Hemolytic Uremic Syndrome (aHUS) Patients (Pts)
Larry A. Greenbaum, Marc Filo, Michel Tislaritos, Gaetano Manni, Alessandro DiRenzo, Sumant L. Al-Akash, Jonathan Evans, Paul H. Hening, Kenneth V. Lieberman, Silvio Maringhini, Lars Pape, Lesley Rees, Nicole Van De Kar, Johan Van de Walle, Masayo Ogawa, Camille L. Bedrosian, Christoph Licht. C10-003 Investigators.

Background: aHUS is a rare, genetic, life-threatening disease of uncontrolled complement activation leading to systemic TMA and severe end-organ damage. ECU, a terminal complement inhibitor, is approved for the treatment of aHUS, and was shown to be safe and effective in a retrospective pediatric study. Here, we report safety and efficacy results at 26 weeks (wks) from the first prospective trial of pediatric aHUS pts.

Methods: This was an open-label, single-arm, Phase 2 trial of ECU in pediatric pts with aHUS. The primary endpoint was complete TMA response at 26 wks. Dosing was based on weight cohorts.

Results: 22 pts (age 1 month to 17 yrs) were enrolled; 19 completed 26 wks. 16 pts (73%) were newly diagnosed (median duration of 6 days prior to ECU). At wk 26, 14 pts (64%) achieved the primary endpoint.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
**SA-PO850**

**Eculizumab (ECU) in Atypical Hemolytic Uremic Syndrome (aHUS) Patients (Pts) with Long Disease Duration and Chronic Kidney Disease (CKD): Sustained Efficacy at 3 Years**

**Background:** aHUS is a rare, genetic, life-threatening disease of chronic complement activation leading to systemic TMA. ECU was shown to inhibit TMA, eliminate PE/PI, and improve renal function in pts with long aHUS duration and CKD in 1- and 2-yr reports of the phase 3 study. Here we provide a 3-yr update.

**Methods:** aHUS pts >2 yrs with CKD receiving chronic PE/PI were enrolled. After 8 wks of eculizumab therapy, stopped PE/PI and started ECU extension.

**Results:** 20 pts were treated—16 pts for >2 mos. Median (med) time from diagnosis was 48 mos. Med duration of ECU was 156 (26—176) wks. Baseline mean eGFR was 31 mL/min/1.73m², and 90% of pts had eGFR ≤60. Efficacy outcomes were consistent with a 2-yr analysis.

**Conclusions:** ECU inhibits complement-mediated TMA, and is safe and effective at the approved dose regimen in pediatric pts with aHUS, including those receiving first-line ECU. Treatment in the clinical trial is ongoing.

**Funding:** Pharmaceutical Company Support - Alexion Pharmaceuticals

---

**SA-PO851**

**Successful Treatment of DEAP-HUS with Eculizumab**

**Background:** DEAP-HUS (deficiency of CFIH proteins and CFI autoantibodies) represents a unique subgroup of complement-mediated aHUS. CFIH autoantibodies block CH50 surface recognition and mimic aHUS-causing mutations. CFIH autoantibodies are found in up to 15% of aHUS patients and typically occur in the background of CFIH/CFHR1 deletions. The principal treatment concept for complement-mediated aHUS hinges on restoring the alternative pathway regulation via plasma-based treatments or eculizumab, a monoclonal C5 antibody. Clinical practice guidelines for DEAP-HUS are lacking; strategies have been adopted from genetically-determined forms of aHUS and other autoimmune diseases. The literature supports PLEX initially, but with the addition of an antibody-suppressing or depleting agent with varied success reported.

**Methods:** We present a retrospective report of the successful use of eculizumab in 2 DEAP-HUS patients and their follow up.

**Results:** We show eculizumab to be safe and effective in the management of DEAP-HUS in 2 patients with confirmed CFIH/CFHR1 deletion. One was dependent on bi-weekly plasma infusions. Successful induction of aHUS remission was achieved in the chronic phase in the other. Immunosuppressive agents and mid-term discontinuation of eculizumab are considered. We propose a biphasic treatment concept for DEAP-HUS with eculizumab, followed by a period to arrest the complement mediated damage and continued for at least 6 months (Phase 1), followed by the use of immunosuppressive agents targeting ongoing antibody production (Phase 2), with antibody titre measurement.

**Conclusions:** The complement C5 inhibitor eculizumab is safe and effective in maintaining a disease-free state in DEAP-HUS in the presence of ongoing anti-CFH autoantibodies. While immunosuppression alone may sufficiently address the autoimmune component of DEAP-HUS, the predisposing lack of CFIHR1—an identified C5 convertase inhibitor—and possible additional but unrecognized complement mutations would be left untreated.

**Funding:** Pharmaceutical Company Support - Alexion Pharmaceuticals

---

**SA-PO852**

**Eculizumab (ECU) Maintains Efficacy in Atypical Hemolytic Uremic Syndrome (aHUS) Patients (Pts) with Progressing Thrombotic Microangiopathy (TMA): 3-Year (Yr) Update**

**Background:** aHUS is a rare, genetic, life-threatening disease of chronic complement activation leading to systemic TMA. In 1 and 2 yr reports from this prospective study (CO8-002), ECU was shown to inhibit TMA, prevent or reverse organ damage, and reduce the need for dialysis in aHUS pts. Here we provide a 3-yr update.

**Methods:** aHUS pts >2 yrs with progressing TMA (platelet decrease ≥25% despite ≥4 PE/PI sessions 1 week [wk] before screening) entered an open-label, Phase 2 trial and continued to the 3-yr extension. Primary endpoints were platelet count change and hematologic normalization.

**Results:** 17 pts enrolled and 13 pts continued in the extension. Median duration of treatment was 100 wks, with a range of 2 to 168 wks. 5 pts remained enrolled >130 wks. Continuous, long-term ECU treatment sustained or improved key hematologic and renal endpoints at 3 yrs.

**Conclusions:** The data demonstrate the safety and continued efficacy of ECU therapy in aHUS pts, highlighting the ongoing inhibition of TMA at this 3-yr update.

**Funding:** Pharmaceutical Company Support - Alexion Pharmaceuticals

---

**SA-PO853**

**An Observational, Non-Interventional, Multicenter, Multinational Registry of Patients (Pts) with Atypical Hemolytic Uremic Syndrome (aHUS): Initial Pt Characteristics**

**Background:** aHUS is a rare, genetic, life-threatening disease of chronic complement activation leading to systemic thrombotic microangiopathy, with renal and other end-organ damage. The global aHUS Registry, initiated in April 2012, prospectively collects information on pts with aHUS. Here we report baseline demographics from the initial pts in the aHUS Registry.

**Methods:** aHUS pts (regardless of treatment) are eligible for enrollment. Demographic, medical, and disease history, treatments, efficacy and safety profiles data are collected initially and every 6 months thereafter.

**Results:** By March 31, 2013, 53 pts from 8 countries were enrolled in the aHUS registry. 32 (60%) were treated with eculizumab [ECU], and 47 (88%) were ≥18 yrs.

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

Underline represents presenting author/disclosure.
Family history of aHUS, prior kidney graft, dialysis, and PE/PI were observed in ECU and non-ECU treated groups.

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levy, Rachael</td>
<td>John O. Connolly, 1 Frank A. Post. 3</td>
</tr>
<tr>
<td>Jones, 6</td>
<td></td>
</tr>
</tbody>
</table>

| RNA <200 c/mL; at 1 and 5 years post-biopsy, 28, 7, 7 % and 54, 21, 14 % of patients had CD4 at biopsy 122, 389, 289. | Severity of CKD (median eGFR 23, 55, 33) (p<0.001 chi squared test for proportions, and log-rank test to compare Kaplan-Meier estimates of patients with HIV AN/FSGS (67), immune complex kidney disease (ICKD, 86) and pts discontinued ECU, with 1 of 2 restarting. |

**SA-PO854**

Spectrum of HIV-Associated Kidney Disease in the Era of Combination Antiretroviral Therapy

**Background:** The spectrum of kidney disease in HIV positive patients has changed under the era of HAART. Patients attending eight clinics in the UK. We describe the clinical characteristics of 199 of 250 patients with HIV/FSGS (67), immune complex kidney disease (ICKD, 86) and tubulo-interstitial disease (TID, 46). Kruskall-wallis test was used to compare medians, chi squared test for proportions, and log-rank test to compare Kaplan-Meier estimates of end-stage kidney disease (ESKD).

**Methods:** We reviewed consecutive renal biopsies (2000-2012) of HIV+ patients attending eight clinics in the UK. We describe the clinical characteristics of 199 of 250 patients with HIV/FSGS (67), immune complex kidney disease (ICKD, 86) and tubulo-interstitial disease (TID, 46). Kruskall-wallis test was used to compare medians, chi squared test for proportions, and log-rank test to compare Kaplan-Meier estimates of end-stage kidney disease (ESKD).

**Results:** Patients with HIVAN and primary FSGS (NOS) were indistinguishable, ICKD encompassed membranous (16), undifferentiated immune complex disease (NOS) (34), IgA (26), MPGN (5) and SLE nephritis (5). TID included TIN (18), acute tubular injury (16) and interstitial fibrosis with tubular atrophy (12). Patients with HIVAN/FSGS, ICKD and TID differed by ethnicity (black: 97, 48, 36 %), median known duration of HIV (0.1, 6.3, 9.6 years), degree of immunodeficiency (median CD4 nadir 56, 128, 117, median CD4 at biopsy 122, 389, 289) and severity of CKD (median eGFR 23, 55, 33) (p<0.01 for all). By biopsy, 35, 68, 76 % of patients had initiated ART and 19, 53, 72 % had HIV RNA <200 c/ml; at 1 and 5 years post-biopsy, 28, 7, 7 % and 54, 21, 14 % of patients had progressed to ESKD (p<0.001 for all).

**Conclusions:** In this cohort, HIVAN/FSGS was typically present at HIV diagnosis. Patients with ICKD and TID were frequently stable on ART with suppressed HIV replication at biopsy. All forms of CKD were associated with a history of advanced immunodepression suggesting that early HIV diagnosis and appropriate ART initiation may constitute a renal risk reduction strategy.

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>John W. Booth</td>
<td>Stephen Paul McAdoo, 2 Emil A. Khatib, 5 Catherine Hors</td>
</tr>
<tr>
<td>Tabitha Turner-stokes</td>
<td>Partha Das, 2 Claire Melinda Naftalin, 3 Nadia Kumar, 2</td>
</tr>
<tr>
<td>Atsuko Ikemori</td>
<td>Masahiko Yazawa, 1 Kayori Tsuruoka, 1 Naohiko Imai, 1 Takashi Yasuda, 1 Kenjiro Kimura. 1</td>
</tr>
<tr>
<td>Matthias Kretzler, 2 Debbie S. Gipson. 2</td>
<td>Kenjiro Kimura. 1</td>
</tr>
<tr>
<td>Kayori Tsuruoka, 1 Naohiko Imai, 1 Takashi Yasuda, 1 Kenjiro Kimura. 1</td>
<td>Takashi Yasuda, 1 Kenjiro Kimura. 1</td>
</tr>
<tr>
<td>John W. Booth</td>
<td>Stephen Paul McAdoo, 2 Emil A. Khatib, 5 Catherine Hors</td>
</tr>
<tr>
<td>Tabitha Turner-stokes</td>
<td>Partha Das, 2 Claire Melinda Naftalin, 3 Nadia Kumar, 2</td>
</tr>
<tr>
<td>Atsuko Ikemori</td>
<td>Masahiko Yazawa, 1 Kayori Tsuruoka, 1 Naohiko Imai, 1 Takashi Yasuda, 1 Kenjiro Kimura. 1</td>
</tr>
<tr>
<td>Matthias Kretzler, 2 Debbie S. Gipson. 2</td>
<td>Kenjiro Kimura. 1</td>
</tr>
</tbody>
</table>

**SA-PO857**

Baseline Immunosuppression Exposure in Neuruphine Study Cohort

**Background:** The Nephrotic Syndrome Study Network (NEPTUNE) includes a multicenter, prospective cohort of adults and children with proteinuria and a clinical indication for initial renal biopsy. We aimed to characterize the pre-biopsy immunosuppressive therapy (IST) and clinical features associated with therapy among the initial 331 enrollees.

**Methods:** IST was categorized as steroids only, calcineurin inhibitor, mycophenolate, cytotoxic, multiple (MIST), and none. Indications for biopsy were classified as steroid dependent (SDNS), frequently relapsing (FRNS), steroid resistant (SRNS), or diagnosis. ANOVA and chi-squared tests were used for analysis. Data are presented as n(%) and median (interquartile range).

**Results:** 51(24%) of adults and 69(71%) of children were treated with IST (p<0.01). Medians months cumulative IST was 2.0(14.0) adults and 6.0(10) children, p <0.01. Compared to adults without IST, adults with IST did not differ in terms of age of onset, obesity or race. Adults with IST compared to those without IST were more likely to have FRNS, SDNS or SRNS as the biopsy indication (8% vs 0%, p<0.02), less likely to have FSGS (14% vs 39%, p<0.01), and more likely to have MCD (27% vs 7%, p<0.01). Children had greater exposure to second line or MIST compared to adults (37% vs 7%, p<0.01). Children without IST were more likely to be black (64% vs 36%, p<0.01), over age 12 years (68% vs 20%, p<0.01) and obese (46% vs 34%, p<0.04) and differed by histopathology (FSGS 44% vs 25%; MCD 19% vs 68%; other 38% vs 5%, p<0.01) compared to children treated with IST.

**Conclusions:** In this contemporary prospective longitudinal cohort, a surprising 24% of adults with proteinuria are exposed to IST prior to initial clinically indicated kidney biopsy. Only a fraction of these have a history of childhood onset disease. Conversely, 29% of children did not have IST pre-biopsy. These children were more common of black race, older age, and obese. Pre-biopsy therapy in these pediatric settings is consistent with North American Clinical Practice Guidelines.

**Funding:** NIDDK Support, Private Foundation Support
SA-PO858
A Noninvasive Biomarker for Aristolochic Acid Exposure Detected in Exfoliated Urinary Cells
Tao Su,1 Xiaomei Li,2 Li Yang,3 Byong Hwa Yun,2 Robert Turesky,2 Arthur P. Grollman,3 Kathleen G. Dickman.3
1Peking Univ First Hospital, Beijing, China; 2NY State Dept of Health, Albany, NY; 3Stony Brook Univ, Stony Brook, NY.

Background: Aristolochic acid (AA), a nephrotoxin and upper tract urothelial carcinogen, is a component of all Aristolochia-based herbal drugs. In cases of suspected exposure, analysis of blood or urine for the presence of AA is not useful, as CKD and/or urothelial cancer can appear months to years following drug withdrawal. However, reactive AA metabolites form stable adducts with DNA that are resistant to repair and persist in cells with low turnover rates. Here we test the feasibility of detecting aristolactam (AL)-DNA adducts in urinary cells and evaluate their utility as a noninvasive biomarker of AA exposure in CKD patients with a documented history of Aristolochia use.

Methods: Cells were collected by centrifugation of 24-12 hour urine specimens from 40 patients; six cases were excluded due to insufficient DNA for analysis or incomplete clinical data. AL-DNA adducts extracted from these cells were measured by 32P-postlabeling methodology or mass spectrometry.

Results: Based on eGFR, 32/34 patients had CKD, the majority at stages 4 or 5. All but two patients reported using Aristolochia: urinary AL-DNA adducts were absent in these two cases. Adducts, with levels ranging from 0.3-581 adducts/10^8 nucleotides, were detected in 28/32 of the remaining cases, representing a wide range of AA exposure times (2 mo-20 yrs), cumulative doses (0.14-19 g), and time following withdrawal (2 d-8 yrs). Adducts were found in 13/13 of cases with recent discontinuation of Aristolochia use (≤3 mo), and could still detected for as long as 8 yrs after the last exposure. Upper tract urothelial cancer patients resistant to treatment at the time of sampling were found to have increased adducts (3/2/3) and developed in three additional adduct-positive patients during an 8-yr follow-up.

Conclusions: AL-DNA adducts can be detected in urinary cells several years after discontinuation of Aristolochia use. This noninvasive biomarker can be used to screen for persons at risk of developing AA nephropathy and upper tract urothelial carcinoma, providing an opportunity for early detection and intervention.

Funding: Other NIH Support – NIEHS P01ES004608 and RO1ES019564, Private Foundation Support

SA-PO859
GQ-16, a New Peroxisomal Proliferator Activated Receptor Gamma Repressor Galleria Cell Proliferation and Tumor Necrosis Factor Alpha Promotor in Human Mesangial Cells
Al-Hadi Zain,1 Michelle Soares Coelho,1 Francisco R. Neves,2 1Molecular Pharmacology Laboratory, Faculdade De Ciências Da Saude, Universidade de Brasilia, Brasilia, DF, Brazil; 2National Institute of Science and Technology for Pharmaceutical Innovation, Universidade Federal de Pernambuco, Recife, PE, Brazil.

Background: Tumor necrosis factor (TNF-α) induces mesangial proliferation and participates in kidney disease. Peroxisome proliferator activated receptor gamma (PPARγ) agonists (pioglitazone – PIO and rosiglitazone - ROSI) improve insulin sensitivity and also ameliorate renal disease by their antiinflammatory characteristics. Gene reporter assays were carried out using luciferase reporter driven by PPARγ promoter and mesangial cells (MC) proliferation upon TNF-α treatment.

Methods: Human MC were incubated at 37°C in DMEM supplemented with 10% fetal calf serum, treated with TNF-α (10 ng/ml) and GQ-16 (1μM to 50 μM) or PIO and ROSI at 10 μM. Three hours incorporation assay was performed to evaluate DNA synthesis and proliferation. Gene reporter assays were carried out using luciferase reporter driven by human TNF-α promoter. Cells were collected by centrifugation of 12-24 hour urine specimens

Results: In MC, GQ-16 significantly impaired TNF-α induced cell proliferation, in a dose-response curve (1μM-32%; 10μM-35% and 50 μM-52%). These results were similar to PIO (10μM-39%) and ROSI (10μM-35%). Also, GQ-16 significantly reduced transcriptional activity of human TNF-α promoter in a dose response manner. The IC50 of GQ-16 was 16 (98 μM) was 26 times higher than ROSI (3.46 μM), but at the highest concentration this response was comparable to ROSI.

Conclusions: These results suggest that in human MC, GQ-16 exerts an antiproliferative and represses the transcriptional TNF-α promoter activity through PPARγ, suggesting an antinflammatory effect similar to ROSI.

SA-PO860
Glemuronelphritis (GN) in a Chronic Kidney Disease (CKD) Population
Andrew John Mallett,1,2,3 Anne Salisbury,1,2,3 Zainmin Wang,4 Helen G. Hailey,5,2 Geoffrey Williams,6 Wendy E. Hoy,1,7,2 GQ-CLD; 1Centre for Chronic Diseases, School of Health Science, Univ of Queensland, Brisbane, Queensland, Australia; 2Dept of Renal Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Queensland, Australia.

Background: GN is a heterogeneous group of disorders accounting for 23% of Australian and New Zealand patients commencing renal replacement therapy in 2011. The characteristics of this group in Australian CKD populations requires definition.

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

SA-PO861
The Spectrum of Glomerular Diseases in Central Region of Saudi Arabia: A 5 Year Retrospective Study

Background: Glomerular diseases continue to be the leading cause of end-stage renal disease globally. Hence it is important to recognize the glomerular disease pattern in any given geographical area to understand the pathobiology, incidence and progression of the disorder in that region.

Methods: A total of 348 native renal biopsies performed on patients with proteinuria > 1 g/m, haematuria or renal impairment during a period of 5 years (between January 2005 and December 2009) in a tertiary care hospital of Kingdom of Saudi Arabia. All the biopsies were studied by histopathologist by (light microscopy, immunofluorescence and electron microscopy) and categorized. SAS version 9.2 was used for statistical analysis.

Results: Primary glomerular disease accounted for 55.1% of all renal biopsies. The most common histological lesion was focal segmental glomerulosclerosis (FSGS) (27.6%). Minimal change disease (MCD) was the second most common lesion (17.7%) followed by membrano-proliferative glomerulonephritis (MPGN) (13.0%) and IgA nephropathy (IgAN) 11.5%. Secondary glomerular disease contributed to 37.9% of glomerular diseases with lupus nephritis (LN) as the commonest lesion (54.5%) followed by hypertension (HTN) (22%), post-infectious (7.5%), diabetic nephropathy (DN) (6.8%) and vasculitis (4.5%). We came across 14 cases of crescentic glomerulonephritis (5 vasculitic, 2 post-infectious, 1 lupus nephritis, 1 IgA nephropathy, 1 mesangio proliferative, 1 diffuse proliferative and 3 not specified). ESRD accounted in 15 % of all renal biopsies whereas inadequate biopsies constituted 2.8 % of all the tissues.

Conclusions: This study demonstrates that SGDS as the most common primary GN encountered in the studied cases, the second most frequent is MCD. Lupus nephritis is the third most common secondary. The proportion of this study of these biopsies is higher than the rest of the world. Pattern of glomerulonephritis seems to vary in different regions of Saudi Arabia. We believe that Renal Biopsy Registry is mandatory to better understand the pattern of glomerular disease and to follow any trend change.

SA-PO862
Glemuronel Descriptors Enhance Standard Renal Biopsy Diagnoses
Carla C. Naz,1 L. Barisone,2 J. Troost,1 A. Gaspar,2 Gerald A. Lopes2,1, Daniel C. Catran,3 Cedars-Sinai U; Miami; U ’Mich; UNC; Columbia U; U’ Toronto.

Background: The Nephrotic Syndrome Study Network (NEPTUNE) has characterized a cohort with membranous, including FSGS and minimal change disease (MCD). In addition to standard morphologic diagnoses, biopsies are assessed using “descriptors” of renal lesions. Based on this evaluation, MCD was subclassified into MCD with only glomerular foot process effacement (FPE) (MCD-FPE) and MCD with any other glomerular lesion (global sclerosis, hyaline, hypercellularity (MCD-HH)). These 3 groups (FSGS, MCD, MCD-HH) were analyzed to discern whether presenting clinical features and FPE extent correlate with this descriptor-based subclassification.

Methods: 75 FSGS, 41 MCD- and 17 MCD + patients had biopsies evaluated for FPE by 2 independent quantitative systems (3 months to years following biopsy), and analyzed relative to patient age, sex, baseline hypertension (HTN), urine PrCr ratio, eGFR, and pre-biopsy steroid treatment.

Results: Sex ratio was similar, but ages differed in the groups (FSGS 36.3 yrs, MCD+ 27.9 yrs, MCD- 12.8 yrs, p<.0001). Urine PrCr ratios were not different, but eGFR was lower in MCD+ (73.0) vs. both MCD- (98.7) (MCD- history and MCD+ p<.0001 vs FSGS). HTN was more common in FSGS and MCD- vs. MCD+ (p<.02). Overall, FPE extent and proteinuria correlated when groups were combined (p<.0001); however, there was no significant correlation when groups were separated regardless of the score system used.
Pre-biopsy steroid exposure was more frequent in MCD (71%), less in MCD+ (56%) and least in FSGS (22%) (p<0.001); this difference occurred in children but more prominently in adults. Prior steroid treatment correlated with FPE extent only in MCD (p=0.05).

Conclusions: At baseline, FSGS patients were older with lower GFR, more frequent HTN, and were less likely to receive pre-biopsy steroids. MCD+ had features between FSGS and MCD+ including HTN, and intermediate age and pre-biopsy steroid exposure, with FPE similar to FSGS. This suggests morphologic glomerular disease may be used to identify a distinct clinical cohort in MCD. FPE overall correlated with degree of proteinuria, but did not discriminate among these diagnostic groups.

Funding: NIDDK Support

SA-PO863

Masked Monoclonal Membranous-Like Glomerulopathy

Christopher Patrick Larsen, Nidia Cordeiro Messias, Larry N. Cossey, Josephine M. Ambruzs, Patrick D. Walker.

Nephropath, Little Rock, AR.

Background: Routine direct immunofluorescence on fresh tissue is the gold standard for the detection and characterization of immune deposits. We recently have observed an unusual form of glomerulonephritis in which the deposits are “masked” and require an antigen retrieval step to be visualized. Correlation with the patient information reveals this to be a unique clinicopathologic syndrome not previously described. We have termed this unusual form of glomerulonephritis in which the deposits are “masked” and require an antigen retrieval step to be visualized as MMGM.

Methods: We identified 14 cases of MMGM in our case files over the past two years. LM, IF, and EM was performed in all cases. Retrospective analysis of clinical information was also gathered.

Results: The cases were characterized by subepithelial deposits and C3-predominant staining. Repeat immunofluorescence after pronase digestion of the FFPE tissue demonstrated strong IgG with kappa restriction. Four patients had evidence of crescent formation without endocapillary proliferation. The remaining cases showed no proliferative changes. The patients were most commonly female (12/14) with a mean age of 24.8 years and 8/14 (62%) had autoimmune phenomena. The clinical and demographic findings in MMGM patients do not correspond with those typically found in patients with monoclonal glomerular membranulopathy or proliferative glomerulonephritis with monoclonal IgG deposition as these patients were significantly older, with a mean age of 69.2 ± 67.3, respectively) and rarely showed evidence of autoimmune phenomenon. Follow-up data in 9 patients showed one complete remission, 2 partial remissions and 6 with persistent disease (mean 14.9 months, range 2–46 months).

Conclusions: We present the first description of a novel form of glomerulopathy that occurs predominantly in young females with vague autoimmune symptoms and proteinuria. The specific glomerulopathy is only revealed after addition of antigen retrieval. Previously, MMGM has likely been misdiagnosed as an atypical form of membranulopathy, infection-related glomerulonephritis, or C3 glomerulopathy.

SA-PO864

Quantitative T2 MRI to Measure Kidney and Liver Disease Progression in Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Ying Gao,1,2 Bernadette O. Erokwu,1 Lan Lu,3 Chris Flask,1,2,3 Katherine MacRae Dell.1,2

1Dept of Radiology, 2Pediatric Imaging, 3Pediatric CWRU Center for the Study of Kidney Disease and Biology, Case Western Reserve University, Cleveland, OH.

Background: ARPKD is associated with significant morbidity and mortality in affected patients; however, there are no clinically-available methods to measure kidney and/or liver disease progression except in advanced stages, severely limiting the study of novel therapies in patients. We previously utilized quantitative T2 MRI to assess kidney and liver disease in the PCK rat. In the current study, we used T2 MRI to longitudinally examine disease progression.

Methods: Eight PCK rats were scanned at 1-, 2- and 3-mos of age in a 7T Bruker Biospec MRI scanner. Multislice, coronal kidney and sagittal liver images were obtained with a flowcompensation gated, multiecho spin echo acquisition. For kidneys, T2 values were calculated using a linear least squares regression of a monoexponential decay model. Cysts (T2 values) and normal tissue (T2 values) were distinguished by manual thresholding. For liver, T2 values were calculated based on mean values of white regions of interest via a nonlinear least squares fitting of a biexponential decay model. Means and standard deviations (SD) for disease and normal tissues were calculated at each time point and analyzed using 2-tailed Student’s t-tests.

Results: For kidneys, the cystic volume increased over the 2个月 study period. Mean±SD (%)cystic at 1, 2, and 3 mos were 27.4±4.2%, 31.1±5.5% and 43.8±3.4%, respectively. Significant differences (p<0.0006) were seen in the 2-3 mos interval but not the 1-2 mos interval. For livers, mean T2 values (indicating increased biliary duct dilatation vs. normal parenchyma) also increased. Mean±SD values (insec) at 1, 2, and 3 mos were 54.3±5.9, 64.4±7.8 and 74.6±6.8. Significant differences were seen at both the 1-2 mos (p=0.032) and 2-3 mos (p=0.035) intervals.

Conclusions: Quantitative T2 MRI assessments of PCK rats detected significant kidney and liver disease progression over the relatively short time intervals studied. These techniques, which are readily translatable to human imaging, may provide a useful assessment of disease progression in ARPKD patients as well.

Funding: NIDDK Support

SA-PO865

Maternal Anti-Human Laminin α5 IgG Causes Anti-GBM Disease in Perinatal Transgenic Mice Expressing Human Laminin α5


Anatomy and Cell Biology, and the Kidney Institute, Univ of Kansas Medical Center, Kansas City, KS.

Background: Mammalian immune systems do not mature until well after birth, but transfer of maternal IgG to the fetus and newborn usually provides sufficient immunoprotection from infectious diseases. This IgG transfer occurs before birth in humans across the placenta and in many mammalian species, including rodents, continues after birth across the intestine. The transfer is selective and occurs by transcytosis across placentally syncytiotrophoblasts and intestinal epithelium, which is mediated by the neonatal IgG Fc receptor (FcRn). Although maternal IgG is generally beneficial, maternal autoimmunity can be transferred to the fetus/infant, causing diseases such as myasthenia gravis, hepatitis, pemphigoid, thyrotoxic purpura, and systemic lupus erythematosus, including lupus nephritis.

Methods: Previously, we generated transgenic (Tg) mice that express human laminin α5 (hLama5) in basement membranes throughout the body (Steenhard et al., PLoS ONE 6(9): e23926, 2011). These Tg mice suppress murine Lama5 mRNA transcription and mouse laminin α5 protein deposition, but heterozygous animals have no renal phenotype.

Results: When we crossed hLama5 Tg males with wildtype (wt) females, we discovered development of a maternal anti-hLama5 immune response (presumably induced by embryonic Tg basement membranes) and maternal sera contained IgG that bound linearly to basement membranes of human kidney cryosections. Maternal alloantibody also crossed the placenta in vivo and bound to bright, linear patterns to glomerular basement membranes (GBMs) of Tg pups but not those of wt siblings. Foster nursing of Tg pups showed post-natal transfer of maternal anti-hLama5 IgG through suckling as well, which also bound to GBMs of Tg pups but not wt. By 18d, most Tg mice had glomerular C3 deposits. Electron microscopy showed neutrophil and monocyte infiltrates, thickened and split GBMs, and podocyte foot process effacement.

Conclusions: This novel model of perinatal anti-GBM disease may be useful for determining effects of autoantibodies on glomerular development in vivo.

Funding: NIDDK Support, Other NIH Support - 9P20GM104936

SA-PO866

Remodeling of Renal Urothelium Characterizes Renal Adaptation to Congenital Obstructive Nephropathy in the Megabladder Mouse

Elizabeth R. Carpenter,1 Brian Becknell,2 Jordan Allen,3 Kirk M. McHugh.1

1Center for Molecular and Human Genetics, Nationwide Children’s Hospital; 2Biomedical Sciences Graduate Program, The Ohio State Univ; 3Div of Nephrology, Nationwide Children’s Hospital; 4Div of Nephrology, Nationwide Children’s Hospital; 5College of Medicine, The Ohio State Univ.

Background: The megabladder (mgb) mouse model of congenital obstructive nephropathy (CON) presents the opportunity to describe renal adaptation to urinary tract obstruction. Mgb-/+ mutants develop functional lower urinary tract obstruction due to a lack of proper detrusor muscle organization in utero, which leads to chronic kidney disease and death in early adulthood. To better understand the molecular mechanisms responsible for renal adaptation in CON, we performed transcriptome analysis of mgb+/− kidneys compared to controls.

Methods: Kidneys from age-matched male mgb−/+ and wild type control mice were evaluated by ultrastruct, Agilent cRNA microarray, qPCR and immunohistochemistry (IHC).

Results: Microarray analysis comparing severe mgb−/− and mgb+/− kidneys with controls identified urothelium-specific genes. These genes encompassed uroplakins (Upk1a, Upk2, 3a and 3b), cytokoters (Kr5, 14, and 19), urothelial transcription factors (Grh3, Foxa1) and additional genes with proposed functions in maintaining the urine permeability barrier (Sper1, Gjb6, and Gsod4). We confirmed increased expression of each of these transcripts by qPCR (p<0.05). Notably, Upk1b and Kr14 mRNA were found to statistically differ in control versus mildly hydropnephrotic mgb−/− kidneys. We characterized expansion of Upk3 and Kr14 protein expression and a significant increase in the number of Ki-67-positive proliferating cells along the renal urothelium as hydropnephrosis worsened.

Conclusions: In the mgb mouse model of CON, proliferation and upregulation of urothelium-specific genes reflect an early adaptive response in the obstructed kidney. Further understanding of the molecular pathways responsible for urothelial proliferation and remodeling during renal adaptation will yield insights into the pathophysioloogy of chronic kidney disease as well as identify early diagnostic and prognostic markers of mgb−/− disease.

Funding: NIDDK Support

SA-PO867

Molecular Basis of Renal Adaptation in a Murine Model of Congenital Obstructive Nephropathy

Ashley R. Carpenter,1 Brian Becknell,2 Melissa Scott,1 Michael Wilhide,1 Susan E. Ingraham,1 Kirk M. McHugh.1

1Research Institute, Nationwide Children’s Hospital; 2Biomedical Sciences Graduate Program, The Ohio State Univ; 3Div of Nephrology, Nationwide Children’s Hospital.

Background: Congenital obstructive nephropathy (CON) is a common cause of pediatric chronic kidney disease (CKD) and a leading indication for renal transplant in children. The cellular and molecular responses of the kidney to CON are incompletely

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

825A
characterized. In this study, we evaluated global transcription in kidneys with graded hydropnephrosis in the megabladler (mgb-/-) mouse.

Methods: Kidneys from age-matched male mgb-/- and control mice were graded by ultrasound, evaluated by Agilent cDNA microarray, and validated by qPCR and immunohistochemistry.

Results: This analysis indicates that CKD in the mgb-/- mouse model of CON involves a dysregulation between three canonical pathways, including TGFβ directed inflammation. First, the results of the skewed expression of a group of sexually dimorphic genes in male mgb-/- kidneys as well as de-repression of Hdc target genes. These observations provide a potential mechanism for gender-based differences in renal pathogenesis.

Conclusions: The results of this study indicate that CKD in mgb-/- mice results in a highly orchestrated adaptive response that is designed to prevent permanent renal injury and permit rapid morphological and functional recovery. These observations will permit the development of novel biomarkers and therapeutic approaches to progressive renal injury.

Funding: NIDDK Support

SA-PO868

Global and Gene-Specific Hypomethylation by Maternal Undernutrition in Rat Embryonic Kidney

Midorik Awazu, Mariko Hida. Dept of Pediatrics, School of Medicine, Keio Univ.

Background: Maternal undernutrition leads to low nephron number. We reported that ureteric bud branching is reduced and that genes involved in ureteric branching are decreased in nephron number. We also observed that ureteric bud branching is reduced and that genes involved in ureteric branching are decreased in nephron number. We also observed that ureteric bud branching is reduced and that genes involved in ureteric branching are decreased in nephron number. We also observed that ureteric bud branching is reduced and that genes involved in ureteric branching are decreased in nephron number.

Methods: The kidneys of embryonic day 18 fetuses from dams fed ad libitum (CON) and those subjected to 50% food restriction throughout pregnancy (NR) were examined. Global methylation was assessed by methylated DNA quantification kit. The methylation landscape of gene promoter regions included in the array, 7330 were hypomethylated in NR.

Conclusions: The results of this study indicate that CKD in mgb-/- mice results in a highly orchestrated adaptive response that is designed to prevent permanent renal injury and permit rapid morphological and functional recovery. These observations will permit the development of novel biomarkers and therapeutic approaches to progressive renal injury.

Funding: NIDDK Support

SA-PO870

Novel TNXB and ROBO2 Mutations Confirm Genetic and Phenotypic Heterogeneity of Hereditary Nephropathy

Vashesh A. Haddad, Patricia D. Brophy, Michelle P. Winn. 1Pediatrics, Medicine and Center for Human Genetics, Duke Univ, Durham, NC; 2Pediatrics and Human Genetics, McGill Univ, Montreal, Canada; 3Pediatrics, Univ of Iowa, Iowa, IA.

Background: Vesiocureteral reflux (VUR) is the most common congenital anomaly of the kidney and the urinary tract and reflux nephropathy is a major cause of chronic kidney disease (CKD) in children. The gold standard for the diagnosis of VUR is VCUG, an invasive and unpleasant diagnostic procedure. VUR shows high heritability in family studies, however the genetic causes remain elusive and opportunities for non-invasive molecular and radiologic diagnosis of VUR have not been explored.

Methods: The objective of this study is to identify genetic causes for VUR as a first step towards identification of non-invasive molecular tools for diagnosis. We have ascertained and obtained clinical data and biologic samples from over 330 individuals with VUR, of these; we identified 27 kindreds with hereditary VUR. As a proof of principle that molecular diagnosis is feasible in VUR, we carried out genome-wide linkage analysis (GWLA) and/or whole-exome sequencing on two families with hereditary VUR.

Results: We identified a nonsense mutation T3257I in TNXB and a novel missense mutation A304D in ROBO2. The two mutations segregated with disease in the two families. Both mutations are conserved in evolution and are predicted to be deleterious with a polyphenon score of 0.99 and 1 respectively. Some affected individuals with TNXB mutation demonstrated an asymptomatic joint hypermobility while the phenotype in the family with ROBO2 is isolated VUR with no underlying renal dysplasia or extra renal manifestations.

Conclusions: Whole exome sequencing analysis identified novel mutations in TNXB and ROBO2 in two families with hereditary VUR showing that non-invasive molecular diagnosis may be feasible in a subset of patients with VUR. Our results highlight the genetic and phenotypic heterogeneity of VUR.

Funding: NIDDK Support, Private Foundation Support

SA-PO871

DNA Copy Number Variations in Human Alpha-Defensin 1-3 Gene Locus Are Associated with Urinary Tract Infections in Patients with Vesicoureteral Reflux

David S. Haims,1,2 Huanyu Wang,3 John David Spencer,1,2 Brian Becknell,1,2 Kirk M. McHugh,2 Andrew L. Schneider,1,2 Pediatrics, Nationwide Children’s Hospital, Columbus, OH; 3The Research Institute at Nationwide Children’s Hospital, Columbus, OH.

Background: DNA copy number variations (CNVs) can have profound effects on gene dosage. Specifically, CNVs in innate immunity genes, such as the alpha-defensin gene family, are associated with diseases involved with infection like HIV susceptibility. The DEFA1A3 locus varies ranging from 2-12 copies per diploid genome. Despite the importance of alpha defensins in the immune response, CNVs in the alpha-defensin gene family have not been evaluated in patients with UTI. This study was designed to quantitate DNA copy number of alpha-defensin 1-3 (DEFA1A3) in patients with vesicoureteral reflux (VUR) and UTI enrolled in the RIVUR study.

Methods: Standard individual copy type: Southern blot and pulsed-field gel electrophoresis were performed to copy-type multiple individuals at the DEFA1A3 locus. RIVUR study patients: 310 individuals from the RIVUR study (children with VUR and at least one UTI) were copy typed using multiplex real-time PCR and normalized to ZNF80. 310 age/ethnicity/gender-matched controls were also copy typed. DNA copy calls: Exact DEFA1 copy number were determined for each individual using known copy-type standard individuals for curve standard. Tissue gene expression: Using validated exo-spanning primers for DEFA1A3 mRNA, we typed copy typed DNA and quantitated DEFA1A3 mRNA using real-time PCR on human kidney samples.

Results: On average, we identified that RIVUR patients had one less copy of DEFA1A3 compared to controls (p <0.0001). Furthermore, copy number distribution showed a significant overall skewing toward a lower copy number of DEFA1A3 in patients with VUR. Finally, DNA copy number correlated with mRNA message in the human kidney.

Conclusions: We demonstrated that the DEFA1A3 locus is associated with increased risk for UTI in children with VUR. Ultimately, decreased DNA copy number results in less transcribed mRNA. These findings serve as a potential risk factor when determining risk of UTIs in these patients.

Funding: NIDDK Support

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

Underline represents presenting author/disclosure.

826A
SA-PO872
APO1 Variants Are Associated with LHV in the CKD Study Robert Woroniecki,1 Cheryl Ann Winkler,2 George W. Nelson,2 Craig S. Wong,3 Mark Mitsnefes,4 Bradley A. Warady,4 Susan L. Furtth,5 Frederick J. Kassel,5 Jeffrey B. Kopp,2 1Columbia U; NIH; 2New Mexico; 3Children's Hospitals; 4Univ, Kumamoto, Japan.

Background: Left ventricular hypertrophy (LVH) is common among adults and children with chronic kidney disease, and is more common among African Americans (AA). We wished to determine whether APO1 kidney risk alleles might contribute to this disparity.

Methods: We carried out a case/control study among AA subjects enrolled in the Chronic Kidney Disease in Children (CKiD) study to assess a role for APO1 variants in LHV. GFR was determined by plasma inulin clearance. Hypertension was defined according to the Fourth Report for subjects ≥18 years and JNC7 for older subjects. LHV was defined by echocardiographic parameters. Proteinuria was assessed as first morning urine protein/creatinine ratio. APO1 variants G1 (rs73885319, S342G) and G2 (rs71785313, NY deletion) were genotyped.

Results: DNA was available for 89 AA subjects, 43 (48%) were diagnosed as ever having had hypertension and 62 underwent echocardiography. LVH was present in 9/33 (27%) of hypertensive children and 7/29 (24%) normotensive children (p=1). As expected, APO1 risk alleles were common, with 23% of CKiD subjects having 2 risk alleles compared to 12-15% in the general AA population. Two APO1 risk alleles were present in 6/16 (38%) children with LHV and 5/45 (11%) without LVH, p=0.028. After adjustment for hypertension history, baseline GFR, and baseline proteinuria, the p value was 0.051. Among subjects with 2, compared to 0 or 1 risk alleles, the average GFR decline rates during the study were similar (10.4% vs. 8.8% respectively, p=0.82).

Conclusions: APO1 kidney risk alleles are associated with LVH in pediatric CKD. APO1 variants have also been associated with increased heart size at autopsy, in the absence of kidney disease (Hoy et al, Int Soc Hypertension 2012). It remains unknown whether the apparent effect of the APO1 variants on the heart arise from APO1 gene expression in the heart or in the kidney. Further data on the duration and severity of hypertension will be required to exclude a role for hypertension as a mediator of cardiac damage.

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

SA-PO873
Mutations in the Insulin Receptor INSR Are Associated with Hypercalcuria and Nephrocalcinosis Arabella Singkomp,1 Velibor Tasic,2 Detlef Bockenhauer,1 1Great Ormond Street Hospital, London, United Kingdom; 2Endocrinology, Addenbrookes Hospital, Cambridge, United Kingdom; 3NIDDK, NIH; 4Children’s Hospital Spojke, Macedonia, The Former Yugoslav Republic of.

Background: The insulin receptor INSR is expressed in kidney and studies in mice suggest a role in proximal sodium reabsorption as well as in podocyte function. Yet its physiological role in human kidney is unclear. Recessive mutations in INSR lead to Rabson-Mendenhall (RMS) or Donohue syndrome (DS). Observations in such patients suggest a role in proximal sodium reabsorption as well as in podocyte function. Yet its physiological role in human kidney is unclear. Recessive mutations in INSR lead to Rabson-Mendenhall (RMS) or Donohue syndrome (DS). Observations in such patients suggest a role in proximal sodium reabsorption as well as in podocyte function. Yet its physiological role in human kidney is unclear. Recessive mutations in INSR lead to Rabson-Mendenhall (RMS) or Donohue syndrome (DS). Observations in such patients suggest a role in proximal sodium reabsorption as well as in podocyte function. Yet its physiological role in human kidney is unclear. Recessive mutations in INSR lead to Rabson-Mendenhall (RMS) or Donohue syndrome (DS). Observations in such patients suggest a role in proximal sodium reabsorption as well as in podocyte function. Yet its physiological role in human kidney is unclear. Recessive mutations in INSR lead to Rabson-Mendenhall (RMS) or Donohue syndrome (DS). Observations in such patients suggest a role in proximal sodium reabsorption as well as in podocyte function. Yet its physiological role in human kidney is unclear. Recessive mutations in INSR lead to Rabson-Mendenhall (RMS) or Donohue syndrome (DS). Observations in such patients suggest a role in proximal sodium reabsorption as well as in podocyte function. Yet its physiological role in human kidney is unclear. Recessive mutations in INSR lead to Rabson-Mendenhall (RMS) or Donohue syndrome (DS). Observations in such patients suggest a role in proximal sodium reabsorption as well as in podocyte function. Yet its physiological role in human kidney is unclear. Recessive mutations in INSR lead to Rabson-Mende

SA-PO874
In Situ Evaluation of INF2 in Normal and Glomerular Diseases in Children Hiroshi Tamura, Pediatrics, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.

Background: Mutations of the inverted formin 2 gene (INF2) are common causes of autosomal dominant and segmental glomerulosclerosis (FGS). It encodes a member of the formin family, which regulates actin and microtubule cytoskeletons. This study investigated the expression of INF2 in glomerular diseases.

Results: The expression of INF2 in normal glomeruli was examined by qRT-PCR and Western blot analysis. INF2 expression in normal glomeruli was significantly lower than that observed in patients with chronic kidney disease.

Conclusions: INF2 expression is decreased in glomeruli with glomerular diseases, and the decreased expression of INF2 may play a role in the pathogenesis of glomerulosclerosis.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO877

Management of Hypertension in Pediatric Pheochromocytoma/Paraganglioma

Mauricio Romero Olivera,1 Gaurav Kapur,2 Rossanna Baracco,3 Tej K. Matttoo,4 Amrish Jain.5 1Pediatric Nephrology, Children’s Hospital of Michigan (CHM), Detroit, MI; 2Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 3Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 4Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 5Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI.

Background: Surgical manipulation of pheochromocytoma/paragangliomas (PH/PG) while being removed can cause hypertensive crisis and post resection hypotension. Guidelines on management of blood pressure (BP) in pediatric patients with PH/PG are lacking. We report our experience with preoperative adrenergic blockade.

Methods: This retrospective study included 7 patients, aged 1-18 yrs old with biopsy proven PH/PG at Children’s Hospital of Michigan from 2003-13. Excluded were patients with elevated catecholamines due to other diagnosis (neuroblastoma). All patients had urinary/plasma catecholamines, imaging, genetic testing & multidisciplinary evaluation. BP was controlled with α blockade for 2-4 weeks and β blockade for 2-3 days before surgery. High salt diet was encouraged after 3 days of α blockade. Intraoperative esmolol/nitropressure infusion ± fluid resuscitation was used for cardiovascular stability.

Results: Of 7 patients (10.4±5.8 yrs; 5 males), 6 had PH & 1 (14.2%) PG. Bilateral disease was noted in 4 (57.1%) & 1 had 2 recurrences. Altogether 9 surgical interventions were done in 7 patients. Plasma normetanephrine, urine normetanephrine and VMA were elevated in 6, 4, and 3 patients respectively. Adrenal mass was seen on CT scan (2/9) & MRI (7/9); confirmed by MIBG Scan(8/9). Nitroprusside was used transiently(<2h) during surgery in 2; esmolol in 2. Five needed albumin/PRBC. All anti-hypertensives were discontinued immediately after surgery(72%) or within 4 days (28%).

Conclusions: A systematic and multidisciplinary approach of BP control with α blockade, volume expansion and β blockade ensures excellent outcome.

SA-PO878

Podocyte Differentiation Arrest Is Associated with Abrupt Response of Notch to Down-Regulated Wnt Signaling

Haichun Yang,2 Taiji Matsusaka,3 Jin-Soon Suh,1 Yumi Choi,2 Byoung-Soo Cho.1 1Dept of Pediatrics, Bucheon St. Mary's Hospital, College of Medicine, The Catholic Univ of Korea, Bucheon, Korea; 2Dept of Pediatrics, School of Medicine, Kyung Hee Univ, Seoul, Korea; 3Dept of Pediatrics, TheAll Medbio Research Institute, Seoul, Korea.

Background: Recent study suggest that dysregulated innate immunity plays an important role in the pathogenesis of immunoglobulin A nephropathy (IgAN). The intestine is an and its receptors can elicit diverse host defense mechanisms during many infectious and inflammatory diseases. In the current study, we investigated the association between the polymorphisms of IL-10 and its receptors, IL-10RA/IL-10RB genes and childhood IgAN.

Methods: 196 patients with IgAN and 288 normal controls were genotyped for two polymorphisms of the IL-10 gene (rs1518111 and rs1554286), two polymorphisms of the IL10RA gene (rs2256111 and rs4252243), and three polymorphisms of the IL10RB gene (rs2228054, rs999788 and rs2834167).

Results: Our case-control analysis showed that genotypes of rs4252243 in IL10RA gene were associated with IgAN. Individuals with genotypes containing the T allele (TC or TT) of rs4252243 had about 2-fold reduced risk of IgAN compared with those with the CC genotype in the codominant model (p=0.011) and in the recessive model (p=0.014). Furthermore, rs2228054 and rs999788 in the IL10RB gene were associated with the presence of proteinuria and nephrotic-range proteinuria during disease course, respectively.

Conclusions: Our data suggest that rs4252243 polymorphism in the IL10RA gene is associated with the reduced risk of IgAN and polymorphisms in the IL10RB are associated with the disease severity in IgAN patients.

SA-PO880

Risk Factors for Progression in Children with IgA Nephropathy: Data from a European Cohort


Background: The European validation study of Oxford classification of IgA nephropathy (IgAN) (VALIGA) has enrolled 1147 patients.

Methods: Children account for 174 cases, from 20 centers of 11 countries. Proteinuria was adjusted for body surface area and mean arterial pressure for gender and age. Schwartz formula estimated eGFR and the functional decline was defined as slope of eGFR.

Results: Mean age at renal biopsy was 12.7±3.7 years; median follow-up was 4.7 years (IQR 2.4-7.8 years); > 80% presented with normal renal function (eGFR > 90 ml/min/1.73m2).

End-stage renal disease (ESRD) was reached by 4%, 50% loss of eGFR by 5%; 7% reached the combined end point (ESRD or 50% loss of initial eGFR).

At renal biopsy 57% presented with mesangial proliferation (M1), 24% endocapillary proliferation (E1), 35% segmental glomerulosclerosis (S1) and 9% tubular atrophy/interstitial fibrosis (T1/2). Patients with segmental sclerosis and TA/IF showed a significantly worse eGFR slope (S0 vs S1 p=0.04; T0 vs T1/2 p<0.003).

At univariate linear regression, clinical data at renal biopsy (eGFR, proteinuria and MAP) were not associated with renal function decline, while data at 6-12 and 12-24 months and TA-proteinuria and MAP significantly predicted eGFR slope.

A multivariate linear regression model (including proteinuria and MAP at 12-24 months together with the difference of eGFR at renal biopsy and at 12-24 months as independent variables) performed well in predicting eGFR slope (R²=0.39). This model was used to derive a formula able to estimate eGFR slope in ml/min/1.73m2/year, which performs well in the VALIGA pediatric population (mean bias between estimated and really observed eGFR slope of 0.5 ± 6.6 ml/min/1.73m2).

Conclusions: The Oxford classification of IgAN showed that in children segmental glomerulosclerosis and tubular-atrophy/interstitial fibrosis being more significantly associated with renal outcome. A formula was developed that predicts renal function decline based on clinical data after 1-2 years from renal biopsy.

Funding: Government Support - Non-U.S.

SA-PO881

Enhanced Functional Complement Regulatory Proteins (CD46)-Induced Regulatory T Cells by High-Dose Pulse-Intravenous Methylprednisolone in Lupus Nephritis Patients

Ching-Yuang Lin.

Background: Defective suppressive regulatory T cell (Treg) function is crucial in lupus nephritis (LN) pathogenesis. Complement regulatory protein (CD46) is a newly defined complement regulatory molecule for Treg. CD46 plays a critical role in immune regulation. Thus, CD46 induction may help suppress kidney inflammation. We examined chemotaxis and adhesion molecule expression on CD3/CD46-activated CD4 T cells (Treg) from Class III or IV LN patients to ascertain whether five-day pulse intravenous methyl-prednisolone (IVMP) therapy enhances CD3/CD46-activated Treg suppressive function.

Methods: During 2009-2011, 40 active LN patients (Class III or IV) with heavy proteinuria, aged 12-18 years, were recruited. Peripheral blood mononuclear cells (PBMCs) were isolated, both from LN patients (before/after IVMP) and from healthy controls.

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

Underline represents presenting author/disclosure.

Poster/Saturday

828A
SA-PO882
Investigation of Principal Mechanism for Renal Sodium Retention in Children with Idiopathic Nephrotic Syndrome
Takeshi Ninchiho, Hiroshi Kaito,1 Kandai Nozu,1 Taketsugu Hama,2 Koichi Nakashima,3 Norishige Yoshikawa,2 Kazumoto Ijima,1 1Pediatrics, Koei Univ Graduate School of Medicine, Japan; 2Pediatrics, Watawawa Medical Univ, Japan.

Background: Renal retention of sodium is one of the principal mechanisms that leads to edema in children with nephrotic syndrome (INS). Some animal experiments have documented that it is the epithelial sodium channel (ENaC) at collecting ducts or the sodium-hydrogen exchanger (NHE3) at proximal tubules that may contribute to sodium retention in INS. However, there are various theories of renal sodium retention and opinion is divided. In addition, another problem is that no structured studies have elucidated possible contributor to renal sodium retention in human with INS.

Methods: We retrospectively analyzed 10 patients with INS group and 10 with age-matched control (CON) group. All cases in INS underwent kidney biopsy during nephropathy, and those in CON underwent during complete remission. Paraffin-embedded serial sections were stained with immunostaining procedure, and the number of positive cells was counted by a single researcher. NHE3 was evaluated with CD10, a specific marker of proximal tubule, and both α- and β-subunit of ENaC with CK34E12, a specific marker of collecting tubule. The ratios of NHE3 to CD10 and ENaC to CK34E12 positive cells were compared each between two groups.

Results: The mean age at kidney biopsy was 5.3±1.9 years old in INS and 5.3±1.2 in CON. All cases showed no interstitial and tubular damage, and no cases deteriorated kidney function at biopsy. Serum albumin level in INS was significantly lower than that in CON (2.4±0.3 g/dl vs 3.5±0.3 g/dl; p=0.027). The ratio of NHE3 to CD10 positive cells in INS was significantly higher than that in CON (0.85±0.06 vs 0.77±0.06; p=0.013). On the other hand, there was no change in the proportion of α- and β-ENaC to CK34E12 positive cells. Distribution of each channel had also no difference between two groups.

Conclusions: We could first elucidate the distribution and the trend of the sodium channel in children with INS. We demonstrated that it may not be ENaC, or collecting ducts, but NHE3, or proximal tubules, that contributes to sodium retention in INS.

SA-PO883
Patient Reported Outcomes in Pediatric Nephrotic Syndrome
David T. Selwek,1 J. Troost,2 Susan F. Massengill,2 Rasheed A. Gbadegesin,2 David T. Selewski,1 J. Troost,2 Susan F. Massengill,2 Rasheed A. Gbadegesin,2 Washington University School of Medicine, Saint Louis, MO; 1University of Michigan, Ann Arbor, MI.

Background: Previous studies have demonstrated that disease duration negatively impacts PRO in these areas.

Methods: We retrospectively analyzed 10 patients with INS group and 10 with age-matched control (CON) group. All cases in INS underwent kidney biopsy during nephropathy, and those in CON underwent during complete remission. Paraffin-embedded serial sections were stained with immunostaining procedure, and the number of positive cells was counted by a single researcher. NHE3 was evaluated with CD10, a specific marker of proximal tubule, and both α- and β-subunit of ENaC with CK34E12, a specific marker of collecting tubule. The ratios of NHE3 to CD10 and ENaC to CK34E12 positive cells were compared each between two groups.

Results: The mean age at kidney biopsy was 5.3±1.9 years old in INS and 5.3±1.2 in CON. All cases showed no interstitial and tubular damage, and no cases deteriorated kidney function at biopsy. Serum albumin level in INS was significantly lower than that in CON (2.4±0.3 g/dl vs 3.5±0.3 g/dl; p=0.027). The ratio of NHE3 to CD10 positive cells in INS was significantly higher than that in CON (0.85±0.06 vs 0.77±0.06; p=0.013). On the other hand, there was no change in the proportion of α- and β-ENaC to CK34E12 positive cells. Distribution of each channel had also no difference between two groups.

Conclusions: We could first elucidate the distribution and the trend of the sodium channel in children with INS. We demonstrated that it may not be ENaC, or collecting ducts, but NHE3, or proximal tubules, that contributes to sodium retention in INS.

SA-PO884
Vitamin D in Pediatric Incident Idiopathic Nephrotic Syndrome
David T. Selwek,1 Ibrahim Shatat,2 Ashton Chen,2 Priya J. Pasis,2 Larry A. Greenbaum,2 Pavel Geier,3 Raoul D. Nelson,2 Stefan Kiessling,2 Patrick D. Brophy,2 Alejandro Quiroga,2 Michael E. Seifert,2 Caroline E. Straattmann,2 John D. Mahan,2 Maria E. Ferris,2 Courtney L. Harkness,2 J. Troost,2 Debbie S. Gipson.3 1Univ of Michigan, 3Midwest Pediatric Nephrology Consortium.

Background: Idiopathic nephrotic syndrome (INS) is a common complication of childhood in children. While studies of children with prevalent NSF have shown 25-Vitamin D (25-VitD) deficiency rates of 20-100%, there has been no longitudinal study of 25-VitD levels in incident INS. We assessed 25-VitD deficiency in children with INS at diagnosis and over time (within 2 weeks of and 2-4 mos. after diagnosis).

Methods: Preliminary analysis of a longitudinal study of children (2-18yo) from 14 centers with incident INS designed to investigate 25-VitD. 25-VitD deficiency defined as < 20 ng/mL. Exclusion criteria: evidence of secondary NS at diagnosis. Follow-up completes in 8/2013.

Results: 57 children are enrolled, 54 children have completed initial labs and 38 completed 2nd visit labs. Their characteristics are: males 70%, white 56%, black 35%, other race 9%, median age 5 yo. Table1 shows lab data by visit (mean±sd). All 54 (100%) had 25-VitD deficiency at diagnosis. 21 (55%) children had 25-VitD deficiency at follow-up. 81% of children were steroid responsive and 19% were steroid resistant. Children prescribed VitD supplements were less likely to have VitD deficiency at follow-up compared to those without (OR 0.2, 95%CI 0.1, 1.0). Steroid response, age, race, and season did not predict 25-VitD deficiency at follow-up.

Conclusions: In this incident INS cohort, all children at diagnosis have 25-VitD deficiency and the majority continue to have a deficiency 2-4 mos. Furthermore, supplemental VitD decreases the odds of 25-VitD deficiency supporting a potential role for supplementation in incident NS.

SA-PO885
An Evaluation of a 6 Month versus 4 Month Steroid Protocol in Childhood Onset Nephrotic Syndrome
Andra Diana Popescu, Allison Dart. Pediatrics and Child Health, Univ of Manitoba, Winnipeg, Canada.

Background: Standard therapy for a first presentation of nephrotic syndrome is a course of corticosteroid, however there exists considerable practice variation in the duration of initial course. This study aimed to evaluate the effect of a 6-mo vs. 4-mo steroid protocol on clinical outcomes at 1 year.

Methods: This is a retrospective analysis of all children (1-18 yrs) with a first presentation of nephrotic syndrome treated at the Children’s Hospital of Winnipeg with a 6-mo course of prednisone (July 2009 to Sept 2011) (Group B) compared to historical controls treated with a 4-mo course (Jan 2005 to June 2009) (Group A). Children with biopsy confirmed FSGS were excluded. Data was obtained from an electronic medical record. Differences in number of relapses, total steroid dose, time to first relapse and time to second relapse were evaluated between groups. Logistic regression models evaluating the association of clinical factors with 0 vs. >1 and 0-1 vs. >2 relapses were conducted. Follow-up time was 12 months.

Results: In Group A (n=20) 3 had 0, 4 had 1 and 13 patients had >1 relapse. In Group B (n=18) 5 had 0, 6 had 1 and 7 patients had >1 relapse. There were no differences in clinical characteristics between groups. The odds of any relapse (A vs. B) was not different between groups (odds ratio (OR)=2.8; 95% CI 0.5-14.9) and for 0-1 vs. >1 relapse the OR = 4.8 (CI 0.9-20.3). Sex, age, and initial albumin were not associated with outcome in either analysis. Survival analysis showed a mean 4.8 mo to first relapse for Group A and 7.1 mo for Group B (NS), and 8.1 mo to initiation of second line therapy for Group A and 9.9 mo for Group B (NS). There was no difference in the total cumulative steroid dose at 12 months in mg/kg (p=0.3). The rates of steroid toxicity were low in both groups.

Conclusions: Our findings suggest that a 6-mo course of steroids for the first presentation of nephrotic syndrome may decrease the odds of frequent relapses, and delay the time to first relapse and time to initiation of a second line agent compared to a 4-mo course without increasing total steroid exposure. A randomized study with a larger sample size is required to confirm these identified trends.

SA-PO886
Vertebral Fractures in the 3 Year Period following Steroid Initiation among Children with Chronic Illnesses

Background: To describe the frequency of incident vertebral fractures (IVF) in steroid-treated children.

Funding: Private Foundation Support

Funding: Other NIH Support - 5-U01-AR-052181-09

189A
**Methods:** IVF were assessed prospectively each year following steroid initiation for 3 years, according to the Genentent semi-quantitative method. To examine associations with baseline clinical factors, the 3-year total number of IVF was analyzed using multivariable Poisson regression.

**Results:** 404 children were enrolled at a median age of 6.2 years, range 1-17; 50% boys; 18% (46%) had leukemia, 136 (34%) rheumatic conditions, and 80 (20%) nephrotic syndrome as baseline. Among children with SDNS within insurance support that means the maximum weekly dose of nephrotic syndrome (SDNS) has been reported to be effective. Unlike preceding studies, screened for thrombotic risk factors.

**Conclusions:** Within 3 years of steroid initiation, 17% of children had IVF. VF incidence peaked at 12 months, and almost half of the IVF were moderate or severe. Of the factors measured at baseline, prevalent VF were most strongly associated with IVF over the ensuing 3 years.

**Funded by:** CHF FRN 64285.  
**Funding: Government Support - Non-U.S.**

**SA-PO887**  
**Thrombosis in Childhood Nephrotic Syndrome: Contributory Risk Factors**  
**Rezan Topaloglu,** 1 Fehime Kara Eroglu, 2 Betul Tavil, 1 Fatih Ozalith, 1 Mualla Cemal, 1,2 Pediatric Nephrology, Hacettepe Univ Faculty of Medicine, Ankara, Turkey; 1 Pediatric Hematology, Hacettepe Univ Faculty of Medicine, Ankara, Turkey.

**Background:** The aim of this study was to evaluate the prevalence and contributory risk factors for development of thrombosis in children with Nephrotic syndrome (NS).

**Methods:** Among 188 children with NS followed up at Pediatric Nephrology Unit in last seven years; 17 children (9%), identified as having thromboembolic complications and screened for thrombotic risk factors.

**Results:** The mean age of patients was 4.5±3.2 years at the diagnosis of NS and that was 7.1±4.9 at the time of thrombosis. The mean time from NS diagnosis to the first thrombosis development was 2.6±2.3 years. More than half of the thrombosis (53%) occurred during the first year of NS. Among these children, 14 (82%) had FSGS, 2 (14%) had congenital NS and 1 had minimal change disease. 88% of the thrombosis was venous and in regards to the localization; 6 deep venous thrombosis, 4 sino venous thrombosis, 2 portal venous thrombosis, 2 intracardiac thrombosis, 1 intracardiac thrombosis and cerebral infarct, and 2 cerebral infarct. Among screened thrombotic risk factors high factor VIII levels (16.5%) was the leading risk factor followed by decreased antithrombin III level (29%) and high homocystein level (23.5%). The distribution of the hereditary risk factors were; factor V Leiden heterozygote mutation in 12.5%, MTHFR 677 heterozygote mutation in 37.5%, MTHFR 677 homozgyote mutation in 6.2%, MTHFR 1298 heterozygote mutation in 23%, MTHFR 1298 homozgyote mutation in 7.6%, PAI (4G/4G) polymorphism in 15.3% and PAI (4G/4G) polymorphism in 7.6%. Thrombotic risk factors were found in all children while 14 had multiple risk factors. Most of the children (70.5%) treated with oral anticoagulation and 14 (7.9%) had received high dose aspirin.

**Conclusions:** Unlike previously reported studies, in our cohort FSGS is associated with the highest incidence of venous thrombosis. All of our patients had predisposition to thrombosis that shows underlying genetic background influences the likelihood of thrombosis in nephrotic syndrome.

**SA-PO888**  
**Interruption High-Dose Mibizobreine Therapy Is Effective for Children with Steroid-Dependent Nephrotic Syndrome**  
Takuya Okamoto, Takeshi Yamaraki, Asako Haya, Yasuyuki Sato, Pediatrics, Hokkaido Univ Graduate School of Medicine, Sapporo, Hokkaido, Japan.

**Background:** Daily high-dose mibizobreine (M2B) for children with steroid-dependent nephrotic syndrome (SDNS) has been reported to be very effective. Unfortunately, it is still unclear if early volume expansion can improve disease’s outcome.

**Method:** All patients with aHUS treated with Eculizumab at our Center, in stable remission were considered eligible for drug discontinuation. Strict routine home monitoring of indicators of disease activity was performed after treatment discontinuation: detection of blood in the urine with dipstick three times per week.

**Results:** Of 15 patients who had aHUS with CNI dependency, 3 patients (60%) could wean off CNI. No significant side effects such as hyperuricemia, liver dysfunction and leukopenia were revealed during the administration of M2B therapy.

**Conclusions:** Our retrospective study demonstrated that intermittent high-dose M2B therapy is effective for eliminating steroid or CNI to children with SDNS.

**SA-PO889**  
**Discontinuation of Eculizumab Maintenance Treatment in Patients with Atypical Hemolytic Uremic Syndrome**  
Gianluigi Ardissino, Francesca Tel, Sara Testa, Stefania Salardi, Rosaria Colombo, Ilaria Possenti, Silvana Tedeschi, Erminio Torresani. Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca’ Granda Osp Maggiore Policlinico, Milan, Italy.

**Background:** STEC-HUS is a severe acute illness for which there is no specific treatment. Among supportive therapy, the management of fluids has been traditionally concentrated on avoiding fluid overload because patients often present with oligo/anuric AKI. Hemococentration at disease onset is associated with more severe disease, however it is still unclear if early volume expansion can improve disease’s outcome.

**Methods:** Since May 2010 a Network connecting pediatric hospitals in Northern Italy (10 million gp) was developed aimed at early diagnosis and referral of STEC-HUS with the working hypothesis that prompt volume expansion with saline solution 0.9% may revert disease severity. All children with STEC-HUS referred to our Center from Jan. 2012 were addressed to intravenous hydration aimed at inducing an overhydration (+10-15%) of the working volume within 48 h. In case of outcome was confirmed we collected a set of variables and sequential group of historical patients (group A) referred to our Center during 2007-2009 when patients were usually restricted in fluid intake.

**Results:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>N. 22</th>
<th>22</th>
<th>N. 22</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M/F</td>
<td>M/F</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Age</td>
<td>11</td>
<td>13</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Creatinine at diagnosis (mg/dl)</td>
<td>1.5</td>
<td>1.7</td>
<td>1.5</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Peak creatinine (mg/dl)</td>
<td>6</td>
<td>9</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Readmission (no. of total)</td>
<td>0.5</td>
<td>0.7</td>
<td>0.5</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Days of hospitalization</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** Our data showed that early hydration of STEC-HUS can improve the outcome. It can be speculated that hypovolemia (due to diarrhea, reduced food intake, endothelial leakage and reduced onchoytic pressure), if uncorrected, favours thrombosis formation and hypoxic/ischemic tissue damage.

**Acknowledgement:** thanks to the members of the North Italian HUS Network whose complete list is available at www.centroseu.org. The project has been supported by the “PROGETTO ALICE ONLUS – Associazione per la lotta alla SEU”.

**Funding:** Private Foundation Support

---

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only  
Underline represents presenting author/disclosure.  
830A
SA-P0891

Interval Extension of Eculizumab Maintenance Treatment in Patients with Atypical Haemolytic Uremic Syndrome  
Gianluigi Ardissino, Sara Testa, Donata Cresseri, Francesca Tel, Fabio Paglialonga, Ilaria Possenti, Samantha Griffini, Massimo Cugno, Stefania Salardi, Silvana Tedeschi. Center for HUS Prevention, Control and Management, Pediatric and Adult Nephrology and Laboratory Unit, Fondazione IRCCS Ca’ Granda Osp. Maggiore Policlinico, Milan, Italy.

Background: Atypical haemolytic uremic syndrome (aHUS) is a rare, systemic, life-threatening thrombotic microangiopathy (TMA). As many as 70% of aHUS patients have mutations in the genes encoding complement regulatory proteins. Since 2009, eculizumab, a humanized recombinant monoclonal antibody targeting C5, that prevents the generation of membrane-attack complex C5b-9, has been successfully used in patients with aHUS. The standard maintenance treatment schedule requires administration of the drug every two weeks or more frequently by the provider. The best treatment schedule is not yet defined. We tested alternative treatment schedules for prevention of relapses with the rationalization of quality of life, reducing the risk of adverse reactions and reducing the heavy costs of the treatment.

Methods: All pts undergoing eculizumab treatment for aHUS in our Center (n: 22) were addressed to an extension of the interval between doses from the standard 2 weeks to 3 or 4 wks with a strict monitor of global complement activity. AP50 was routinely determined towards a target AP50 <25 before subsequent eculizumab dose. Strict home monitoring of disease reactivation with blood in the urine with dipstick, was performed at home.

Results: In the 12 pts (9 CFH, 1 CFH+CFI, 1 idiopathic, 1 C3) addressed to interval extension (five at 3 weeks and seven at 4 weeks), no aHUS relapses were observed over a cumulative observation period of 130 mos.

Conclusions: This experience supports the possibility of tailoring eculizumab schedule for maintenance treatment in patients with aHUS based on global complement activity.

Funding: Private Foundation Support

SA-P0892

Eculizumab Hepatotoxicity – When to Change Therapy?  
Wesley N. Hays,1 Sibylle Tschumi,1 Simon Ling,1 Janusz Feber,1 Christoph Licht:1 1Div of Nephrology, Hospital for Sick Children, Toronto, Canada; 2Div of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, Toronto, Canada.

Background: Eculizumab is a first-in-class humanized anti-C5 antibody approved for treatment of paroxysmal nocturnal hemoglobinuria and atypical Hemolytic Uremic Syndrome (aHUS) in adults and children. It is used in increasing in children following reports of its safety and efficacy in inducing thrombotic microangiopathy response. No hepatic side effects have been reported to date.

Methods: We performed a retrospective review of case notes and investigations for patients treated with eculizumab for aHUS in a single pediatric center. A standard dosing regimen based on patient weight was used.

Results: Seven of 11 children aged 6 to 11 years experienced elevated aminotransferases following eculizumab treatment for aHUS. One patient with no pre-existing liver disease developed transient hepatomegaly 3 days following the first dose. Alanine transaminase (ALT), hepatic alkaline phosphatase (ALP), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) rose to over 20 times the upper limit of normal. Bilirubin, INR and albumin remained within normal limits. Liver biopsy taken following improvement in liver enzymes showed mild hepatocellular injury with no evidence of infectious or autoimmune hepatitis. Recurrent progressive elevation of ALT following improvement in liver enzymes showed mild hepatocellular injury with no evidence of infectious or autoimmune hepatitis. Recurrent progressive elevation of ALT following improvement in liver enzymes showed mild hepatocellular injury with no evidence of infectious or autoimmune hepatitis. Recurrent progressive elevation of ALT following improvement in liver enzymes showed mild hepatocellular injury with no evidence of infectious or autoimmune hepatitis. Recurrent progressive elevation of ALT following improvement in liver enzymes showed mild hepatocellular injury with no evidence of infectious or autoimmune hepatitis.

Conclusions: Hepatotoxicity is a potentially important yet previously unreported and so far unexplained adverse effect of eculizumab. We recommend monitoring liver enzymes in all patients receiving eculizumab. In patients with excessive hepatic enzyme disturbance or clinical symptoms of hepatitis in association with eculizumab we would change to plasma therapy. Further research is required to clarify the magnitude of the issue, to characterize the mechanism of hepatotoxicity and to identify which patients are most at risk.

SA-P0893

Frontline Treatment for Atypical Hemolytic Uremic Syndrome: Plasma-Exchange or Eculizumab?  
Gianluigi Ardissino, Fabio Paglialonga, Sara Testa, Francesca Tel, Ilaria Possenti, Silvia Consolo, Silvana Tedeschi, Stefania Salardi. Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca’ Granda Osp. Maggiore Policlinico, Milan, Italy.

Background: The introduction of Eculizumab for atypical haemolytic uremic syndrome (aHUS) has quickly changed the management and the outcome of the disease. It is not clear what is the best option left for “old” treatment, mainly plasma exchange (PEX) in the management of aHUS. The aim of the study is to retrospectively assess the outcomes of treatment with PEX vs Eculizumab at our Center.

Methods: All patients with aHUS treated with PEX or Eculizumab since 2000 where considered for the present analysis. Patients who either remained dialysis dependent or who switched to the other treatment modality because they did not reach remission, were considered non responders. PEX was performed with FFP in all cases, with an exchange volume of 50-150% (depending on the historical period) with a variable number of sessions (2-29).

Results: Twenty-eight patients underwent PEX for aHUS (16 CFH, 4 CFI, 2 MCP, 1 C3, 1 AβAnt/FH, 4 Idiopathic) and since 2009, 26 patients were treated with Eculizumab (12 CFH, 4 CFI, 1 MCP, 1 C3, 2 AβAnt/FH, 6 Idiopathic). Overall, the responders were 32% and 88% with PEX and Eculizumab, respectively. The response rate was not substantially different when analyzed separately for specific etiology: CFI Defect + AntiCFH Antibodies (41 Vs 100%), CFI Defect (25 Vs 75%), MCP (50 vs 100%), Idiopathic (0 Vs 66%).

Conclusions: In our experience, PEX was of limited efficacy for preventing ESRD in patient with aHUS compared to Eculizumab. Based on this finding, Eculizumab should be considered as the first-line treatment for aHUS.

Funding: Private Foundation Support

SA-P0894

Presentation of Apolipoprotein L-1 (APOL1) Nephropathy in Pediatric (Ped) and Young (Yg) Adult African American (AA) Patients (Pts) 
Elizabeth I. Anyaegbu, Keith A. Hruska, Andrey S. Shaw, Sanjay Jain. Washington Univ in St. Louis, St. Louis, MO.

Background: 2 coding variants in the APOL1 gene have recently been found to associate with increased incidence of ESRD in the adult AA population (pop). Prevalence of 2 APOL1 risk variants (rvs) in the general AA pop is 9% compared to 0.04% in Caucasians. These rvs associate with hypertension (HTN) attributed ESRD, FSGS and HIVAN in adult AA pts. We hypothesized that as a genetic disease, APOL1 nephropathy (APOL1N) has a ped phenotype, but it remains unclear if the APOL1 rvs influence progression to ESRD in yg AA pts with HTN or FSGS and a family history (FHs) of ESRD.

Methods: We conducted a case-control study of 85 ped and yg AA who presented with either HTN (n= 39) or FSGS (n= 22) with a FHs of ESRD were cases. 24 healthy AA participants without a FHs of ESRD were controls. Mean ages (SD) for the FSGS and HTN pts were 24.3 (7.4) and 23.6 (6.9) years respectively; 27% of pts were < 18 years old. 66% of pts (40/61) had 2 APOL1 rvs; significantly higher than the prev in the general AA pop (p = 0.001). 24/29 pts with HTN attributed ESRD had 2 APOL1 rvs while none of the HTN pts who presented without kidney disease had more than 1 APOL1 rvs. Of the ped pts, 35% (6/17) had 2 APOL1 rvs; with majority of these rvs in the ped FSGS pts.

Conclusions: We demonstrated for the first time that 2 APOL1 rvs in HTN yg AA with a FHs of ESRD are strongly associated with ESRD (p< 0.01). We also found that 2 APOL1 rvs in yg AA with a FHs of ESRD were significantly associated with FSGS and not essential HTN in ped and yg AA pts. This study demonstrates that the ped presentation of APOL1N is not primary HTN.

Funding: Pharmaceutical Company Support - Genzyme Fellowship Grant

SA-P0895

Cytoskeletal Changes in the Proteins of Podocytes by Interleukin-13  
Se Jin Park.1 1Moin Saleem,2 Tan-Su Ha,1 Jae Il Shin.4 1Dept of Pediatrics, Ajou Univ Hospital, Ajou Univ School of Medicine, Suwon, Republic of Korea; 2Children’s and Academic Renal Unit, Southmead Hospital, Univ of Bristol, Bristol, United Kingdom; 3Dept of Pediatrics, Chungbuk National Univ College of Medicine, Cheongju, Republic of Korea; 4Dept of Pediatrics, Severance Children's Hospital, Yonsei Univ College of Medicine, Seoul, Republic of Korea.

Background: The aim of this study was to determine whether pathologic changes in the cytoskeletal proteins of podocytes are induced by interleukin-13 (IL-13) in the experimental minimal-change nephrotic syndrome (MCNS) model and to investigate whether montelukast, a leukotriene receptor antagonist, has an effect on the production of the cytoskeletal proteins in cultured human podocytes.

Methods: Human podocytes cultured on bovine serum albumin-coated plates were treated with different doses of IL-13 and montelukast and examined for permeability using monolayer semi-permeable membranes, for distribution using confocal microscopy, and for ZO-1 protein levels using Western blotting.

Results: As the concentration of IL-13 increased, the contents of ZO-1 and synaptopodin were decreased and their redistribution and rearrangement were observed in immunofluorescence studies. The redistribution of α-actinin & CD2AP by IL-13 were also found around the nucleus of the cell. α-actinin & CD2AP significantly decreased at 20 ng/mL IL-13 (both P < 0.05), whereas β-catenin and p30Cas significantly increased (both P < 0.05). At higher doses, IL-13 gradually increased the permeability of monolayered podocytes. ZO-1 was internalized and shown to accumulate in the cytoplasm of human podocytes in an IL-13 dose-dependent manner. High doses (50 and 100 ng/mL) of IL-13 decreased the levels of ZO-1 protein by 12 and 24 hr (both P < 0.01; n=3), which were significantly reversed by a high dose (0.5 μM) montelukast treatment (P<0.01, n=3).

Conclusions: Our results indicate that IL-13 may increase podocyte permeability through the modulation of several cytoskeletal proteins in podocytes, and such alterations in the content and localization of the molecules may be relevant to the pathogenesis of proteinuria in the IL-13-induced MCNS model.
SA-PO896

Economies of Scale and Cost of Dialysis across the World: A Macroeconomic Perspective Akash Nayak Karopadi,1 Giacomo Mason,1 Enrico Rettore,2 Claudio Ronco.3 1Dept Nephrology - IRCCS, S. Bortolo Hosp, Vicenza, Italy; 2Dept Chem Eng and Dept Econ, BITS, Pilani, India; 3Dept Statistical Sciences, Uni Padua, Padua, Italy.

Background: ESRD treatment is a large expense in most health systems. The main dialysis methods, hemodialysis (HD) and peritoneal dialysis (PD), have significant differences in cost composition and production factors. In this paper we identify macroeconomic variables that influence the relative cost of such modalities across a sample of 51 countries, and finally draw policy-relevant conclusions.

Methods: We retrieved 75 articles from PUBMED and EMBASE estimating PD and HD costs in a 46 countries. We augmented this data with targeted surveys to prominent nephrologists in countries not covered by available literature. For each country, we estimated the ratio between cost of HD and PD. We finally conducted a multivariate regression analysis using the HD/PD cost ratio in each country as dependent, with several country-level indicators as regressors.

Results: We found a strong effect of the following variables on the HD/PD ratio: positive effect of a country’s development (approximated by minimum wage or HDI); large positive effect of a country’s economies of scale in PD equipment (presence of local manufacturing or absence of tariff restriction on PD equipment imports); negative effect of the percentage of private healthcare expenditure and APD usage. Actual and model-predicted ratios are in Figure 1.

SA-PO897

Mortality-Predictability of Parathyroid Hormone in Peritoneal Dialysis Patients Connie Rhee,1 Wei Ling Lau,1 Vanessa A. Ravel,1 Elani Streja,1 Csaba P. Kovessy,2 Rajnish Mehrotra,3 Kamyar Kalantar-Zadeh.1 1Harold Simon Center, Orange, CA; 2Univ of Tennessee Health Science Center, Memphis, TN; 3Memphis VA Medical Center, Memphis, TN; 4Harborview Medical Center, Seattle, WA.

Background: Kidney Disease Improving Global Outcomes guidelines recommend parathyroid hormone (PTH) level measurements in dialysis patients. Other studies have found a strong association between increased mortality and high PTH levels in PD patients. We wanted to determine if correction of PTH to target ranges improves outcomes in PD patients.

Conclusions: Ceteris paribus, local manufacturing and the absence of import duties on PD equipment imply less costly PD: local manufacturing and no duties have a similar effect on the HD/PD cost ratio (0.42 vs. 0.33). The policy implication is that, in the absence of a market large enough to make local production of PD equipment feasible, a country can still reap the benefits of economies of scale by eliminating restrictions on import such as tariffs or quotas.

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

Results: In PD patients, there was a U-shaped association between PTH and death risk, with PTH levels <200pg/ml and ≥700pg/ml associated with increased mortality (reference: PTH 200–300pg/ml): HRs (95% CI) 1.25 (1.12-1.41), 1.12 (1.02-1.23), 1.06 (0.96-1.18), 1.09 (0.97-1.24), 1.12 (0.97-1.29), 1.18 (0.99-1.40), and 1.23 (1.09-1.38) for PTH levels <100, 100–<200, 200–<400, 400–<500, 500–<600, 600–<700, and ≥700pg/ml, respectively.

Conclusions: In PD patients, both lower and higher PTH levels are associated with increased mortality. Further studies are needed to confirm findings, elucidate underlying mechanisms, and to determine if correction of PTH to target ranges improves outcomes in PD patients.

Funding: NIDDK Support
In analyses of time-averaged AP measurements, HD patients had increased mortality at all levels with the greatest risk in the highest and lowest AP categories, whereas PD patients had increased mortality with AP 150–190 U/L only (ref: PD patients with AP 70–90 U/L).

Conclusions: Higher AP levels are associated with increased mortality in PD patients. Further study of AP as a marker and/or mediator of vascular calcification and other underlying mechanisms, as well as the utility of AP in the management of chronic kidney disease-mineral bone disorders is needed.

Funding: NIDDK Support

SA-P0999

Prevalence of High Parathyroid Hormone and Alkaline Phosphatase Levels among Peritoneal Dialysis versus Hemodialysis Patients

Conclusions: Higher AP levels are associated with increased mortality in PD patients. Further study of AP as a marker and/or mediator of vascular calcification and other underlying mechanisms, as well as the utility of AP in the management of chronic kidney disease-mineral bone disorders is needed.

Funding: NIDDK Support

SA-P0900

NT-proBNP Is a More Significant Prognostic Biomarker for Mortality among Three Cardiac Biomarkers in Incident Peritoneal Dialysis Patients

Conclusions: NT-proBNP may be a useful predictor of CV and all-cause mortality in these patients.

Funding: NIDDK Support

SA-P0901

Serum Beta-2 Microglobulin Significantly Predicts Survival in Association with the Residual Renal Function in Japanese Patients on Peritoneal Dialysis – A Prospective Multicenter Cohort Study (PDR-CS)

Conclusions: NT-proBNP and cTnT may be useful biomarkers for adverse outcomes in incident PD patients, suggesting that NT-proBNP could be a useful biomarker for adverse outcomes in these patients.

Funding: Government Support - Non-U.S.

SA-P0902

Vintage-Related Improvement in Peritoneal Dialysis Patient Survival in the BRAZPD II Cohort

Conclusions: In the BRAZPD II cohort, patients with serum levels of less than 30 mg/L exhibit significantly better patient survival and technique survival in association with the residual renal function based on the renal Kt/V. The serum B2M level is thus considered to be a potential prognostic indicator in PD patients.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
SA-PO903

Switching to Hemodialysis without a Functioning Arteriovenous Shunt
Increased Risk of Mortality in Peritoneal Dialysis Patients
Shin Hsing Tsai,1 Jinh-Yang Chen,2 Div of Nephrology, Cheng Hsin General Hospital, Taipei, Taiwan; 2Div of Nephrology, Taipei Veterans General Hospital, Taipei, Taiwan.

Background: Switching to hemodialysis was frequently encountered in peritoneal dialysis (PD) treatment. Whether switching to Hemodialysis without a functioning arteriovenous shunt will increase risk of mortality has not been fully addressed in the literature.

Methods: Incident PD patients, aged ≥ 20 y/o, started dialysis therapy between January 2006 and December 2009, and had stayed on PD for ≥ 180 days were reviewed for our study. Switching to HD for ≥ 60 days was defined as a successful switching. Acute cardiovascular event (defined as admission due to acute heart failure, acute myocardial infarction or angina pectoris) and first peritonitis were analyzed as time-dependent covariates in the regression.

Results: Among 4333 incident PD patients, 163 (3.8%) patients switched with a functioning arteriovenous shunt, 470 (11.1%) switched with a central venous catheter (CVC) and 442 (10.2%) patients died within 60 days of hemodialysis with a CVC. Patients who switched with CVC were older (55.3±14.4 years), had higher prevalence of cardiovascular disease (41.3%) at baseline and had more episodes of acute cardiovascular events and peritonitis after initiating switching. After adjusting acute cardiovascular events, peritonitis and other baseline covariates in the Cox model, patients who switched with CVC had increased risk of mortality (HR:1.41, 95% CI:1.07-1.86, p<0.05). Patients who switched with CVC also had higher non-dialysis out-patient and in-patient medical cost.

Conclusion: Switching to hemodialysis without a functioning arteriovenous shunt increased risk of mortality in PD patients. A planned arteriovenous shunt creation for patients not doing well in PD would avoid the increased mortality risk after initiating hemodialysis with a central venous catheter.

Funding: Government Support - Non-U.S.

SA-PO904

High Serum Cholesterol and Low Density Lipoprotein Predicted a Lower Early Death but Higher Late Death in Peritoneal Dialysis Patients
Qionghong Xie,1 Xiaoling Ge,1 Da Shang,1 Dongyi Ren,2 Jianghua Chen,1 Huiping Zhao, Jie Dong,1 Hai Yan Wang,2 Chuanming Hao,1 Tongying Zhu,1 Huashan Hospital, Fudan Univ; 2Peking Univ First Hospital; 3Peking Univ Third Hospital; 2Second Affiliated Hospital of Harbin Medical Univ; The First Affiliated Hospital, Zhejiang Univ; 3Peking Univ People's Hospital.

Background: Among 4333 incident PD patients, 163 (3.8%) patients switched with a functioning arteriovenous shunt, 470 (11.1%) switched with a central venous catheter (CVC) and 442 (10.2%) patients died within 60 days of hemodialysis with a CVC. Patients who switched with CVC were older (55.3±14.4 years), had higher prevalence of cardiovascular disease (41.3%) at baseline and had more episodes of acute cardiovascular events and peritonitis after initiating switching. After adjusting acute cardiovascular events, peritonitis and other baseline covariates in the Cox model, patients who switched with CVC had increased risk of mortality (HR:1.41, 95% CI:1.07-1.86, p<0.05). Patients who switched with CVC also had higher non-dialysis out-patient and in-patient medical cost.

Conclusion: Switching to hemodialysis without a functioning arteriovenous shunt increased risk of mortality in PD patients. A planned arteriovenous shunt creation for patients not doing well in PD would avoid the increased mortality risk after initiating hemodialysis with a central venous catheter.

Funding: Government Support - Non-U.S.

SA-PO905

Comparison of Three Comorbidity Indices as Predictors of Survival in Chinese Peritoneal Dialysis Patients
Terry Kw Ma, Cheuk-Chun Szeto. Div of Nephrology, Dept of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese Univ of Hong Kong, Shatin, New Territories, Hong Kong, China.

Background: In patients undergoing peritoneal dialysis (PD), various indices have been used to quantify the burden of comorbid conditions. The aim of this study is to compare the performance of three commonly used comorbidity indices in incident Chinese PD patients.

Methods: The cohort included 461 incident PD patients (245 males). Clinical information and presence of comorbid conditions were obtained by review of medical records. Comorbidity scores using the original Charlson Comorbidity Index, Brenda’s modified Charlson Comorbidity Index, and Liu’s Comorbidity Index were calculated. Patients were followed up for 45.5±33.0 months for survival analysis.

Results: The mean age of our patients was 57.3±13.5 years and 36.4% had diabetes. The median (inter-quartile range) of the Charlson, Brenda’s, and Liu’s scores were 6 (4-7), 1 (0-2), and 4 (2-5), respectively. There was a strong internal correlation between all three scores (r=0.30 for all comparisons). By univariate analysis, all three comorbidity scores significantly correlated with patient survival, with unadjusted hazard ratios (HR) 1.34, 1.31 and 1.21, respectively (p<0.001 for all). Multivariate analysis showed that only the original Charlson’s score was independent predictor of patient survival (adjusted HR 1.34, 95% confidence interval 1, 26-1.43, p<0.001).

Conclusion: When used alone, all three comorbidity scores have satisfactory performance in predicting patient survival of Chinese incident PD patients. However, the original Charlson’s score appears to be the best predictor of patient survival amongst the three.

SA-PO906

Visit-to-Visit Variability in Systolic Blood Pressure Is Associated with Mortality in Incident Peritoneal Dialysis Patients
Han Ro,1 Ae Jin Kim,1 Hyung Soo Kim,1 Chungsik Lee,2 Sun Moon Kim,3 Ji Yong Jung,1 Jae Hye Chang,1 Hyun Hee Lee,3 Wookyoung Chung.1 Div of Nephrology, Dept of Internal Medicine, Gachon Univ Gil Medical Center, Gachon Univ of Medicine and Science, Incheon, Republic of Korea; 3Div of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea; 4Div of Nephrology, Dept of Internal Medicine, Changbuk National Univ Hospital, Cheongju, Republic of Korea.

Background: Visit-to-visit blood pressure variability has been well known to be associated with mortality in general population. However, the relationships between the variability in blood pressure and mortality have not been studied in peritoneal dialysis (PD) patients.

Methods: In 98 patients who started PD in Gachon University Gil Medical Center between May 2007 and December 2011, 84 patients who continued PD until 36 weeks were retrospectively analyzed. The coefficient of variation (CV) of systolic blood pressure (SBP) was calculated from office blood pressures between 12 week and 36 week after PD. The patients were divided in to low and high BP variability groups consistent with a adjusted hazard ratio. The median value of CV of SBP was 8.3%.

Results: Higher BP variability predicted all cause mortality (log-rank test, P=0.008). Diabetes mellitus, congestive heart failure, history of previous cardiovascular event, serum sodium at 12 week, serum albumin at 12 week, and use of β-blockers were the main correlates of CV of SBP. Higher BP variability was an independent risk factor of death after adjusting for confounding factors (hazard ratio 12.363, 95% confidence interval 1.017-150.293).

Conclusion: Peritoneal dialysis patients with high visit-to-visit variability in systolic blood pressure increased all cause mortality.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
SA-P0907

Ankle-Brachial Index Is Correlated with Mortality, Morbidity and Peritoneal Transport in Peritoneal Dialysis Patients
Ana Rita Mateus Martins, Ricardo Vizinho, Patricia Quadros Branco, Maria Augusta Cabrita Silva Gaspar. Nephrology, Santa Cruz Hospital, Carnaxide, Portugal.

Background: Peripheral artery disease (PAD) is highly prevalent among patients with end stage renal disease. PAD is associated with high cardiovascular risk and is often unrecognized in peritoneal dialysis pts. Ankle-Brachial Index (ABI), a non-invasive method to diagnose PAD, show a U-shaped association with mortality. The ABI is highly correlated with subclinical PAD, but little is known about its association with morbidity and peritoneal transport in peritoneal dialysis pts.

Methods: We studied 72 pts (65.8% male, 27.4% diabetic, mean age 55±13.8 years) during 8±6±2 months. Measurements of ABI were performed in supine position. Blood pressure was measured in the both arms (brachial artery) and ankles (posterior tibial arteries). High ankle SBP/Highest brachial SBP was used to calculate ABI. An ABI value greater than 0.9 was defined as normal. Subclinical PAD was defined as an ABI less than 0.9 in either extremity. FPG (B=6.983, P=0.008), Systolic blood pressure (B=3.921, P=0.048), LDL-C (B=4.549, P=0.033) were independent predictors for the development of subclinical PAD.

Results: A normal ABI were found in 84.9%. Vascular calcification were found in 14.8% (27.4%). During the follow up period, 7 pts died. In a multivariate analysis abnormal ABI (p=0.04) and high peritoneal transport (p=0.03) were independent predictors for amputation events, adjusted to diabetes and age. A survival cox regression showed that C reactive protein (p=0.06), albumin (p=0.003) and dialysis additional energy and BMI along with FPG, were independent predictors for the development of subclinical PAD.

Conclusions: ABI is correlated with peritoneal transport level, C reactive protein, diabetes, albumin and BMI in PD patients.

SA-P0908

Metabolic Syndrome Investigation and the Risk Factors Analysis in Peritoneal Dialysis Patients: A Clinical Cohort Study in a Mono-Center
Yiwen Li. Kidney Disease Dept, Zhejiang Province Hospital.

Background: To investigate metabolic syndrome status in peritoneal dialysis patients. To observe the effects of glucose-based peritoneal dialysate on the prevalence of metabolic syndrome in peritoneal dialysis patients. To identify the risk factors in peritoneal dialysis patients with metabolic syndrome.

Methods: A retrospective self-controlled study was performed with 77 peritoneal dialysis patients who had been long-term peritoneal dialysis treated in Division of Nephrology, Affiliated Hospital, Zhejiang University School of Medicine during January 1, 2009 to February 23, 2012. According to time after peritoneal dialysis (0 months, 6 months, 12 months, 18 months and 24 months) they were divided into 5 groups.

Results: 1. The prevalence of obesity was 14.86% in ESRD patients at the initiation of PD. There were no significant differences in the prevalence of obesity in PD patients with PD duration. 2. The FPG level of PD patients rose significantly with their prolonged dialysis duration, especially at 1 year after PD treatment (p<0.05), but there were no significantly high incidence rate of hyperglycemia.3. The prevalence rate of high TG was 98.68% in ESRD patients and diabetes (p<0.05) were independent predictors for dyslipidemia.4. The level of HDL-C increased significantly with PD duration (P<0.05), but the prevalence rate of high HDL-C level decreased (P=0.032). 5. The level of LDL-C increased significantly with PD duration (P=0.001) 6. The baseline prevalence rate of MS in ESRD patients was 59.21%. It increased up to 73.68% at 2 years after the initiation of PD therapy, though they did not reach statistical significance. 7. FPG (B=4.549, P<0.01), BMI (B=0.838, P=0.002), FPG (B=0.983, P<0.008), Systolic blood pressure (B=3.921, P=0.048), LDL-C (B=4.549, P=0.033), HDL-C (B=5.968, P=0.015), albumin (B=4.42, P=0.035) and diabetes additional energy (B=4.24, P=0.013) were independent predictors for the development of MS.

Conclusions: The prevalence of obesity, dysglycemia, dyslipidemia and MS were high in PD patients. ESRD and PD patients were high risk groups of MS. Long PD duration did not affect the incidence of MS. Dialysis additional energy and BMI along with FPG, Systolic blood pressure, LDL-C, HDL-C and albumin were the risk factors of MS.

SA-P0909

Urgent Start Peritoneal Dialysis Increases Peritoneal Dialysis Utilization within Compromising Outcomes

Background: Peritoneal dialysis (PD) utilization remains low. A contributing factor is that until recently urgent dialysis required initiation using an intravascular catheter (IVC) on hemodialysis (HD) accounting for 60% of HD initiations. IVC usage is associated with increased morbidity and mortality, thus decreasing IVC use may lead to improved outcomes. Urgent start PD (UPD) allows for urgent initiation on PD by using the PD catheter prior to the standard 2 week healing time. We studied short term effects of UPD at a large academic center.

Methods: Clinical and outcomes data were collected on concurrent incident UPD and traditional patients using chart review. Incident PD patient was defined strictly as a patient having record 1 day of PD training. Effect of UPD on PD prevalence (PD total dialysis census) was evaluated using Poisson regression. Outcomes were analyzed comparing UPD versus traditional cohorts. Pearson correlation was used to analyze IVC prevalence (total patients with IVC/total HD census) with relation to PD prevalence.

Results: UPD (N=11) and traditional (N=27) cohorts were similar in clinical characteristics. PD prevalence 6 months prior to UPD was stable at 15% (SD 0.002).

After inception PD prevalence increased over a 6 month period to 15.7% of the total UAB dialysis population (p=0.0006).

Outcomes including need for a second PD related operation, major leaks, peritonitis, admissions and patient retention were similar (p values 0.55, 0.52, 0.20, 0.65, and 0.61 respectively). For every 1% increase in PD prevalence, there was a 0.6% decrease in IVC prevalence, though not statistically significant (p=0.25).

Conclusions: UPD increases PD utilization.Short-term clinical outcomes of urgent versus non-urgent start are similar. Increased PD prevalence may decrease IVC catheter prevalence although longer follow up will be needed to evaluate for significance.

Funding: Other NIH Support - S1UL1R025777 -Center for Clinical and Translational Science

SA-P0910

Urgent Start PD: A Viable Mode of Dialysis Delivery to Increase PD Patients in the United States
Heather L. Henderson, Quresh T. Khairullah, Heather M. Statam, Robert Provenzano. Nephrology, St. John Hospital and Medical Center, Detroit, MI.

Background: There are over 500,000 people in the US with ESRD, of which only 7% use PD. There are many reasons for this low PD percentage, but the fact 60% of patients progressing to ESRD lack dialysis education or planning is a major factor. We developed an "Urgent-Start" PD program to address these issues.

Methods: Encouraged by Gaffari and others showing urgent start PD (using the catheter earlier than 2 weeks) is a safe and viable option to initiate dialysis a protocol was devised involving a dedicated surgeon/nephrologist to place the Tenckhoff catheter, education of nurses, nephrologists, and one participating outpatient dialysis unit to deliver urgent start PD. All new start dialysis patients without prior dialysis education or plan were offered UPD as their initial dialysis modality to avoid placement of a tunneled central venous catheter (CVC). After consent was obtained, a Tenckhoff catheter was placed and low volume exchanges were initiated immediately inpatient or at the outpatient unit as clinically appropriate. Once they were transitioned to the outpatient unit they received intermittent PD treatment weekly until full volume exchanges were tolerated and training was complete. After learning more about dialysis options those that chose to change to HD, an AVF was placed. While awaiting AVF maturation they continued in center IPD to avoid CVC placement.

Results: 19 new dialysis patients were enrolled in the program from May 2012 through May 2013. Two patients developed catheter complications requiring replacement or repositioning of their catheter and two patients developed a minor leak which resolved with holding PD temporarily. At six months of follow up, 6 patients (32%) transitioned or plan to transition to hemodialysis once their AVF has matured. No episodes of peritonitis and one exit site infection were observed.

Conclusions: Our urgent start PD program has resulted in increased PD growth (urgent and non-urgent starts) by 46% over last year with acceptably low incident complication rates. We believe our program should be considered to increase the use of PD by incident patients as well a method of CVC avoidance.

Funding: Private Foundation Support

SA-P0911

Urgent Start Peritoneal Dialysis: A Centre’s Experience
Sunita K. Naik, Rajinder S. Singh, M. Stamat, Robert Provenzano. Nephrology, St. Paul’s Hospital, Vancouver, Canada; Dept of Nephrology, Vancouver General Hospital, Vancouver, Canada.

Background: Traditionally, Hemodialysis (HD) is the usual adopted initial modality for patients who need urgent unplanned dialysis. Peritoneal dialysis allows better quality of life than centre hemodialysis and gives the option to dialyse at home. It offers an early survival advantage over HD (1). PD is cost effective (2). Recently it was shown by Gaffari that starting PD in unplanned patients needing urgent start is safe and feasible (3).

Methods: Retrospective study that looked at the urgent starts who were offered PD in the year Jan 2012- Feb 2013. These patients may or may not be followed up in the CKD clinics. PD catheter was inserted either at bedside by a Nephrologist or in the operating room by a Surgeon. Intermittent low volume PD (IPD) was commenced within three weeks of insertion. The study aimed to look at mortality retention at 90 days since commencing on IPD and the complications encountered during their treatment.

Funding: Other NIH Support - S1UL1R025777 -Center for Clinical and Translational Science

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: A total of 22 patients received PD as initial mode of dialysis in the period between Jan 2012-Feb 2103. IPD was commenced within three weeks of PD catheter insertion. 20 of these catheters were inserted bedside and 2 were surgical catheters. 11 patients remained on CCPD (Continuous Cycler Peritoneal Dialysis), 5 patients stayed on CAPD (Continuous Ambulatory Peritoneal Dialysis). So a total of 16 out of 22 (72%) patients remained PD modality beyond three months of commencing therapy. 2 patients died on PD and 1 patient moved territory. 3 patients were transitioned to HD. Of the patients, 2 developed Exit site leaks and 2 patients had peritonitis. 1 patient needed brief HD for a hernia repair in between IPD and training for CAPD/CCPD. 2 patients had bloody effluent which subsequently cleared up.

Conclusions: PD can certainly be the initial modality for patients needing urgent start in a centre that has support in terms of bedside catheter insertion, space for allowing IPD within the hospital and rooms and staff for training at the earliest.

SA-PO912

Impact of a Dedicated Laparoscopic Peritoneal Dialysis Access Program on Clinical Outcomes

Tarek M. Alzahrani,1 Mina Kashani,2 Daniela Ghiculete,1 Benjamin Shiff,1 Philip McFarlane,2 Jeffrey Perl,2 Jason Y. Lee.1 1Urology, St. Michael’s Hospital, Univ of Toronto; 2Nephrology, St. Michael’s Hospital, Univ of Toronto; 1Faculty of Medicine, Univ of Toronto.

Background: The success of peritoneal dialysis (PD) rests on the establishment of a functional access at time of PD initiation. Optimal methods of PD catheter insertion, which include laparoscopic (LAP), open surgical (OS), and fluoroscopic-guided (FG) techniques, continue to be debated. After the addition of a dedicated laparoscopic surgical access program, we compared the outcomes of PD catheters inserted at our institution using LAP, OS, and FG techniques.

Methods: After REB approval, a retrospective chart review was conducted on all PD catheters inserted at St. Michael’s Hospital between January 2007 and March 2013. Patient demographic data, operative details, and clinical outcomes data were collected from the chart for all patients who had PD catheters inserted during this time period. The patients were divided into three groups: LAP (n=40), OS (n=36), and FG (n=154), based on the method of catheter insertion. The LAP group had the lowest rate of post-insertion (≤2 months post-insertion) mechanical complications (2.5% vs 39% OS vs 20% FG, p=0.001), a higher rate of successful PD initiation (94% vs 84% OS vs 79% FG, p<0.01), a higher rate of catheter technical survival (87% vs 39% OS vs 38% IR, p<0.01), and a lower rate of late (>2 months post-insertion) mechanical complications (5% vs 33% OS vs 18% FG, p=0.01). The LAP group also had a lower rate of catheters requiring surgical/fluoroscopic revision (8% vs 40% OS vs 18% FG, p<0.01).

Conclusions: Across all insertion methods, most PD catheter insertions result in successful PD use. N-I was associated with higher PD use. This may relate to the timing of insertion rather than the technical success of the technique.

Funding: Government Support - Non-U.S.

SA-PO913

Peritoneal Dialysis Use after Peritoneal Dialysis Catheter Implantation: A Population-Based Study

Jeffrey Perl,1 Brendan McCormick,2 Gokulan Kandasamy,3 Matthew J. Oliver,1 1Nephrology, Univ of Toronto, Tor, Canada; 2Nephrology, Univ of Western Ontario, London, Canada; 3Nephrology, Univ of Ottawa, Ottawa, Canada; 1Chronic Disease Program, ICES, Tor, Canada; 2Ont. Renal Network, CCO, Tor, Canada.

Background: Little is known regarding outcomes of patients after peritoneal dialysis (PD) catheter implantation and predictors of the successful initiation of PD. We examined receipt of PD after catheter implantation exploring outcomes of PD non-use stratified by the method of catheter insertion.

Methods: Administrative data from Ontario identified 3886 predialysis adults with a first PD catheter implanted between 2002 and 2010. Patients were stratified by the method of PD catheter insertion: surgical (Su-O, n=1884), surgical-laparoscopic (Su-L, n=1154), nephrology-inserted (N-I, n=498), radiology-inserted (R-I, n=350). Patients were followed for at least 1 year to the successful receipt of PD (4 consecutive weeks of PD). The percent PD use among inserted catheters was: 85% of Su-O, 79% of Su-L, 87% of N-I and 79% of R-I. Diabetes, age, prior hemodialysis (HD) were associated with a lower risk of PD use. Relative to the Su-O group, the adjusted hazard ratio (AHR) of PD utilization was greater for N-I PD catheters AHR 1.4 (95% CI 1.2-1.5), similar for R-I inserted catheters AHR 1.0 (95% CI 0.9-1.2) but lower for the Su-L group, AHR 0.8 (95% CI 0.7-0.8). Across groups, the majority of PD non-use resulted in the receipt of HD. More PD non-use in the Su-L, Su-O and in the R-I groups was driven by patients who remained predialysis and died prior to dialysis initiation.

Six Years Experience with Blind Percutaneous Insertion of Peritoneal Dialysis Catheters at a Brazilian Interventional Nephrology Center

Rossana Francini,1 Marcelo M. Nascimento,1 Natasha Silva Constancio,1 Joao otavio Ribas Zahdi,1 Luciana Schmitt Cardon De Oliveira,1 Leonardo Claudino Ribeiro,1 Itamar P. Danaculov,1 Tobias August Siemens,1 Margarete Mara Da Silva,1 Marcia Tokunaga De alcantara,1 Miguel C. Riella,1,2 Domingos Candioti Chula,1,2 Interventional Nephrology Center, Pro-Renal Brazil Foundation, Curitiba, Parana, Brazil; 1Internal Medicine, Federal Univ of Curitiba, Curitiba, Parana, Brazil; 2Catholic Univ of Paraná, Curitiba, Parana, Brazil.

Background: Percutaneous peritoneal catheter insertion can be performed by trained nephrologists although the ideal method for inserting peritoneal dialysis catheters (PDC) remains controversial. This study was performed to evaluate the efficiency, the complication profile and the outcome of percutaneously placed PDC.

Methods: Our study population comprised 455 patients (55±17 years; 51%males) in whom 532 PDC were inserted blindly with a Tenckhoff trocar between January 2006 and December 2011 at our Interventional Nephrology Center (Pro-Renal Brazil Foundation). Our study population comprised 455 patients (55±17 years; 51%males) in whom 532 PDC were inserted blindly with a Tenckhoff trocar between January 2006 and December 2011 at our Interventional Nephrology Center (Pro-Renal Brazil Foundation).

Results: Early complications related to insertion included: four (0.7%) placement failures, three cases (0.5%) of bowel perforation, eight (1.0%) tip catheter migration (twenty-six out of them (47%) were successfully repositioned). Most common late complication and frequent cause for catheter removal was intractable and recurrent peritonitis which has been verified in eighty one patients (15%). In addition, exit site infection was present in twenty two patients (4%). Technical survival at 1 and 2 years was 80% and 60%, respectively, After 2-months follow-up, the survival rate by Kaplan–Meier analysis was significantly different according

Conclusions: Percutaneous peritoneal catheter insertion can be performed by trained nephrologists although the ideal method for inserting peritoneal dialysis catheters (PDC) remains controversial. This study was performed to evaluate the efficiency, the complication profile and the outcome of percutaneously placed PDC. 

Funding: Government Support - Non-U.S.
to the presence of peritonitis (p=0.1385, p>0.001). Finally, in the multivariate analysis only the presence of peritonitis was a significant risk factor for decreased catheter survival (HR=1.385, CI 1.057-1.817, p<0.05).

Conclusions: PDC inserted percutaneously, by trained nephrologists, was associated with a very low complication rate and high primary success rate. This approach had reduced waiting time for PDC insertion and increased PD penetration in our dialysis population.

SA-PO915
Evaluating Outcomes of Patients with Bedside Peritoneal Dialysis Catheters Placed by Nephrologists Compared to Surgeons
Rham Prasad Tikshety,1 Cathy Nadiger,2 Jennifer St.onge,2 1Nephrology, Regina Qu’Apelle Health Region, Regina, Canada; 2Research and Health Information Service, Regina Qu’Apelle Health Region, Regina, Canada.

Background: Limitations in allocated OR time and staff resources in the RQHR have caused long wait times for patients to receive a catheter placement. Since 2007, nephrologists have also begun to perform PD catheter placements for non-complex patients. The purpose of this project was to evaluate whether nephrologists can also successfully insert PD catheters in non complex patients and therefore improve access.

Methods: We reviewed data from 68 chart of patients who received a PD catheter placement from 2007-2012 (Surgeon n=39; Nephrologist n=38). Our primary analyses examined the wait-time from referral to physician consult and the wait-time from physician consult to procedure between patients treated by a surgeon compared to a nephrologist. We also examined the percentage of patients with immediate (within one-month) and delayed complications following the procedure.

Results: The complication rate for nephrologists was 18% for immediate and 16% for delayed. Patients had to wait significantly less time to see a nephrologist (median 1.36 weeks) compared to a surgeon (5.71 weeks, p<0.05). Similarly, patients only waited a median 1.14 weeks from the time of consult to have the procedure by a nephrologist but 6.29 weeks for a surgeon placement (p=0.05).

Conclusions: This research shows that nephrologists can successfully insert PD catheters in patients with few patients experiencing immediate or delayed complications. The rates of complications were similar or lower than previous studies examining insertion of PD catheters. Given the current discrepancies in access to OR time and resources, this research suggests that nephrologists could continue to place PD catheters in non-complex cases, which could reduce wait times without increasing the risk of complications for these patients. Surgeons should continue to handle complex cases. Decreasing the wait-time for PD catheters could also avoid some patients having to go on hemodialysis in the meantime, which is more costly to the region and disruptive to the patient.

SA-PO916
Long Term Results of Fluoroscopy-Guided Placement of Peritoneal Dialysis Catheter
Joo Hee Cho, Hong Joo Lee, Dongyoung Lee, Ju Young Moon, Sang Ho Lee, Chunj-Gyoo Ihm, Kyung Hwan Jeong, Taewon Lee. Dept of Nephrology, Kyung Hee Univ School of Medicine, Seoul, Korea.

Background: Percutaneous fluoroscopy-guided insertion of peritoneal dialysis catheter provides accurate placement with little waiting time. Limited data suggest that this approach provides similar outcomes compared with more invasive techniques. Therefore, we report our experience with fluoroscopy assisted placement of PD catheters.

Methods: A Single- center, retrospective review of 401 consecutive PD patients from July 2001 to July 2012. We assessed post procedure pain scores using a 10-point visual analog scale. We also assessed complications related to PD catheter insertions, causes of catheter removal and catheter survival. We also reviewed 89 PD patients undergoing fluoroscopic manipulation for mechanical failure of their PD catheter.

Results: We placed 537 PD catheters in 401 patients using fluoroscopy. There were 3 placements failures (0.56%). The average post procedure pain scores were 1.61 and 1.77 (44.13%) subjects had pain score of zero by 24 hour after procedure. Early complications defined as those occurring within 14 days of catheter insertion. Early complications related to PD catheter insertion occurred in 29 patients (7.23%) included 8 cases of leakage (27.58%) and 7 cases of peritonitis (24.13%). The most common cause of catheter removal was recurrent peritonitis (27.79%). 89 patients underwent fluoroscopic manipulation of PD catheters because of mechanical failure of PD catheters. The success rate of fluoroscopic manipulation was 86%. The 1- year catheter survival was 84%.

Conclusions: Percutaneous fluoroscopy-assisted placement and manipulation of PD catheters are safe and effective. The survival rate of PD catheters placed using fluoroscopy was comparable to that of more invasive method. Radiological insertion of PD catheters to be available to a large proportion of patients who require PD.

SA-PO917
Outcomes of Fluoroscopic and Ultrasound Guided Placement versus Laparoscopic Placement of Peritoneal Dialysis Catheters
Dalia Dawood,1 Ahmed Elsayed,1 Ahmed Kamel Abdel Aal,2 1UB; 2UB.

Background: Peritoneal Dialysis (PD) is a renal replacement modality, with overall survival benefits that is higher or at least similar to hemodialysis. The timely and successful placement of PD catheters is crucial for the success of PD, especially in the urgent-start setting. Our aim is to compare the outcomes of PD catheter placement using fluoroscopy (FL) and ultrasound guidance (UG) with those placed using laparoscopic (LAP) technique.

Methods: We retrospectively compared the outcome of two groups of patients who initiated PD from January 2005 to December 2012: (1) Those who received (PD) catheter insertion using FL and UG under local anaesthesia by Interventional Radiologists/ Nephrologists, and, (2) those who received PD catheter insertion using LAP under general anaesthesia by surgeons. Patients with history of prior surgery were excluded from both groups. The primary endpoint was the occurrence of dialysis catheter complications at 1 year. Catheter complications including; technical, mechanical, and infectious complications were recorded. Differences between groups were analyzed using the Chi-square test.

Results: The overall complications at 1 year was significantly higher for the second group (p = 0.0019). The LAP approach is more likely to be complicated by catheter malfunction and peritonitis. The other complications occurred at a higher rate in the second group but the difference e was not statistically significant (Table).

SA-PO918
Vasopressin-2-Receptor Antagonist, Tolvaptan Preserved Residual Renal Function on Peritoneal Dialysis Patients with Diabetes Mellitus
Takeyuki Hiramatsu. Dept of Nephrology, Konan Kosei Hospital, Konan-City, Aichi, Japan.

Background: The contribution of residual renal function (RRF) as an independent predictor of survival or better cardiovascular health in dialysis patients has been confirmed by many observational studies. Vasopressin-2-receptor antagonist, tolvaptan was reported to improve water excretion without changes in renal function. So we evaluated the short-term effect of tolvaptan on peritoneal dialysis (PD) patients with DM.

Methods: We studied 20 incident PD patients with DM. Patients were divided into group A and group B. Patients in group B received 15 mg/day of tolvaptan 2 weeks after PD initiation for 12 months, but not in group A. During study period, diuretics and PD prescription were not changed in both groups. Urine volume (UV), weekly Kt/V and weekly creatinine clearance (Ccr) were evaluated at baseline, days 3, 6, and 12 months after PD initiation.

Results: RRF in group B were significantly increased from baseline to 3 days after PD initiation, (UV, P<0.005, renal Kt/V, P<0.001, for at baseline and 3 days after PD initiation, respectively). After 6 and 12 months, RRF in group B were significantly greater than that in group A (*P<0.005, **P<0.001, ***P<0.005).

Conclusions: Short term treatment with tolvaptan preserved residual renal function, suggesting that tolvaptan might prevent cardiovascular events and improve quality of life in PD patients with diabetic end stage renal disease.

SA-PO919
Predictors of Residual Renal Function Decline in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis
Chi-bon Leung, Bonnie Kwan, Cheuk-Chun Szeto. Carol and Richard Yu Peritoneal Dialysis Research Centre, Dept of Medicine & Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong.

Background: Residual renal function (RRF) is an important prognostic indicator in continuous ambulatory peritoneal dialysis (CAPD) patients. We determine the predictors of RRF loss in a cohort of new CAPD patients.

Methods: We reviewed the record of 645 new CAPD patients. RRF loss is represented by the slope of decline of residual glomerular filtration rate (GFR) as well as the time to anuria.

Results: The average rate of residual GFR decline was -0.083 ± 0.094 ml/min/month. The rate of residual GFR decline was correlated with proteinuria (r=-0.258, P<0.001) and baseline residual GFR (r=-0.355, p<0.001). Multivariate analysis showed that proteinuria, baseline residual GFR, and the use of diuretics had independent correlations with residual GFR decline. Cox proportional hazard model showed that proteinuria, baseline residual GFR, body weight, and the number of peritonitis episode were independent predictors of progression to anuria. Each 1 g/day of proteinuria is associated with 22.3% excess in the risk of progressing to anuria, each 1 ml/min higher baseline GFR is associated with 11.3% reduction in risk, while each peritonitis episode confers 7.9% excess in risk.

Conclusions: We conclude that proteinuria, baseline residual GFR, body weight, and the number of peritonitis episode are independent predictors for the development of anuria. The role of anti-proteinuric therapy and measures to prevent peritonitis episodes in the preservation of RRF should be tested in future studies.

Funding: Private Foundation Support, Government Support - Non-U.S.
V2 Receptor Antagonist Tolvaptan Ameliorates Left Ventricular Mass Index (LVMl) and Urinary Output without Reduction in Residual Renal Function in Patients on Peritoneal Dialysis (PD) Kenji Koizumi, Takefumi Mori, Ikuo Oba, Sadayoshi It0. Nephrology, Endocrinology and Vascular Medicine, Tohoku Univ Graduate School of Medicine.

Background: Left ventricular (LV) hypertrophy is commonly observed in PD patients with poor control in volume overload. Loop diuretics and/or enhanced ultrafiltration are the common treatments for volume overload in PD patients, which may result in a decrease in residual renal function (RRF) and deterioration in peritoneal function, respectively. The V2 receptor antagonist, tolvaptan, has been available for the treatment of heart failure to control volume overload in Japan. This study was conducted to examine whether tolvaptan could control volume status without reduction of RRF and improve left ventricular mass index (LVMl) in PD patients.

Methods: We studied 7 patients on peritoneal dialysis whose urinary volume (UV) increased more than 400mL/day after treatment with tolvaptan at Tohoku University hospital (Sendai, Japan). Body weight (BW), UV and weekly renal Kt/V (rKt/V) were compared between the first administration of Tolvaptan for volume control. Left ventricular mass index (LVMl), left ventricular ejection fraction (LVEF), E/E’ and brain natriuretic peptide (BNP) were examined before and at least 18 weeks after the treatment. The difference of p<0.05 was considered as statistical significance.

Results: An increase in UV was observed in all patients. BW and BNP were not significantly reduced. An increase in rKt/V was observed and maintained over 4 to 6 months. On the other hand, significant reductions in LVMl and E/E’ were observed (p<0.05) without changes in LVEF.

Conclusions: Tolvaptan increased urinary output and improved LVMl in patients on PD without deterioration in cardiac functions or residual renal function. This could be an effective novel strategy for volume control in PD patients.

Funding: Government Support - Non-U.S.

SA-PO921

Overhydration among Patient’s Undergoing Peritoneal Dialysis in Relation to Age Dorota Sikorska, Justin Nealis, Krzysztof Hoppe, Krzysztof Schwemer, Maria Wanic-kossowska, Krzysztof Pawlaczek, Andrzej P. Oko. Poznan Univ of Medical Sciences, Poland.

Background: Overhydration is a prevalent problem in peritoneal dialysis (PD) patients and is associated with numerous complications. Multi-frequency bioimpedance analysis (BIA) offers the potential to accurately determine a patient’s dry body weight (DBW). The main aim of this study was to assess the impact of age on fluid overload, and its relationship with markers of cardiovascular risk in PD patients.

Methods: The study was performed on 70 PD patients. The cohort was divided into two subgroups according to gender (A, 45 patients, <65 YO, mean age 47.98±12.76; group B, 25 patients, <65 YO, mean age 74.16±6.02). In both subgroups the degree of overhydration was assessed with BIA and clinical criteria. NT-proBNP and tropon T (TroT) concentration in the serum and the patient’s nutritional status (SGA) was measured. Echocardiography and chest X-ray examinations were performed.

Results: There is a correlation between age and overhydration in BIA (r=0.30;p=0.01). The older group of patients had higher BIA overhydration (1.57±2.15 vs 3.08±2.12 kg; p=0.001) and higher NYHA (6.4±2.03 vs 9.2±1.29; p=0.01). The SBP and DBP (136.6±18.79 vs 140.36±22.92 mmHg; 82.66±12.06 vs 76.00±14.71 mmHg) was comparable in both subgroups. The data revealed a tendency for higher NT-proBNP (31187.6±6672.7 vs 11377.2±13415.5 pmol; p=0.03) and TroT (0.04±0.03 vs 0.17±0.17 ng/ml; p=0.01) concentration in the older group. There was a correlation between BIA overhydration and NT-proBNP (r=0.40;p=0.02), TroT (r=0.48;p=0.01), SGA (r=0.28;p=0.02) and ejection fraction (EF, r=-0.31;p=0.04). The older group of patients were more overhydrated and presented with more aortic atherosclerosis changes (10v.16;p=0.02) and had a reduced EF (r=-0.49;p=0.05).

Conclusions: Older age may be a risk factor determining a higher tendency for overhydration. Overhydration seems to be a potential predictor for the development of cardiovascular complications. BIA appears to be a super technique for monitoring the hydration status, DBW and cardiovascular risk among PD patients as compared with clinical assessment alone.

SA-PO922

Is N-Terminal Pro-Brain Natriuretic Peptide a Useful Marker of Cardiovascular Disease or Volume Status in Peritoneal Dialysis Patients? Ruth J. Pepper, Debbie Falconer, Andrew Davenport. Centre for Nephrology, Royal Free Hospital, London, United Kingdom.

Background: N-terminal pro-brain natriuretic peptide (NTproBNP) is used to diagnose heart failure in general medicine, and has been associated with both left ventricular hypertrophy (LVH) and extracellular water (ECW) expansion in haemodialysis (HD) patients. However whether NTproBNP has a role in peritoneal dialysis (PD), who typically have residual renal function remains to be determined.

Methods: Serum NTproBNP was measured in 287 PD patients and correlated with factors such as ejection fraction, echocardiogram findings and Kt/V. A linear regression model was used to delineate the relationship between the significant variables and log NTproBNP.

Results: The mean serum BNP was 776 pmol/l (SD 1883), and log NTproBNP 2.34 pmol/l (SD 0.64). Using the linear regression model, log NTproBNP was demonstrated to significantly correlate with log Kt/V (co-efficient of B = 0.184 (p=0.002), low dialysis adequacy as measured by total Kt/V [B=0.168] (p=0.000). To assess for fluid overload the ratio of extracellular water to total body water (ECW/TTB) was calculated and was also significant [B=7.711] (p=0.01). With respect to gender, log NT-proBNP was significantly associated with males [B=0.202] (p=0.001). Although there was a significant correlation with ejection fraction [B=0.017] (p=0.000). However no relationship was observed with left ventricular mass index, urine output or residual renal function.

Conclusions: Serum NTproBNP was associated with reduced left ventricular ejection fraction, over hydration with ECW expansion, systemic inflammation as measured by CRP, reduced dialysis adequacy (total weekly Kt/V), and male sex. Therefore, serial NTproBNP measurements in stable PD patients may aid the clinical assessment of volume status, in the context of adequately dialysed patients with stable cardiac function and absence of systemic inflammation.

SA-PO923

Comparison of Cardiac Function via Echocardiography between Icodextrin and Glucose-Based Peritoneal Dialysis Patients: A Prospective One-Year Study J. B. Chen. Nephrology, Kaohsiung Chang Gang Memorial Hospital, Kaohsiung, Taiwan.

Background: Icodextrin dialysis solution had been demonstrated effective ultrafiltration in a long dwell time in peritoneal dialysis (PD) patients. However, it is uncertain whether cardiac function preservation will be resulted from icodextrin ultrafiltration capacity. The aim of study was to assess the cardiac function in incident PD patients with icodextrin-based PD solution.

Methods: The study design was a prospective, open-label, parallel control groups. The incident PD patients were enrolled with 1:1 ratio by assigned dextrose and icodextrin-based PD solutions. Thirty patients were in icodextrin group, twenty-nine patients in dextrose group. The enrolled patients received echocardiography examinations at baseline and one-year apart in each groups. The variables of echocardiography including systolic and diastolic parameters were compared between two groups.

Results: At baseline cardiac examination, patients in icodextrin group showed inferiority in the variables of cardiac systolic function than those in dextrose group, i.e. LVESV (left ventricular end-systolic volume)(mm), LVEF (LV end-systolic diameter)(mm). The comparison of variables at baseline and one-year apart in each groups demonstrated patients in dextrose group had significantly decreased LVDD (47.7 vs 45.5 mm) and LVEDV (109.5 vs 98.1 mm3) values at one-year period. In contrast, only one variable was found significantly increased in icodextrin group at one-year period, i.e. deceleration time (172.4 vs 201.3 ms).

Conclusions: Icodextrin-based PD solution could improve cardiac function both in systolic phase and in diastolic phase when those compared to dextrose-based PD solution in incident PD patients.

SA-PO924

Very-Low-Density Lipoprotein Affects Atherosclerosis of Peripheral Artery in Peritoneal Dialysis Patients Elichiro Kanda, Masumi Ai, Mitsuyo Okazaki, Yoshitaka Maeda, Sei Sasaki, Masayuki Yoshida. Nephrology, Tokyo Kyosai Hospital, Meguroku, Tokyo, Japan; Nephrology, J Toride Medical Center, Toride, Ibaraki, Japan; Tokyo Medical and Dental Univ, Bunkyoaku, Tokyo, Japan.

Background: Peripheral artery disease (PAD) represents atherosclerotic disease and is a risk factor for death in peritoneal dialysis (PD) patients, who tend to show an atherogenic lipid profile. In this study, we investigated the relationship between lipid profile and ankle-brachial index (ABI) as an index of atherosclerosis.

Methods: Thirty-five PD patients were enrolled in this cross-sectional study in Japan. The proportions of cholesterol level to total cholesterol level (cholesterol proportion) in 20 lipoprotein fractions and the mean size of lipoprotein particles were measured using an improved method, high-performance gel permeation chromatography.

Results: The mean (standard deviation) age was 61.6 (10.5) years; PD vintage, 38.5 (28.1) months; ABI, 1.07 (0.22). A low ABI (0.9 or lower) was observed in 7 patients (low-ABI group). The low-ABI group showed significantly higher cholesterol proportions in the chylomicron fraction and large very-low-density lipoproteins (VLDLs) (Fractions 3 and 4) than the high-ABI group (B=0.014). Adjusted multivariate linear regression analysis showed that ABI was negatively associated with serum VLDL cholesterol level (p=0.0074) and the cholesterol proportions in large VLDLs (Fractions 4 (p=0.038; 5, p=0.0039) and medium VLDL (Fraction 6, p=0.014). ABI was also negatively associated with the size of VLDL, particles (r=0.1032), which was associated with serum triglyceride level (Pearson’s correlation coefficient r=0.798, p=0.0001).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
Conclusions: This study showed that, among PD patients, the characteristics of VLDL particles were associated with atherosclerosis. Lowering serum VLDL level may be an effective therapy against atherosclerosis in PD patients.

SA-P0925


Background: Overhydration is associated with increased morbimortality in peritoneal dialysis (PD) patients. Health professionals are capable of estimating our patients’ hydration volume through clinical perception but, using other tools such as bioimpedance, it is possible to assess it more objectively. Objectives: Determine if there is a correlation between the hydration status of the PD patients treated in our unit when estimated using bioimpedance and when estimated by health professionals’ clinical perception. Evaluate whether it is possible to improve the professional’s clinical perception.

Methods: Descriptive, observational study. 37 PD patients were included. Residents, nephrologist and nurses took part in the study. The estimation of the patients’ hydration status was compared using the two methods. The data are given as mean±SD and 111 determinations performed on PD patients were analysed. The mean overhydration estimated by bioimpedance was 2.77±2.05 litres vs 2.04±1.67 litres by correlation and the Bland-Altman plot were used for the statistical analysis.

Results: 111 determinations performed on PD patients were analysed. The mean overhydration estimated by bioimpedance was 2.77±2.05 litres vs 2.04±1.67 litres by correlation and the Bland-Altman plot were used for the statistical analysis.

Conclusions: Paricalcitol was found to decrease cardiac fibrosis. PD treatment alone did not improve this finding, whereas addition of paricalcitol significantly reduced cardiac fibrosis. Due to its beneficial effects on heart, paricalcitol could be preferred in peritoneal dialysis patients.

Funding: Pharmaceutical Company Support - Abbott, Private Foundation Support

SA-P0927

Relation between Volume Status and Health-Related Quality of Life in Peritoneal Dialysis Patients Yun Jun Oh, Chungsik Lee. Internal Medicine, Cheju Halla General Hospital, Jeju, Korea.

Background: Volume status is an important predictor of outcomes in patients with end stage renal disease, and chronic fluid overload contributes to the high mortality in dialysis patients. However, it has not yet been identified whether to achieve euvolemia contributes to improve health-related quality of life (HRQOL) in peritoneal dialysis (PD). We investigated the relationship between volume status and HRQOL in PD patients.

Methods: This study is a cross-sectional, noninterventional, and observational. We enrolled 41 prevalent PD patients, and accessed volume status using Body Composition Monitor (BCM). Korean version of Kidney Disease Quality of Life short form (K-DQOL-SF), version 1.3 was used to evaluate HRQOL. We determined scores of three components summary of K-DQOL, Kidney Disease Component Summary (KDCS), Physical Component Summary (PCS), and Mental Component Summary (MCS). The hydration status (HS) was normalized to extracellular water (ECW) (Relative hydration - ECW) for the analysis, and overhydrated status was defined as OH/ECW value greater than 0.15.

Conclusions: Overhydrated status showed a significant negative association with scores of KDCS and MCS, indicating that volume status is an important factor affecting HRQOL in PD patients. Close monitoring of volume status and a correct dialysis prescription to maintain euvolemia seem to be warranted to improve HRQOL in PD patients.

SA-P0928

Sympathetic Overactivity in Chronic Peritoneal Dialysis Patients Dan Sapoznikov, Aharon Bloch, Haya Assayag, Dvora Rubinger. Nephrology and Hypertension Services, Hadassah Univ Medical Center, Jerusalem, Israel.

Background: Sympathetic overactivity is not well defined in chronic peritoneal dialysis (PD) patients.

Methods: Continuous heat-to-beat intervals (IBI) and systolic blood pressure (SBP) were monitored in 13 PD patients (pts.), 112 chronic hemodialysis (HD) pts. and in 32 control subjects (C).IBI and SBP oscillations in the low frequency range (0.04–0.15 Hz) were considered to be indicative of sympathetic activation. The prevalence of baroreflex and nonbaroreflex episodes (which in heart rate and SBP change in opposite or in the same direction) was interpreted as representative of vagal or central sympathetic activation, respectively.

Results: Mean SBP and IBI, sdIBI (a measure of overall autonomic activity), LF IBI/HF IBI (the ratio between amplitudes of IBI oscillations in LF and HF (high frequency ranges), an index of sympathetic-vagal balance) and LF (baroreflex sensitivity in LF range) were (median and interquartile range).

Conclusions: Mean IBI and sdIBI (a measure of overall autonomic activity), LF IBI and SBP oscillations in HD patients were not significantly changed compared to C. However, PD patients showed a significant increase in LF IBI/HF IBI, an index of sympathetic-vagal balance, and more baroreflex sensitivity in LF range compared to C and HD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Conclusions: These results show: 1. Decreased IBI variability and baroreflex sensitivity are suggestive of sympathetic overactivity in both HD and PD. 2. The increased heart rate, the higher LTF IBI and the increased prevalence of nonbaroreflex episodes point to a more pronounced sympathetic tone in PD. The prognostic significance of these findings remains to be defined.

Methods: Dialysis unit and pathology department records from two large academic centers were searched to identify calciaphylaxis cases diagnosed between January 2002 and December 2012. Demographic features, medical history, laboratory and medication data were compared between PD and HD calciaphylaxis patients using a Fisher exact test (categorical variables) or a Wilcoxon test (continuous variables).

Results: We identified 69 cases of calciaphylaxis; 7 were on PD (all on continuous ambulatory PD) and 62 were on HD. PD calciaphylaxis patients were younger than HD calciaphylaxis patients (median age 50 vs. 62 years, p<0.003) and were more likely to be non-Caucasian (62% vs. 36%, p=0.04). There were no significant differences between calciaphylaxis patients on PD vs. HD for dialysis vintage (median 5.1 vs. 4.8 years, difference (95% CI) 0.3 (–0.9 to 1.5), p=0.51), macroversus disease (31% vs. 34%, p=0.10), calcium based phosphate binder use (29% vs. 33%, p=0.13), and vitamin D therapy (45% vs. 49%, p=0.11). Warfarin use (71% vs. 44%, p<0.01), obesity (57% vs. 37%, p=0.01), and hyperalbuminemia (100% vs. 65%, p>0.02) were more prevalent in PD calciaphylaxis patients compared to HD calciaphylaxis patients. Dialysis adequacy and serum calcium, phosphorous, and parathyroid hormone levels were similar.

Conclusions: Higher prevalence of calciaphylaxis risk factors (such as warfarin, obesity and hyperalbuminemia) rather than dialysis modality likely explains calciaphylaxis development in HD patients. Prospective studies are needed to confirm these findings.

Funding: Private Foundation Support

SA-PO932

Metabolic Syndrome and Body Fat Content of Peritoneal Dialysis Patients Cheuk-Chun Szeto,1 Terry Kw Ma.2 1Dept of Medicine & Therapeutics, The Chinese Univ of Hong Kong, Shatin, Hong Kong; 2Dept of Medicine & Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong.

Background: In the general population, metabolic syndrome (MES) is strongly associated with cardiovascular risk. However, the definition of MES and its prognostic impact among patients undergoing peritoneal dialysis (PD) remains controversial.

Methods: We studied 329 prevalent PD patients and compared 4 sets of diagnostic criteria: the original WHO criteria, the International Diabetes Federation (IDF) criteria, the original National Cholesterol Education Program (NCEP) criteria, and the modified NCEP criteria. Nutritional status, body composition, and arterial pulse wave velocity were measured. Patients were followed for 31.7 ± 15.5 months for survival and hospitalization.

Results: Amongst the 329 patients, 175 (53.2%) fulfilled the WHO criteria, 177 (53.8%) by the IDF criteria, 199 (60.5%) by the original NCEP criteria, and 218 (66.3%) by the modified NCEP criteria. Nutritional status, body composition, and arterial pulse wave velocity were measured. Patients with MES defined by all 4 criteria had higher adipose tissue mass than the others, although the difference was most pronounced with the IDF criteria (18.2 ± 7.9 vs 10.7 ± 5.9 kg, p<0.0001), and the IDF criteria was least affected by overhydration. Furthermore, patients with MES, as defined by the IDF criteria, were hospitalized longer than those without MES (3.82 (inter-quartile range [IQR] 0.00 – 12.61) vs 1.07 [IQR 0.00 – 6.43] days per year of follow up, p = 0.01). There was no difference in overall survival, cardiovascular survival, or technique survival between patients with and without MES, irrespective to the diagnostic criteria after adjusting for diabetic status.

Conclusions: We conclude that the IDF criteria is probably the preferred choice for the definition of MES in PD patients as it best reflects the adipose tissue mass, least affected by overhydration, and best associated with the need of hospitalization during follow up.

Funding: Clinical Research Support

SA-PO933

Does Increased Peritoneal Dialysis Adequacy Correlate with Physical Activity and Energy Expenditure? Sally Salah El-kateb,1 Sivakumar Sridharan,2 Kirsten L. Rennie,3 Ken Farrington,2 Andrew Davenport.1 Royal Free Hospital; 1Lister Hospital; 3Univ Hertfordshire.

Background: Whereas there is an established relationship between dialysis adequacy, nutrition and survival for haemodialysis patients, the same relationship has not been demonstrated for peritoneal dialysis (PD) patients. We therefore looked at the relationship between total energy expenditure (TEE), resting energy expenditure (REE), active physical energy expenditure (AEE), and dialysis adequacy and body composition.

Methods: All patients included are receiving PD treatment at the Royal Free hospital. Patient demographics, body composition measured using bioimpedance and PD adequacy (Total weekly urea KT/V and weekly litres of creatinine cleared (CrCl), along with residual urine output assessed by 24-hour urine collection) were recorded. Dietary protein intake (nPNP) and albumin serum levels were used as an indicator of the nutritional status. TEE,REE and PEE were calculated such that (TEE = REE + Mean daily MET) and (REE --2.497 + (4.0011 * age) + 83.573 * weight kg−0.467 ) 6.187. A physical activity assessment questionnaire was designed to determine daily MET.

Results: Seventy five patients (M=43,F=32) were included in this study, of which 25 were diabetic. Average age was 59.99±17.32(21-88) years. There was a significant association between total AEE and MET (r=0.504 and age=-0.47, p=0.040) and long vintage (β=−0.770.32, CI 95% (−1.346.56 – −194.09), p<0.01). REE was significantly associated with skeletal muscle mass (SMM) (β=−88.51, CI 95% (72.23-104.79), p<0.0001), extracellular weight/total body weight β=−66.78, CI95% (−24.10-95.9), p<0.003, BMI=β=−35.73, CI95% (−49.11-−22.35), p<0.005 and age=β=−20.21, CI 95% (8.81 – 31.61), p<0.001). Finally, a significant association was depicted between TEE and SM(β=-129.84, CI 95% (25.56 – 234.11), p=0.016). No significance was detected between any and nPNP, CCr or residual urea KT/V.

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

Underline represents presenting author/disclosure.
Conclusions: There is no relationship between nPNA or dialysis adequacy measured by total weekly urea Kt/V or litres of creatinine cleared per week or residual urine output and either total, resting or activity energy expenditure in PD patients.

SA-P0934

Lepitin as a Key Factor in Obesity Pathophysiology: Clinical Relevant Associations in PD Patients Ana Paula Bernardo, 1, 2 Silvia Coelho, 1 Maria João Carvalho, 1 António Manuel Nunes Cabrita, 1 Ana Isabel Rodrigues. 1, 2 Nephrology, CHP, 1 UMBIC/ICIAS/UP

Background: In peritoneal dialysis, obesity is assumed to result from intraperitoneal glucose absorption, and doubts still remain about its impact on patient survival, since most studies are simply based on body mass index (BMI) to characterize obesity. In general population, adipokines are known to play an important role in obesity pathogenesis and their associated metabolic complications such as dyslipidemia and inflammation. Until now, no study of obesity and its comorbid conditions with adipokines and inflammation in PD patients has been reported. Our aim was to explore in a PD prevalent population the link between leptin and tissue mass (Rel. LTM), relative fat mass (Rel. Fat), body cell mass (BCM), BMI, leptin, adiponectin and IL6 and fat mass evaluated with body composition monitor (BCM®).

Methods: We performed multifrequency bioimpedance assessment in 66 prevalent PD patients. We assessed lean tissue index (LTI), fat tissue index (FTI), relative lean tissue mass (Rel. LTM), relative fat mass (Rel. Fat), body cell mass (BCM), BMI, leptin, adiponectin, IL-6, and fat mass evaluated with body composition monitor (BCM®).

Results: 48.5% female, 18.2% diabetics, 28.1% anurics, 20% fast transporters, mean age 50.3 years, PD vintage 18.7 months. Leptin correlated better with FTI and Rel.Fat than with BMI (r=0.67, r=0.63 and r=0.45, p=0.001,respectively). Leptin also correlated with adiponectin (r=-0.24, p=0.04), Tg (r=0.39, p<0.001) and nPCR (r=0.41, p=0.004) but no correlation was found with IL-6, albumin, peritoneal membrane small solute transport (0.24, 0.21 and 0.11 respectively). No correlation was found with IL-6, albumin, peritoneal membrane small solute transport (0.24, 0.21 and 0.11 respectively).

Conclusions: Leptin shows better correlation with FTI and Rel.Fat assessed by bioimpedance than with BMI, and has important and clinically relevant associations with dyslipidemia and nutrition parameters in PD patients.

SA-P0935

Body Composition Evaluation and Adipokines Preference in Risk PD Patients Ana Paula Bernardo, Olivia Santos, Maria João Carvalho, António Manuel Nunes Cabrita, Ana Isabel Rodrigues. Nephrology, CHP, Porto

Background: Peritoneal dialysis has improved clinical results in the last decade. However aged patients, diabetics, anurics and fast transporters, lead to less favorable outcomes, still challenge therapy. Our aim was to document relevant corporal composition changes and adipokines preference alterations amenable to intervention in specific risk PD patient groups.

Methods: We performed multifrequency bioimpedance assessment in 66 prevalent PD patients, under updated PD therapy, treated with low-GDP solutions, elective automated PD and free cisternex use. We assessed relative fluid overload (ReLOH), lean tissue index (LTI), fat tissue index (FTI), relative lean tissue mass (Rel. LTM), relative fat mass (Rel. Fat), body cell mass (BCM), leptin, and adiponectin.

Results: 18.2% diabetics, 28.1% anurics, 20% fast transporters, mean age 50.3 years, PD vintage 18.7 months. Diabetic patients had higher ReLOH (15.3±8 vs 15.9±10 mg/dL, p=0.01) but similar fat and lean tissue mass as well as adipokines profile. Anuric patients did not present significantly higher volume overload but had lower LTI (12.5±3.2 vs 12.7±5.0%, p=0.05), and lower BCM (18.3±2.2 vs 18.7±3.7 kg/m2, p=0.05), lower FTI (0.6±0.3 vs 0.8±0.4 kg/m2, p=0.05). Leptin correlated better with FTI and Rel. LTM than with BMD, and has important and clinically relevant associations with adiponectin and delivery. Whether managed by CAPD or APD, most reports describe reduced dwell volumes with increased number of exchanges, either manually or with a cycler device. Patients hospitalized in the last trimester often received extended APD shorter dwells in lieu of a long day dwell.

Conclusions: Two trials of patients on APD had been managed throughout gestation and delivery. Whether managed by CAPD or APD, most reports describe reduced dwell volumes with increased number of exchanges, either manually or with a cycler device. Patients hospitalized in the last trimester often received extended APD shorter dwells in lieu of a long day dwell.

SA-P0936

Gabanapent Therapy for Pruritus in Automated Peritoneal Dialysis Patients: A Randomized Controlled Trial Arturo R. Marin, Nephrology, Hospital Regional ESEEMT-Tlahuapan, Mexico, Estado de Mexico, Mexico

Background: Uremic pruritus is a common and unpleasant symptom in patients with chronic kidney disease (CKD), the incidence is 42-52% and impact on quality of life in peritoneal dialysis and hemodialysis patients. Available treatments are not completely effective. Evidence of gabapentin and imetitine increase variable effective in these patients.

Objective: To compare efficacy and side effects of gabapentin and loradine in uremic pruritus in patients on automated peritoneal dialysis (APD).

Methods: We did a randomized, prospective, open, comparative clinical trial in APD patients with uremic pruritus. 60 patients were randomized to receive 12 weeks of treatment with gabapentin (n=30) 300 mg and loradine (n=30) 10 mg every 24 hours, at night. To assess the severity of pruritus was used visual analogue scale (VAS), a reduction of pruritus of 50% was considered effective. To assess other features was used 5D itch scale, a reduction of 2 points on the scale was used as considered effective.

Results: The gabapentin group were 22 male and 8 female patients, with 56.7±12.4 years old and the loradine group were 21 male and 9 female patients, with 48.5±14.6 years old. All patients completed 12 weeks of treatment. Effects were reported in 20 patients in the gabapentin group vs 10 patients in the loradine group (P=0.025). With respect to the intensity of pruritus was found effective in 18 patients in the gabapentin group vs 9 in the loradine group (P=0.006), in terms of effectiveness duration was found in 15 patients in the group with gabapentin vs 7 in the loradine group (P=0.025). In the loradine group was reported good tolerance to treatment and in the gabapentin group the more important adverse effect was somnolence (8 patients) but well tolerated in 6 patients, 2 decreased the dose. No statistically significant differences were found between ages, sex, underlying cause of CKD, TH, laboratory parameters reported.

Conclusions: The use of gabapentin for treatment of urticaria pruritus, in patients on PD is better than loradine and is a good option for use in the treatment of urticaria pruritus, in APD population of patients.

Funding: Government Support - Non-U.S.

SA-P0937

Use of the Mid-Day Exchange in a Large USA Peritoneal Dialysis Cohort Bethany Greer Costello, Sue A. Tendler, Steven Guest. Baxter Healthcare.

Background: In peritoneal dialysis (PD), a mid-day exchange (MDE) is performed to increase total daily solute clearance or prevent ultrafiltration (UF) loss during the long dwell overnight automated PD (APD). The potential benefits of a MDE are offset by the additional burden of needing to exchange in the middle of the day. We wanted to evaluate how often MDEs were used in a large US PD cohort.

Methods: The data used is maintained in a custom, purpose built, data warehouse containing PD supply shipment information for 1.36 million US users using Baxter PD solutions, disposables, and cyclers devices. The parameters were patients who ordered supplies from Nov 2012-Jun 2013, and ordered CAPD supplies (48,232 individual orders by 13,489 patients) implying a MDE. Three months of data were used to smooth the data in order to number of days in the month and patient ordering patterns. A three month average of 15-36 CAPD solution bags per month were included.

Results: 971 clinics with a total APD population of 20,161 patients were analyzed. 16% were receiving CAPD solution shipments consistent with a MDE. 16% of APD patients managed to use a mid-day exchange (MDE) for a MDE. Average number of CAPD solution shipments ordered per month was 26- suggesting the patients were consistent in the use of the MDE. Discussion: This analysis has revealed that 16% of APD patients in this USA cohort received CAPD solution shipments implying use for a MDE. This estimate may be conservative as it would not capture patients using the cycler for a MDE. If the MDE is used to improve long-dwell UF, use of ciscodrin could favorably impact the therapy as it is indicated for a single daily exchange for the long (8 to 16-hour) dwell for APD or CAPD.

Conclusions: Analysis of a large USA PD cohort has suggested 16% of APD patients are prescribed a MDE and reasons for the MDE should be clarified. A significant number of these patients would be considered candidates for a prescription change to ciscodrin. Funding: Pharmaceutical Company Support - Disclosure of Financial Relationships: All authors are employees of Baxter Healthcare Corporation

SA-P0938

Peritoneal Dialysis Prescriptions during the Third Trimester of Pregnancy: A Meta-Analysis Steven Guest, 1 Rodolfo Batarse, 1 Ralph M. Steiger, 1 Baxter Healthcare Corporation, Deerfield, IL; 2Nephrology, Hypertension, Transplant Medicine, Rancho Mirage, CA; 3Desert Regional Medical Center, Palm Springs, CA.

Background: Management of the pregnant patient on PD is complicated by the uterine enlargement that may restrict dwell volumes and/or create catheter dysfunction or discomfort. A variety of publications describe successful outcomes of pregnancy in the PD literature. A meta-analysis of the 3rd trimester PD prescription was performed to describe prescription options.

Methods: A systematic review and meta-analysis was performed of the English literature to identify ESRD patients managed by PD in which sufficient information was provided to determine the PD prescription used during the 3rd trimester of pregnancy to the end of gestation. Pregnancy outcomes were also determined.

Results: Twenty-five publications describing 37 pregnancies were reviewed. Twenty-nine pregnancies were included in the analysis. These were selected as they were deemed to provide sufficient clinical and prescription information. Both APD and CAPD modalities were reported. Eight-five of 29 pregnancies were managed with dwell volumes of 2L or greater per exchange. The remaining 36% of pregnancies were managed by lower volume dwell levels with increased number of exchanges, either manually or with a cycler device. Patients hospitalized in the last trimester often received extended APD shorter dwells in lieu of a long day dwell.

Conclusions: Pregnancy PD patients have been managed thru full term gestation and delivery. Whether managed by CAPD or APD, most reports describe reduced dwell volumes with increased number of daily exchanges with dialysate dwelling throughout the 24-hour period. APD patients often had increased number of cycles prescribed with...
SA-PO939
Peritoneal Dialysis for Stage 5 Chronic Kidney Disease Patients in China: Twenty-Seven Years of Experience in a Single Centre  Huling Wang, Div of Nephrology, Jinin Hospital, Shanghai, China.

Background: We present the demographics, patient and technique survival as well as peritonitis rates of 841 stage 5 chronic kidney disease (CKD) patients, who started continuous ambulatory peritoneal dialysis (CAPD) between 1 January 1985 and 31 December 2011 at renal division of Shanghai Jinin Hospital in China.

Methods: A retrospective cohort study of individuals 15 years of age and older, divided into three cohorts according to the year they started peritoneal dialysis (PD): the first cohort (1985-1994), the second cohort (1995-2004) and the third cohort (2005-2011). Demographic and biochemical variables, clinical outcomes, patient and technique survival, peritonitis rate, and factors affecting mortality were analyzed.

Results: Mean age at the start of PD was 58.5±16.7 years. Chronic glomerulonephritis (CGN) was the most common cause of end stage renal disease (ESRD) (52.4%). ESRD incidence as a result of diabetes (p<0.05) and hypertension (p<0.05) were significantly more frequent in the second and third as compared with the first cohort. Cardiovascular disease was the main cause of death (41.9%); the common cause of transfer to haemodialysis (HD) was peritonitis (59.2%), psychosocial causes of technique failure were reported in only 3.9%. Patient and technique survival at 1, 3 and 5 years were estimated by Kaplan-Meier for each of these three cohorts. The patients in the third cohort had significantly better 5-year survival rate (p=0.000) and longer technique survival (p=0.000). The peritonitis rate reduced to an average of 0.25 episodes per year at risk in the third cohort from 1.33 episodes per year at risk in the first cohort. In the Cox proportional hazards model analysis, age, diabetic nephropathy, transfer to PD from HD, serum albumin level, serum C-reaction protein (CRP) level, Total creatinine clearance (Ccrl) and dialyse-to-plasma creatinine ratio (P creatinine) predicted mortality.

Conclusions: Patient and technique survival have significantly improved, and peritonitis rate has reduced in the most recent cohort compared with earlier periods. The causes of this improvement are likely to the appointment of dedicated PD nurses, a standardized follow-up system, and a “PD first” principle since 2005.

SA-PO940
Physical Activity: Peritoneal Dialysis versus Hemodialysis Patients Daniel Teta, 1 Marie Paule Guillodo, 2 Anne Kolko-Labadens, 3 Catherine Deforges-lasseur, 4 Martial Levannier, 5 Marine Panaye, 6 Denis Fouque. 7

1Nephrology, University Hospital, Lausanne, Switzerland; 2AUB Santé, Brest, France; 3Hémodialyse, AURA Nord, Saint Ouen, France; 4AURD Aquitaine, Gradiquin, France; 5Amen, Neuilly/Seine, France; 6Néphrologie, Hôpital H.E.Herriot, Lyon, France; 7Néphrologie, U1060 CHLS, Pierre Bénite, France.

Background: Physical activity, a risk factor for mortality in maintenance dialysis (MD) patients, has been essentially studied in hemodialysis patients (HD). We aimed to assess the physical activity from peritoneal dialysis (PD) patients included in the Step by Step initiative, a large cohort of MD patients.

Methods: All French nephrologists were invited to participate in a national prospective multicenter observational trial. 149 investigators included 1163 adult prevalent (~3 months) MD patients. Physical activity was assessed by the number of daily steps using a pedometer (NO PE317C, USA) for 7 consecutive days. All PD patients from the cohort (n=63, 5.4%) were analyzed and compared with randomly-matched computer-selected HD patients (n=123), 1:2 ratio, by age (10-year intervals) and dialysis vintage (3-months intervals), which mostly determined daily step number in the whole cohort.

Results: Median age (57 yr) and dialysis vintage (1 yr) were not different in PD vs HD patients, as expected. Sex ratio (males: 60% in PD vs 68% in HD), prevalence of diabetes (30% vs 25%), ischaemic heart, peripheral arterial, neurological and joint diseases were comparable. The groups only differed by the prevalence of hypertension (89 vs 63%, p=0.0002) and median body mass index (25.9 vs 24.2 kg/m2, p: 0.036). Median daily step number was comparable in PD vs HD patients (3321: Q1 1478-Q3 5926 vs 3903: Q1 2158-Q3 7346; p: 0.193). 64% PD vs 61% HD patients were sedentary (~5000 steps/day), and 36% PD vs 39% HD patients had a low physical activity (~5000 steps/day) (< 1.1 mp/12.7). Significantly higher risk of mortality with SBP <120 mmHg compared to SBP of 140-159 mmHg after adjusting for age, sex, and race. Subsequent models with stepwise addition of baseline albumin, KTV, normalized protein catabolic rate, and etiology of ESRD further strengthened the association of SBP >120 mmHg with higher mortality as compared to SBP of 140-159 mmHg by stepwise increase in hazard ratio.

Conclusions: Reverse epidemiology manifested as higher mortality associated with lower blood pressure is described in patients with end stage renal disease (ESRD) on hemodialysis, but is not well described in peritoneal dialysis (PD). We evaluated the effect of baseline blood pressure at initiation of PD on all-cause mortality.

SA-PO943
Tolvaptan Increases Urine and Ultrafiltration Volume for Patients with Oliguria Undergoing Peritoneal Dialysis  Tomo Ishihara, 1 Shinya Nagasaka, 2 Akira Shimizu. 3

1Nephrology & Hypertension, Chiba Medical University, Chiba, Japan; 2Department of Medicine, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.

Background: Hypoalbuminemia caused by peritoneal dialysate protein loss, frequently occurs in patients on peritoneal dialysis (PD) and is associated with an increased risk of death. We investigate whether PD dialysis exchange volume (PD volume) could be reduced with Tolvaptan (TVP) through increased urine volume (UV).

Methods: In 23 stable patients with oliguria undergoing peritoneal dialysis, the following parameters were examined diuretic response and the effect of TVP on peritoneal ultrafiltration (UF), body weight (BW), serum albumin, sodium, arm muscle area (AMA), PD volume, KTV, and urine and serum osmolality (OSM).

Results: The average UV increased from 428 ± 178 mL to 906 ± 285 mL (p = 0.018 by paired t-test). Average weekly PD volume decreased from 28,836 ± 5,699 to 23,872 ± 3,569 mL (p = 0.04 by paired t-test). Average UF increased from 283 ± 147 to 575 ± 135 mL (p = 0.019 by paired t-test). On the other hand, there was no significant difference in the average diuresis KTV before and after TVP treatment. Serum sodium, AMA, and serum albumin levels were not statistically different before and after TVP treatment. The urine and serum OSM (us OSM) ratio of effective cases before TVP treatment was higher than that of ineffective cases (p = 0.024 by unpaired t-test).

Conclusions: Our results indicate that TVP is useful for patients on CAPD who have oliguria and high urine osmolality. Furthermore, we can reduce PD volume to maintain their nutritional status.
SA-PO944
The Effect of Folic Acid Therapy on Anemia in Patients with End Stage Renal Disease on Peritoneal Dialysis Subir K. Paul, Shejtu Paul, Rajesh Boorgu, Jamie N. Cockrell, Narasimha Rao Boorgu, Cassandra (cassie) A. Miller. Shools Kidney and Hypertension Center, Florence, AL.

Background: Despite maintenance of adequate iron saturation with intravenous iron and utilization of appropriate dose of Epoegen therapy, anemia management remains sub-optimal in some patients with End Stage Renal Disease (ESRD) on peritoneal dialysis. We found macrocytosis and folate acid deficiency in some patients on peritoneal dialysis. This study tests the effect of folic acid treatment on plasma hemoglobin concentration in peritoneal dialysis patients with anemia.

Methods: 16 patients with ESRD on peritoneal dialysis with plasma hemoglobin concentration less than 11g/dl, folate acid level of 5 ng/ml or less, and iron saturation more than 20% were treated with 3 to 5 mg of oral folic acid daily. All patients had adequate KT/V and were free of infections or known inflammatory conditions. Vitamin B12 level was found to be normal in all patients. Mean age was 47.81 years. 7 were male and 9 were female. 9 were white and 7 were black. Serum folate acid level and plasma hemoglobin concentration were evaluated at 4 weeks prior, initiation, and 4 weeks after initiation of therapy. Maintenance therapy with intravenous iron and Epoegen were continued according to standard protocol. No subject received blood transfusion. Statistical analysis was done with student’s t test.

Results: At four weeks prior to initiation, and at initiation mean folate acid level was 3.93 +/- 0.20 ng/ml and 3.96 +/- 0.22 ng/dl respectively (p=0.89). Following therapy with folic acid, mean folate acid level increased from 3.96 +/- 0.22 ng/dl to 19.26 +/- 0.53 ng/dl (p<0.0001). During pre-treatment phase, mean plasma hemoglobin concentration remained unchanged from 10.42 +/- 0.25 g/dl to 10.29 +/- 0.25 g/dl (p=0.97). Following treatment with folic acid, mean plasma hemoglobin concentration improved from 10.29 +/- 0.25 g/dl to 11.30 +/- 0.22 g/dl (P=0.005). Following treatment with folic acid, mean Epoegen dose decreased from 1412 units to 1043 units every 2 weeks (P=0.043).

Conclusions: We conclude that oral folic acid therapy may be a cost-effective addition to anemia management in patients with ESRD on peritoneal dialysis.

SA-PO945
Change in Body Composition Measurements in Peritoneal Dialysis Patients According to Dialyze Seokhui Kang1, Tae woo Kim1, Kyu-hyang Cho1, Jong-Won Park1, Kyung woon Yoon1, Jun-Young Do1. 1Internal Medicine, Yeungnam Univ Hospital, Daegu, Republic of Korea; 2Internal Medicine, Soonchunhyang Univ Gumi Hospital, Gumi, Republic of Korea.

Background: The accurate estimation of body composition is associated with prediction of morbidity or mortality in peritoneal dialysis patients. The aim of this study is to evaluate changes in body composition measurements according to dialyze.

Methods: A total of 41 patients on maintenance peritoneal dialysis were enrolled in the study. Body composition analysis using bioimpedance spectroscopy (BIS) and multi-frequency bioimpedance analysis (MF-BIA) were performed in all patients, in the study. Body composition analysis using bioimpedance spectroscopy (BIS) and change in body composition measurements according to dialysate.

Results: MF-BIA underestimated the lean mass in D+ and BIS overestimated the lean mass in D+. Differences in body compositions with D- and D+ were investigated. Biases were calculated as follows: 

Weight measurement in D- – measurement in D+. MF-BIA underestimated the lean mass in D+ and BIS overestimated the lean mass in D+.

Conclusions: This study demonstrates that MF-BIA may be useful to evaluate fat mass, regardless of dialyze. Lean mass or free fat mass can be reliably done without dialyze.

SA-PO946

Background: Transplant renal artery stenosis (TRAS) has been implicated in poor allograft function and survival. As such, the prevention and early detection of TRAS may provide benefit to patient outcomes. This study aims to define the incidence, risk factors, and outcomes of kidney transplant recipients with TRAS in a large Canadian patient cohort.

Methods: This is a retrospective cohort study of 1224 kidney transplant recipients from January 1, 2000 and 31 December 2010. Follow-up was considered to have ended at the time of early-onset NODAT, and 112 developed late-onset NODAT. Risk factors for early-onset NODAT were recipient age (HR 1.05 [95% CI: 1.03, 1.07]), deceased donor kidney (HR 2.04 [95% CI: 1.32, 3.13]) and expanded criteria donor kidney (HR 1.92 [95% CI: 1.15, 3.18]). Risk factors for late-onset NODAT were age (HR 1.04 [95% CI: 1.03, 1.06]), allograft race (HR 2.04 [95% CI: 1.12, 3.83]), HLA mismatches (HR 1.21 [95% CI: 1.06, 1.39]), positive CMV serostatus (HR 1.69 [95% CI: 1.16, 2.50]), and deceased donor kidney (HR 1.69 [95% CI: 1.16, 2.50]).

Conclusions: The differences in risk factors for early- and late-onset NODAT suggests that they are likely the product of both shared and distinct mechanisms. Based on these results, the targets for diabetes risk reduction may partially depend on the timing of NODAT occurrence.

SA-PO948
Transplant Renal Artery Stenosis in Kidney Transplant Recipients: Incidence, Risk Factors, and Outcomes Joseph Kim, Ching Lucy Chau, Yanhong Li, Olusegun Famure. Multi-Organ Transplant Program, Toronto General Hospital, Univ Health Network, Toronto, Canada.

Background: Transplant renal artery stenosis (TRAS) has been implicated in poor allograft function and survival. As such, the prevention and early detection of TRAS may provide benefit to patient outcomes. This study aims to define the incidence, risk factors, and outcomes of kidney transplant recipients with TRAS in a large Canadian patient cohort.

Methods: This is a retrospective cohort study of 1224 kidney transplant recipients from January 1, 2000 and 31 December 2010. Follow-up was considered to have ended at the time of TRAS as a time-varying exposure on the risk of total graft failure (i.e., return to dialysis or death with graft function) was also studied.

Results: A total of 106 incident cases of TRAS were observed over a median follow-up of 3.24 years. The incidence rate of TRAS was 0.46 cases per 100 person-years. The relative hazard of TRAS was significantly associated with living donor transplant (HR 2.69 [95% CI: 1.59, 4.56]) and male sex (HR 1.80 [95% CI: 1.16, 2.78]). Our analysis showed an era effect with a lower relative hazard of TRAS in the most recent eras (HR 0.62 [95% CI: 0.41, 0.95]) for 2005-2007 vs. 2000-2004 and HR 0.29 [95% CI: 0.15, 0.58] for 2008-2011 vs. 2000-2004). TRAS was associated with an increased risk for total graft failure (HR [1.41 [95% CI: 0.58, 3.44]), although this failed to reach statistical significance.

Conclusions: Our results suggest that male sex and living donor recipients are at an increased risk for TRAS. A decrease in the risk of TRAS was also observed with the most recent transplant era. Further study is required to confirm and explore these associations in other kidney transplant populations.

SA-PO949
Infection-Related Mortality Is Higher for Kidney Allograft Recipients with Diabetes Mellitus – A Population Based Cohort Study Manvir Kaur Hayer, Daniela Farrugia, Adnan Sharif. Renal Institute of Birmingham, Queen Elizabeth Hospital, Birmingham, United Kingdom.

Background: Strong epidemiological evidence linking diabetes with risk for serious infections is lacking despite sufficient experimental evidence. The risk for infection-related mortality in kidney allograft recipients with diabetes, on immunosuppression, is unknown. This study investigates whether diabetes mellitus predicts mortality from infection post kidney transplantation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author/disclosure.
Methods: We identified all kidney alone transplants done in England from April 2001 to March 2012 through a national database called Hospital Enquiry Statistics. Patient demographics were recorded, and all deaths in the study group were identified via data linkage analysis with the Office for National Statistics. The primary outcome was death from infection post transplantation in diabetics versus non-diabetics. Cox proportional hazard models identified independent factors associated with infection-related mortality (p<0.05).

Results: Infection-related mortality is commonplace post transplantation especially common in diabetic kidney allograft recipients with pre-existing diabetes mellitus. Diabetes is a risk factor for infection-related death post kidney transplantation independent of confounders. Further work is needed to decide whether personalised immunosuppression is beneficial for diabetic kidney allograft recipients.

Funding: Private Foundation Support

SA-PO952

Distinct Localization of HCMV-Encoded Chemokine Receptor US28 and Immediate Early Antigen after Renal Transplantation Suggests Microenvironment-Specific Expression

Wouter Lollinga,1 Afsar Rahbar,2 Martine J. Smit,3 Annelies Riezebos-brilman,4 Cecilia Söderberg-naeulcer,2 Willem Van Son,1 Johannes S. Sanders,2 Jacob van den Born.1 1Nephrology, UMCG, Groningen, Netherlands; 2Medicine, Karolinska Institutet, Stockholm, Sweden; 3Medical Chemistry, VU University, Amsterdam, Netherlands; 4Medical Microbiology, UMCG, Groningen, Netherlands.

Background: Human cytomegalovirus (HCMV) is associated with decreased renal function and survival, possibly through expression of chemokine receptor US28. US28 enables HCMV to instigate (chronic) transplant dysfunction through US28. The effect of US28 on transplant dysfunction is now well-established.

Methods: Renal transplant biopsies (n=50) from HCMV-seropositive donors were obtained pre-transplantation, on indication or by protocol one year post-transplantation. Immunohistochemical staining was performed for US28 and immediate early antigen (IEA). Localization of both HCMV antigens were semi-quantitively scored in renal compartments and analyzed by Spearman rank correlation.

Results: Both HCMV antigens were detected during recipient active and latent HCMV infections, with IEA exclusively localized in the nucleus and US28 mainly in the cytoplasm. Localization can overlap in renal compartments, but is regularly distinct. IEA and US28 expression within a single compartment didn’t correlate.

Conclusions: We are the first to demonstrate US28 in renal transplant biopsies, and its specific localization. More pronounced than for IEA, the distinct localization of US28 in vascular smooth muscle and tubular epithelial cells, linking HCMV infection to transplant dysfunction.

Funding: Government Support - Non-U.S.

SA-PO953

The Impact of Hepatitis C Virus Infection on the Incidence of Post-Transplant Lymphoproliferative Disorder among Epstein-Barr Virus and Cytomegalovirus Seropositive Kidney Transplant Recipients: An Analysis of UNOS/OPTN Data

Anjali Gupta,1 Graciela De Boccardo,2 Enver Akalin, Liise K. Kayler. 1Nephrology, 2UCI Dept of Internal Medicine; 3UCLA-Olive View Dept of Medicine, Nephrology Div; 4UCU Of Medical, Nephrology Div & Kidney Transplant Program.

Background: Post-transplant lymphoproliferative disorder (PTLD) is a serious complication after organ transplantation. Hepatitis C virus (HCV) infection is a well-established risk factor for the lymphoproliferative syndrome type II mixed cryoglobulinemia. In this study, we hypothesise that pre-transplant HCV infection increases the risk of PTLD among kidney transplant recipients who have Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) seropositivity.

Methods: Adult kidney transplant recipients (≥ 21 years old), of a deceased or living donor kidney transplant in the U.S., with PTLD diagnosis between 1999 and 2011 from the UNOS/OPTN data, were included in the analysis using SAS. The difference of distributions of categorical variables between groups was investigated using chi-squared tests. Effect modifications of HCV antibody status on PTLD risk by selected demographic characteristics (age, sex, ethnicity) and clinical factors (CMV serology, EBV serology, pre-transplant malignancy, HLA mismatch, acute rejection episodes, use of medications for induction and maintenance of immunosuppression) were evaluated under the multiplicative model in the Cox regression models.

Results: There were a total of 923 PTLD cases (incidence, 1.78 patients per 1000 person-years) among 169,196 primary kidney transplant recipients between 1999 and 2011 (accrued 517,739.76 person-years at risk during the follow-up period). HCV prevalence at transplantation was 5.58% (N = 9,445). HCV infection did not increase PTLD risk in the total cohort even after adjusting for demographic and clinical risk factors. No significant effect modifications were found for HCV infection on the incidence of PTLD among EBV and CMV seropositive kidney transplant recipients.

Conclusions: Our findings suggest that HCV is not a major risk factor for PTLD among kidney transplant recipients, which is consistent with previous studies among other solid organ transplant recipients.

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

Underline represents presenting author/disclosure.

844A
Prevalence and Risk Factor of Epstein-Barr Virus Viremia in Kidney Transplant Patients

Keun Suk Yang, Byung Ha Chung, Bum Soon Choi, Cheol Whee Park, Yong-Soo Kim, Chul Woo Yang. Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary’s Hospital, College of Medicine, The Catholic Univ of Korea.

Background: Epstein-Barr Virus (EBV) infection is an important risk factor for post-transplant lymphoproliferative disease and increase in viral load of EBV also associated with the development of chronic allograft injury. In this study, we evaluated the prevalence and risk factors for the development of EBV viremia in renal transplant recipients.

Methods: One hundred ninety three patients were included in this study. The follow-up period from KT was 82.26±68.09 months and the mean age was 46.88±11.19 years. Plasma EBV loads were measured by real-time quantitative polymerase chain reaction and EBV Viremia was defined as having at least 500 copies EBV/ml.

Results: EBV viremia developed in 35.23% (68/193) of study population. Donors for the majority of patients in this study were living (74.1%). The patients with proteinuria showed significant difference in both groups (p<0.01). EBV viremia were more frequent in the patients treated with cyclosporine than with tacrolimus (p<0.01). Glomerular filtration rate was lower in EV group (53.74±21.39 ml/min/BSA) than NV group (60.54±17.58 ml/min/BSA) (p<0.05) and immunosuppression period was longer in EV group (124.92±83.63 months) than NV group (78.33±73.45 months) (p<0.01). No significant difference was shown between EV group and NV group on age at transplant, pre-transplant dialysis type, and risk factors for the development of chronic allograft injury. In this study, we evaluated the prevalence and risk factors for the development of EBV viremia in renal transplant recipients.

Conclusions: The prevalence of EBV viremia in stable renal transplant recipients was 35.23 % and follow up period and the type of immunosuppressant may be associated.

SA-PO955


Univ of North Carolina, Chapel Hill, NC; Nephrology and Hypertension, Univ of North Carolina, Chapel Hill, NC.

Background: The morphology of Polyomavirus Nephropathy (PVN) resolution has not been systematically studied. It is unclear whether PVN contributes significantly to the development of chronic allograft injury over time.

Methods: Paired renal biopsies for cause from 14 patients (total biopsies n=28) were evaluated at time of initial PVN diagnosis and at time of PVN clearance following standard protocols (weeks between biopsies:mean=128; range=3-4392). At time of index biopsy, 9 cases were PVN stage A (minimal virally induced injury) and 5 were stage B (florid virally induced injury). Biopsies were scored using BANFF criteria.

Results: 12% had no change in BANFF scores from index to clearance. Increases in acute lesion scores were seen in 5% (cg, ci, ah, cv, pt, t), chronic scores in 4% (cg, ci, ah, cv, ptc, t), and in 6% both acute and chronic. Each group showed significant clinical differences between index and clearance biopsies.

Conclusions: In healed PVN stages A & B, renal function improved compared to time of PVN diagnosis. PVN does not necessarily contribute significantly to acute or chronic graft injury during disease resolution.

SA-PO956

Bk-Virus and the Impact of Transient versus Persistent BK Viremia on Graft Function and Survival after Kidney and Kidney/Pancreas Transplantation – 5-Year Results

Nissreen S. Elfadlawa, Stuart M. Flechner, Jesse D. Schold, Titte Srinivasa, Emilio D. Poggio.

Glickman Urological and Kidney Institute, The Cleveland Clinic; Dept of Quantitative Health Sciences, The Cleveland Clinic, Cleveland, OH; Div of Nephrology, Medical Univ of South Carolina, Charleston, SC.

Background: BK virus (BKV) reactivation is a serious complication after kidney transplantation. Currently there are limited data regarding long-term impact of transient BK viremia.

Methods: 609 patients who had kidney or kidney/pancreas transplant from 2007 to 2011 were screened for BKV infection. 130 patients (21.7%) developed positive BKV viremia. Patients were followed up for a median of 36 months (3-66). BKV associated nephropathy (BKVAN), acute rejection, and the 1-year graft function were assessed and compared with the negative group.

Results: Patients and graft survival were comparable among the groups (p>0.05). High BKV infection does not have a negative impact on graft outcomes. Although transient high viremia was not associated with BKVAN, poor graft function and high incidence of graft rejection in this patient group may suggest a new mechanism for the negative impact of BKV. In general, BK viremia and BKVAN are associated with excellent patient and graft survival in the era of BKV screening.

Conclusions: Low BKV infection does not have a negative impact on graft outcomes.
SA-PO957
The Genomics of BK Viremia and Nephropathy in Kidney Transplant Recipients Reveal a Heightened T Cell and Natural Killer Cell Response
Michelle L. Lubetzky, Yi Bao, Maria Ajaïmy, Graciela De Boccado, Enver Akalin.
Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

Background: The genomics of polyomavirus BK viremia and nephropathy (BKVN) have not been well described. We aimed to study gene expression profiles of BKVN and BK viremia samples using microarrays.

Methods: 17 biopsy and 40 whole blood PAXGene samples from patients enrolled in our IRB approved “Immune Monitoring Study” were used for analysis. Biopsy samples were divided into 3 groups, Group 1: Normal biopsy, n=11, Group 2: BKVN, n=3, and Group 3: BK viremia with normal biopsy, n=3. Whole blood PAXGene samples were divided into 3 groups, Group 1: Stable renal function, n=14, Group 2: BK viremia, n=19, and Group 3: samples taken 1-2 months prior to BK viremia, n=7. All samples were analyzed using Affymetrix Human Gene 1.0 ST Arrays.

Results: When comparing BKVN biopsy samples to Group 1 and 3, there were 1442 differentially expressed genes, respectively (FDR<0.05 and fold change >2). There was no significant difference between Group 1 and 3. Pathogenesis based transcript (PBT) analysis revealed a significant increased expression of interferon-gamma and rejection induced (GRIT), cytotoxic T cell (CAT), constitutive and alternate macrophage, B cell and natural killer cell-associated transcripts (NKAT), indicating an active inflammatory immune response in BKVN biopsies. The top 50 differentially expressed genes were involved in immune activation such as toll-like receptor 10, CD40 ligand, B and T lymphocyte associated, CD4, and MHC-Class II DQ beta. Gene ontology analysis revealed pathways involved in immune activation, T cell activation and costimulation, B cell activation, and defense response to virus. While there were no significant differentially expressed genes in whole blood gene expression profiles of Group 1 and 3, the PBTS of BK viremia revealed significant increased expression of GRIT, QCAT and NKAT when compared to Group 1 and 3.

Conclusions: Our results showed increased activity of cytotoxic T cells and natural killer cells in BKVN and viremia samples resembling acute rejection. Whether such response is to allergen or virus requires further studies.

SA-PO958
BK Nephropathy: A Paired Kidney Analysis from a Single Center
Marilida Mazzari, André Ba Esteves, Luiz R.S. Ulisses, Leonardo F. Camargo, Gabriel G. Rivelli. Renal Transplant Program–Div of Nephrology, School of Medical Sciences–State Univ of Campinas–UNICAMP, Campinas, Brazil.

Background: Polyomavirus nephropathy (PV AN) has a negative impact on graft survival, and is related to donor and recipient risk factors. In order to identify recipient related factors, we analyzed a series of renal transplants from deceased donor, where one recipient developed PVAN and compared to their controls, recipients from a paired kidney, with persistent negative BK V viruria.

Methods: From our Transplant Unit database, 16 patients with biopsy proven PVAN, recipients from a deceased donor kidney were identified. For analysis, we considered 12 pairs of kidneys, one with biopsy proven PVAN (PVANs) and the paired kidney (Controls) with persistent negative BKV viruria. Two pairs, were both kidneys developed PVAN were excluded. All patients were screened for BK viruria every 3 months during the first 3 years post transplant.

Results: PVANs and Controls were comparable for age at transplant, primary renal disease, % PRA, induction therapy, and baseline immunosuppression, with a higher prevalence of male recipients in PVANs (91.6% vs 66.6%, P=0.05). Despite a trend to a lower cold ischemia time (p=0.08) in PVANs, the incidence of delayed graft function and CMV infection were similar to Controls. However, incidence of acute rejection and severity of acute rejection. After a 5 year follow up, 50% of the grafts in PVAN group remained functioning, with a mean serum creatinine of 3.3 ± 1.6 mg%.

Methods: We performed a systematic review of index and surveillance renal allograft biopsy findings in individuals with biopsy proven BKVN. We evaluated the change in the histology scores associated with inflammation and fibrosis following a decrease in BK viral load.

Results: We studied 22 patients with BKVN: 12 with BKVN stage A, 7 with stage B, and 3 with stage C. The surveillance biopsies were performed at mean of 9 months following BKVN diagnosis. Histological scores, renal function, and BK viral load at the time of BKVN diagnosis and at surveillance biopsy are summarized in the Table.

Conclusions: The striking decrease in BK viral load was associated with a significant decrease in intragraft inflammation but tubulointerstitial fibrosis either increased (in BKVN stage A) or remained the same (in BKVN Stage B/C). Our new findings, in addition to providing a mechanistic basis for the poor long-term outcome in BKVN patients, suggest the hypothesis that anti-fibrosis therapy (e.g., anti-TGF-beta antibody) may retard the progression of BKVN.

SA-PO960
Utility of ImmuKnow Assay in BK Infection after Kidney Transplantation

Background: By quantifying cellular AT production after mitogenic stimulation, ImmuKnow assay values(IKA V) can provide an estimate of immune function. We studied the utility of this assay in patients with and without BK viremia (BKV) after kidney transplantation.

Methods: In this retrospective case-control study, IKAV and BK PCR was obtained in kidney transplant recipients at 1 month post-transplantation and then quarterly for a year. BKV was subdivided into groups based on PCR values: A=101, B=1010, C=1010 and D=1010. Delta IKAV was defined as IKAV on the date that BK was first ≥10^6 minus immediate previous IKAV. General linear mixed model was used to compare IKAV between different BK infection groups over time. Paired t-test was used to test the null hypothesis (i.e. no significant change in delta IKAV in incident BKV patients).

Results: We had 79 BKV cases and 99 of selected controls. Time-group interaction term was significant (P<0.0001) indicating that differences between groups depend on time. In BK cases, IKAV were significantly lower at months 3, 6, 9 and 12 when compared to the immediate previous IKA V. Groups A, B, C and D had significant decrease in delta IKAV between month 1 to 3 (P<0.0001). On an average, there is a 367 point decrease in IKAV (SD=346, 95% CI: 269,486). Beyond 3 months, delta IKAV was not associated with incident BKV (P=0.07).

Conclusions: Compared to controls, kidney transplant recipients who develop BKV have significantly lower IKAV after 3 months when compared to first month. Also, incident BKV is associated with a significant decrease in delta IKAV only in the first 3 months. Beyond that period, delta IKAV did not correlate with incident BKV.

SA-PO961
BK Viremia in Kidney Transplant Recipients

Background: BK virus associated nephropathy is a threat to kidney transplant (KT) graft survival. BK viremia precedes BKV nephropathy. We aimed to study the risk factors and outcome BK viremia in KT recipients with graft dysfunction.

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

Underline represents presenting author/disclosure.

846A
Methods: KT Recipients who underwent transplantation at Christian Medical College, Vellore from January 2006 to December 2011 were included. Patients underwent BK viremia screening at least once weekly by qualitative PCR (for BKV DNA) and quantitative PCR (qualitative BK viral load). Positive samples were confirmed by sequencing.

Results: Of 535 KT recipients, 294 patients were monitored for BK viremia. Baseline characteristics, transplant demographics, and 1-year incidence of BK viremia and nephritis were similar between the two groups. The cumulative incidence of BK viremia at one year after transplantation was significantly reduced in CP group (11.3% versus 24.8% in NP, \( P<0.005 \)). Among recipients who developed BK viremia, the median time to BK viremia was 145 days in CP group, compared to 210 days in NP group (\( P=0.03 \)). However, the incidence of BKV nephritis was comparable between the two groups (CP group: 0.4%, NP group: 0.6%, \( P=0.03 \)).

Conclusions: Ciprofloxacin prophylaxis appears to be effective in preventing BK viremia within one year after transplantation. Future prospective, randomized studies are needed to determine the impact of ciprofloxacin prophylaxis for BKVN.

SA-PO965

Efficacy of Intravenous Immunoglobulinin the Treatment of BK Virus Nephropathy in Renal Transplant Recipients

Tariq Shah,1,2,3 Robert Naraghi,4 Don Vu,1,2 Cameron Sheedy,3 Yasir A. Qazi,4 Elizabeth Cadag,1 Caron Hutchinson,1 David I. Min.3

Background: BK virus nephropathy (BKVN) is a common viral infection that affects renal transplant recipients (TPRs), causing graft dysfunction or graft loss. Fluoroquinolones have been shown in vitro to inhibit BK viral replication by direct inhibition of the BKV-encoded DNA gyrase. The aim of the study is to investigate the efficacy and safety of IVIG treatment for BKVN.

Methods: We retrospectively evaluated all TPRs in our center from January 2006 to January 2012 who received IVIG for BKVN.

Results: Of 535 TPRs, 294 were evaluated for BKVN. Of these, 20 patients received IVIG for BKVN. The average total amount of IVIG was 102.4 ± 52.1 g per patient and the average cost per IVIG treatment was $7,657.00.

Conclusions: IVIG administration appeared to be safe and effective in treating BK viremia, BKVN, and preventing graft loss in patients who had inadequate response to immunosuppression reduction and leflunomide therapy.

SA-PO966

The BK:KIDNI Trial – BK Viremia: Kinase Inhibition to Decrease Nephropathy Intervention Trial

Pietro Ravani, Brenda Hemmelgarn, Lee Anne Tibbles.

Background: Although infection with human BK virus is common, this polyomavirus remains dormant in the kidney of affected individuals. However, following kidney transplantation (KT), BK virus reactivates and replicates, causing progressive interstitial nephritis in the renal allograft.

Key: 847A

SA-PO962

HLA-A2, HLA-B44 and HLA-DR15 Associate with Lower Risk of BK Viremia while BK Viruria Is HLA Independent

Kosuke Masutani,1,2 Parmjeet S. Rangnjeet,1,2 Tariq Shah,1,2,3 Robert Naraghi,4 Don Vu,1,2 Cameron Sheedy,3 Yasir A. Qazi,4 Elizabeth Cadag,1 Caron Hutchinson,1 David I. Min.3

Background: Human leucocyte antigens (HLA) modulate immunity to polyomavirus BK (BKV). Identification of HLA-antigens that alter the course of infection will facilitate risk stratification, and customization of preventive strategies.

Methods: We performed a retrospective cohort study with 998 kidney transplant patients with BKV infection. Clinical and demographic parameters and donor-recipient matching for specific HLA-antigens were examined in relation to occurrence of viremia and viruria. Emphasis was placed on donor-recipient matching rather than the actual frequency of specific HLA-alleles, since a successful immune response requires sharing of HLA antigens between a virus infected target cell and the anti-viral effector cell.

Results: In multivariate statistics incorporating known risk factors of BKV, low risk of BK viremia was independently associated with matching of HLA-A2 (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.28-0.89), HLA-B44 (HR 0.31, 95%CI 0.17-0.57), and HLA-DR15 (HR 0.35, 95%CI 0.19-0.64) and BK viremia at one year after transplantation was significantly increased in CP (11.3% versus 28.3%, OR =3.23, p=0.036). Among recipients who developed BK viremia, the median time to BKV was 145 days in CP group, compared to 210 days in NP (P=0.05), however the CP group developed a significantly lower peak BK viral load, versus the NP group (median, 10.8 x 10^6 copies/ml vs. 10.4 x 10^6 copies/ml, P=0.044). The overall incidence of BKV viremia was 2.2 % in CP group and 6.7 % in NP group (P=0.39, OR=3.1). Additionally, patients in CP group were not found to experience a higher risk of fluoroquinolone-resistant infection.

Conclusions: Ciprofloxacin prophylaxis appears to be effective in preventing BK viremia within one year after transplantation. Future prospective, randomized studies are needed to determine the impact of ciprofloxacin prophylaxis for BKVN.
Observational studies suggest that reduction of immunosuppression can lead to clearance of BK viremia. However, reducing immunosuppression may also increase the risk of rejection. In addition, no consensus regarding how to reduce immunosuppression has been reached and studies on treatments other than reduction of immunosuppression are not available to inform clinical practice.

**Methods:** We are conducting a Phase III multi-centre randomized, parallel-group trial involving 300 patients (150 per arm), at 15 sites in Canada. De novo kidney transplant patients with positive PCR for plasma BK (viremia) are randomized to either reduced immunosuppression (control arm) or Sirolimus/Leflunomide (treatment arm). Biopsies are taken at first viremia and one year follow-up. Biopsy proven rejection is treated according to site-specific guidelines. The study period is at least one year in duration (last subject randomized will be followed for one year). Since recruitment will occur over approximately 3 years, the total duration of the trial and thus follow-up of first patients will be an estimated 4 years.

**Results:** To date we have screened 146 patients and recruited 27 across Canada.

**Conclusions:** The BK-KIDNI trial will test whether specific kinase inhibition is superior to standard therapy in reducing the risk of the multiple outcome of doubling of serum creatinine, need for renal replacement therapy for graft failure and death (primary objective). Secondary outcomes include rate of decline in renal function based on decline in eGFR, time to 50% increase in serum creatinine, time to clearance of viremia, biopsy proven acute rejection, grade of BK nephropathy on biopsy at 12 months, chronic allograft nephropathy at 12 months, change in Health Related Quality of Life measures, and differences in health care costs between the two strategies (secondary objectives).

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

SA-PO968

**The Outcome of Steroid Pulse Therapy in BK Viremia Patients Who Demonstrated Acute Rejection Like Lesion** Hyosang Kim, Jong Cheol Jeong, Jae Seok Yang, Wonseok Yang, Curie Ahn, Duck Jong Han, Su-Kil Park

**Methods:** The study population consisted of 112 kidney transplant recipients with high BK viremia who received steroid pulse therapy for pathologic diagnosis of acute cellular rejection (ACR) along with BK nephropathy(BKN).

**Results:** Kidney biopsies were performed in 61 patients and 31 received steroid pulse therapy (>500mg) around the time of kidney biopsy.

**Conclusions:** We conclude lack accuracy of current formulae to detect changes in GFR in kidney Tx.

SA-PO969

**How to Estimate Kidney Function in Kidney Transplant Recipients with Mild to Moderate Kidney Impairment** Makoto Tsutjita, Daiso Inaguma

**Background:** With the recent increase in renal transplantations in Japan, accurate assessment of renal function is required.

**Methods:** This study included 73 patients who had undergone renal transplantation at Nagoya Daini Red Cross Hospital at least 6 months previously and had stable renal function for more than 3 months. Glomerular filtration rates (GFRs) were measured by inulin clearance (mGFR) and compared with estimated creatinine-based GFRs (eGFRcre), estimated creatinine-based GFRs (eGFRcys) and their averaged values (eGFRave).

**Results:** mGFR was 43.3 ± 14.1 mL/min/1.73 m² and, eGFRcre was 39.6 ± 11.7 in eGFRcre, eGFRcys was 56.0 ± 17.1, and eGFRave was 47.8 ± 13.7 mL/min/1.73 m², respectively. Serum creatinine was 1.39±0.37 mg/dL and serum creatinine was 1.58±0.51 mg/dL. The correlation coefficients between mGFR and eGFRcre, eGFRcys, and eGFRave were 0.768, 0.831, and 0.841, respectively (p<0.001, for all). The intraclass correlation coefficients were 0.754, 0.816, and 0.840, respectively (p<0.001, for all). The mean differences between measured and estimated GFR values were -3.74 mL/min/1.73 m² with a root-mean square error (RMSE) of 9.06 for eGFRcre, +12.64 with RMSE of 9.48 for eGFRcys, and +4.45 with RMSE of 7.86 for eGFRave. Bland-Altman plots showed that eGFRcre overestimated GFR values compared with mGFR in most cases and that eGFRcys overestimated GFR values in 53 of 73 cases, whereas eGFRcys underestimated the values in 53 of 73 cases.

SA-PO968

**Precision of Current Formulae to Detect Changes of GFR in Middle Eastern Kidney Transplant Recipients** Osama M. El-Mainehawy, Eman Elbasuny

**Background:** Assessment of graft function is crucial in kidney transplantation (Tx). Most formulae were developed for estimation of GFR in white and African Americans, Australian and Canadian people. Also their accuracy to detect changes of GFR in middle eastern kidney recipients has not well studied. Aim of this work is to find out the precision of current formulae to detect GFR changes in kidney Tx recipients.

**Methods:** The study included 79 kidney Tx recipients; 46 (58%) were males, 45 (57%) were Egyptian, 34 from different Arab countries age 46±13 years, body weight 70±7 Kg, BSA 1.8±1.1m², BMI 25±4 Kg/m², serum creatinine 1.8±1 mg/dl, blood urea nitrogen 29±11 mg/dl. Serum albumin 3.7±0.6 g/dl. Their immunosuppression: prednisone, CNI, and MMF in 70 patients (89%), prednisone, and MMF in 9 patients (11%). GFR was measured by 99mTc- DTPA clearance twice for each patient after follow up time 14±3 months and estimated twice at the same days of measurements by MDRD, abbreviated MDRD, Walser, Nankivell, Mayo clinic, Cockroft-Gault and CKD-EPI formula.

**Results:** mGFR were: 8-90 ml/min/1.73m² (44±21), absolute changes of measured GFR between 1st & 2nd measurement range from -45 to 46. Changes of estimated GFR range from -52 to 48 by CKD-EPI, from -57 to 44 by Cockroft-Gault from -92 to 57 by Mayo Clinic formula, from -60 to 37 by MDRD, from -82 to 37 by aMDRD, from -53 to 43 by Nankivell, and from -53 to 40 by Walser.

<table>
<thead>
<tr>
<th>Measured GFR</th>
<th>Discordant</th>
<th>Concordant</th>
</tr>
</thead>
<tbody>
<tr>
<td>KD-EPPI</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>Cockroft-Gault</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>MDRD</td>
<td>35</td>
<td>26</td>
</tr>
<tr>
<td>Nankivell</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>38</td>
<td>27</td>
</tr>
</tbody>
</table>

**Conclusions:** We conclude lack accuracy of current formulae to detect changes in GFR in kidney Tx.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author/disclosure.
Results: Though each GFR test displayed a significant correlation (P<0.0001) with 99mTc-DTPA clearance, Pearson’s correlation coefficients (r) were only 0.596 for aMDRD, 0.584 for c-aMDRD, 0.583 for CKD-EPI, and 0.556 for CG. Bias ranged from -46.07 to 34.39 ml/min/1.73m² for aMDRD, -49.68 to 36.97 ml/min/1.73m² for c-aMDRD, -40.36 to 49.33 ml/min/1.73m² for CG, and -45.13 to 49.33 ml/min/1.73m² for CKD-EPI. Correlation, bias, precision and accuracy within 15%, 30%, 50% and 70% of true GFR were 51%, 86.5% and 98.1% for CG respectively; 47.7%, 79.4% and 94.8% for c-aMDRD respectively; 44.5%, 83.9% and 98.1% for aMDRD respectively; 41.9%, 79.4% and 94.2% for c-aMDRD respectively; 49.7%, 79.4% and 98.4% for CKD-EPI respectively; 51%, 86.5% and 98.1% for CG respectively.

Conclusions: All of these equations can just roughly estimate the GFR of kidney transplant recipients. None of them can substitute for 99mTc-DTPA plasma clearance. In clinical trials, renal graft function should be measured by a standard method.

SA-PO971
Modified Schwartz Formula Accurately Reflects GFR in Pediatric Renal Transplant Recipients
Omar M. A.A. Alkandari,1 Diane Hebert,1 Valerie Langlois,1 Lisa Robinson,2 Rulan S. Parekh,1
1Hospital for Sick Children; 2Hospital for Sick Children.

Background: Kidney function is best assessed by measured GFR, however, this is impractical, complex, and costly especially in children. Our aim is to assess the validity of modified Schwartz formula in a pediatric renal transplant recipients.

Methods: We conducted a retrospective cross-sectional data analysis of pediatric kidney transplant patients younger than age 18 (n=174) followed at our center between 2001-2012. We compared estimated GFR using modified Schwartz with enzymatic measured serum creatinine (Scr) to the two point 99mTc-DTPA nuclear GFR (mGFR) and determined bias, precision, accuracy (within 30%), and agreement by Bland-Altman analyses in 505 paired measures. The eGFR was also determined using Counahan and Leger formulas.

Results: The study population included 62% males, 70% between ages 10 and 18 years, 46% with CAKUT as cause of ESRD and 34% of patients were living donor transplant recipients. Baseline median eGFR and mGFR were 77 and 86 ml/min/1.73m², respectively. Out of the 505 mGFRs, 83% had a GFR ≥ 60 ml/min/1.73m². Overall, the modified Schwartz formula has a bias of 6.9 ml/min/1.73m² and accuracy within 30% of 83.6%. Bland-Altman analyses demonstrates good agreement across the range of GFR especially in the normal range of GFR.

Conclusions: eGFRave may be the best marker to estimate kidney function in Japanese renal transplant recipients with mildly reduced or normal kidney function.

SA-PO970

Background: Accurate estimate of glomerular filtration rate (GFR) is crucial in the care of kidney transplant recipients. Since the reference methods to measure GFR cannot be easily implemented, several formulas for estimating GFR have therefore been developed. However, little is known about their diagnostic value in kidney transplant recipients. The aim of this study is to evaluate the performance of four creatinine-based formulas for estimating the GFR in this population.

Methods: Performances of the modified abbreviated Modification of Diet in Renal Disease (aMDRD) equation, aMDRD for Chinese chronic kidney disease patients (c-aMDRD), Cockcroft and Gault (CG) formula, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula were compared with the dual plasma sampling 99mTc-DTPA plasma clearance method as the gold standard for measuring GFR in 155 stable patients after kidney transplantation. Correlation, bias, precision and accuracy within 15%, 30%, 50% and 70% of true GFR were determined.

Results: Though each GFR test displayed a significant correlation (P<0.0001) with 99mTc-DTPA clearance, Pearson’s correlation coefficients (r) were only 0.596 for aMDRD, 0.584 for c-aMDRD, 0.583 for CKD-EPI, and 0.556 for CG. Bias ranged from -46.07 to 34.39 ml/min/1.73m² for aMDRD, -49.68 to 36.97 ml/min/1.73m² for c-aMDRD, -40.36 to 49.33 ml/min/1.73m² for CG, and -45.13 to 49.33 ml/min/1.73m² for CKD-EPI. Correlation, bias, precision and accuracy within 15%, 30%, 50% and 70% of true GFR were 51%, 86.5% and 98.1% for CG respectively; 47.7%, 79.4% and 94.8% for c-aMDRD respectively; 44.5%, 83.9% and 98.1% for aMDRD respectively; 41.9%, 79.4% and 94.2% for c-aMDRD respectively; 49.7%, 79.4% and 98.4% for CKD-EPI respectively; 51%, 86.5% and 98.1% for CG respectively.

Conclusions: All of these equations can just roughly estimate the GFR of kidney transplant recipients. None of them can substitute for 99mTc-DTPA plasma clearance. In clinical trials, renal graft function should be measured by a standard method.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
lumbar and femoral neck BMD compared with controls (0.061 g/cm², 95% CI 0.039-0.082 and 0.056 g/cm², 0.020-0.093, respectively). This corresponded to an unweighted improvement in BMD of 7.8% in lumbar spine and 7% in femoral neck. Bisphosphonate therapy had no effect on serum creatinine or calcium. There was no difference in fracture incidence in the two groups.

**Conclusions:** Bisphosphonate therapy was associated with improved lumbar and femoral neck BMD in kidney transplant recipients without adversely affecting serum creatinine or calcium. Although there was no difference in fracture rates, this may have been due to short follow-up times or the small number of studies reporting clinical outcomes. Future studies should report fracture rates and plan for longer follow-up intervals to better evaluate whether bisphosphonates reduce fracture incidence in kidney transplant recipients.

**SA-PO974**

**Comparison of Endothelial Microparticles and Serum Creatinine after Kidney Transplantation**

**Zahida Qamri, Ronald Pelletier, Jon R. Von Visger, Kyung M. Watan, Anjali A. Satoskar, Tibor Nadasyi, Sergey V. Von Visger.** *Dep. of Pathology and Comprehensive Transplant Center, The Ohio State Univ, Columbus, OH.*

**Background:** Endothelial microparticles (EMP) are membrane vesicles shed from endothelial cell in response to injury, activation or apoptosis. Kidney transplantation (KTx) is the treatment of choice for patients with end-stage kidney disease (ESKD). The aim of this study was to compare changes in EMP and serum creatinine (Scr) in patients following KTx.

**Methods:** Blood was periodically collected from patients the day before (pre-KTx) and two months after KTx. EMP were identified as 1 µm CD31+/CD42b+ microparticles and quantified by fluorescence-activated cell sorting. 

**Results:** This study included 212 KTx or kidney/pancreas (KPTx) recipients and 20 healthy donors (HD) (for comparison) prior to donation. The recipients were divided into 5 groups based on the cause of ESRD: 1: ESRD due to diabetes mellitus (DM) type 1 that received a KTx; 2: ESRD due to DM (type 1 or type II) that received a KTx only; 3: congenital obstructive causes of ESRD; 4: ESRD due to immune complex disease; 5: ESRD due to unknown causes. No differences in the quantity of circulating EMP were seen in the pre-KTx or KTx recipient sera and HD sera (Figure 1, A). At day 60 after KTx, Groups 2, 3, and 4 had a reduction in both circulating EMP and Scr from pre-KTx values (Figure 1, B).

**Conclusions:** In our patient cohort the quantity of circulating EMP were similar in HD and ESRD patients before KPTx or KTx. Reduction in both circulating EMP and Scr was seen after KTx in selective groups. Mechanisms of these variations in post-KTx EMP in different patient groups are not clear yet, but may be related to an underlying systemic disease or immune suppression therapy.

**Funding:** NIH/NIKDK Support.

**SA-PO975**

**Oral Paricalcitol Ameliorates Post-Transplant Hyperparathyroidism and Proteinuria in Kidney Transplantation**

**Matias Trillini, Jorge Arturo Reyes Loaeza, Karen Courville, Claudia Ferrer Siles, Silvia Paradini, Flavio Gaspari, Antonio Cannata, Alessandro Villa, Annalisa Perna, Eliana Gotti, Norberto Perico, Piero Ruggenenti, Giuseppe Remuzzi.** *IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Italy.*

**Background:** Secondary hyperparathyroidism (SHPT) is a major clinical problem in renal transplant recipients. In renal patients Paricalcitol (PAR) ameliorates SHPT and even reduces proteinuria, a major determinant of disease progression. Effects of PAR in SHPT renal transplant recipients are unknown.

**Methods:** In a randomized (1:1 computer-generated sequence), cross over trial (NCT01220050) we compared the effect of 6-month oral PAR added-on standard therapy vs 6-month standard therapy alone on serum intact parathyroid hormone (iPTH, primary outcome), bone markers of bone remodeling and proteinuria in 43 stable renal transplant recipients aged 54±9 yrs with iPTH persistently>80 pg/ml and no vitamin D therapy. PAR was started at 1 µg/d and, if tolerated, at 3 months was up-titrated to 2 µg/d. We compared treatment effects by repeated measures ANOVA, with participants as random and treatment and period as fixed factors.

**Results:** Serum creatinine averaged 1.39±0.33 mg/dl at baseline and was stable thereafter. Compared to standard therapy, PAR significantly reduced iPTH, ostease and osteocalcin levels, without affecting calcium and phosphate levels. Proteinuria significantly decreased on PAR, but not on standard treatment (Table). Reductions in iPTH, ostease and osteocalcin levels vs standard therapy were already significant at 3 months with PAR 1 µg/d. PAR was well tolerated.

**SA-PO976**

**Functional Status Predicts Hospital Length of Stay and Rehospitalizations following Kidney Transplant (KTx)**

**Elizabeth C. Lorenz, Hatem Amer, Andrea L. Cheville, Fernando G. Cosio.** *Mayo Clinic, Rochester, MN.*

**Background:** Decreased functional status has been associated with increased hospital stay of (LOS) and rehospitalizations (RH) in patients with CKD. The goal of this study was to determine whether functional status predicts LOS and RH following KTx.

**Methods:** We performed a prospective cohort study including all patients receiving KTx at our center between 12/2010 and 1/2013 (n=141). Providers assessed functional status with the following scoring system: A=regular exercise and no limitations, B=no regular exercise and no limitations, C=no regular exercise but slight limitations, D=no regular exercise and significant limitations. Providers assigned scores during the pre-KTx evaluation. The relationship of score to initial hospital LOS and number of RH during the first 4 months post-KTx was studied.

**Results:** Mean age was 51.0±13.6 yrs, 57.2% were male, 84.8% were Caucasian, 85.8% received LD KTx and 26.9% were diabetic (DM). Overall, 34.0% received a score of A, 46.1% a score of B, 16.3% a score of C and 3.5% a score of D. Scores of C or D were associated with DM (38.5% vs 12.8%, p<0.0006) but not with age, gender or dialysis status. Median initial hospital LOS was 4 days (range 3-15). A score of C or D independently predicted a hospital LOS longer than 4 days (OR 3.4, CI 1.4-8.1, p<0.003).

**Conclusions:** Functional status independently predicts morbidity following KTx. Limitations in functional status were associated with longer hospital LOS and more RH early post-KTx. Further study is needed to determine whether improving functional status prior to KTx could decrease hospital utilization post-KTx.

**SA-PO977**

**A Pedometer-Based Exercise Prescription Is Associated with Improved Metabolic Parameters following Kidney Transplant (KTx)**

**Elizabeth C. Lorenz1, Hatem Amer1, Fernando G. Cosio, Andrea L. Cheville2.1Nephrology and Hypertension, Mayo Clinic; 2Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN.**

**Background:** Exercise is associated with improved metabolic parameters in patients with chronic kidney disease. However, studies of exercise in KTx recipients are lacking. The aim of this study was to examine the effect of a pedometer-based exercise prescription on metabolic parameters following KTx.

**Methods:** We performed a prospective cohort study involving all patients who received KTx at our center between 12/2010 and 1/2013 (n=307). Patients transplanted between 12/2010 and 12/2011 received usual care (n=162) while patients transplanted between 1/2012 and 1/2013 received a 90-day pedometer-based exercise prescription beginning at KTx (n=145). Weight gain, glucose, lipids and automated office blood pressures (BP) were assessed 4-months post-KTx.

**Results:** Mean age was 51.5±13.3 yrs, 57% were male, 87% were Caucasian, 83% underwent LD KTx, 48% underwent preemptive KTx and 25% were diabetic. Mean BMI was 88.1±5.5 kg/m² and steroid-containing maintenance immunosuppression was used in 80%. Baseline demographics were not significantly different between cohorts. At 4 months post-KTx, patients in the pedometer cohort had lower BP and less impaired fasting glucose.

**Conclusions:** Low-intensity exercise is associated with improved metabolic parameters following KTx. Limitations of this study include the short observation period and lack of long-term follow-up.

**Funding:** NIH/NCRR K12 grant.
**SA-PO978**

Long-Term Outcomes of Angiographic Evaluation for Transplant Renal Artery Stenosis

**Authors:** Anum Ali, Muhammad Ahmad Mujtaba, Dennis P. Mishler, Tim E. Taber, Muhammad S. Yaqub, Asif A. Sharfuddin.

**University:** Nephrology/Transplant, Indiana Univ.

**Background:** The purpose of the present study was to evaluate graft survival, patient survival, and long-term outcomes after angiographic evaluation and treatment for suspected transplant renal artery stenosis (TRAS).

**Methods:** From January 1999 to Aug 2012, 74 patients had an angiographic evaluation for suspected TRAS. Outcome measures were death-censored graft failure, all-cause mortality, and long-term effects of TRAS treatment on efficacy, blood pressure (BP) control, and graft function.

**Results:** TRAS was angiographically confirmed in 42 (56.7%) of the patients. The median time of angiographic evaluation in the TRAS group was 8.8 months, as compared to 48.3 in those who did not have TRAS (p<0.05). Primary Angioplasty (PTA) alone was 67 months (range, 7-166) with a mean pre-procedure creatinine level of 2.2 ± 0.8 mg/dl.

**Conclusions:** Adhered to the prescription was 44.8%.

**SA-PO979**

Urinary Clusterin Predicts Poor Recovery of Renal Function within Four Hours of Transplantation

**Authors:** Timothy J. Pianta,1,2 Philip Peake,3 Nicholas Buckley,1 John W. Pickering,3 Michaela Kelleher,2 Zoltan H. Endre.1,2,3

**University:** 1Prince of Wales Medical School, 2Univ of New South Wales, Australia; 3Department of Nephrology, Prince of Wales Hospital, Sydney, Australia; 4Department of Medicine, Univ of Otago, New Zealand.

**Background:** Impaired graft function after renal transplantation is common and has negative impact on early graft survival post-KTx. Further study of personalized exercise prescriptions following KTx is needed.

**Methods:** A pedometer-based exercise program was associated with lower BP and less impaired fasting glucose early post-KTx. Further study of personalized exercise prescriptions following KTx is needed.

**Results:** Overall transplant graft and patient survival was similar. Graft function at last follow-up in TRAS treated group was 1.9±0.7mg/dl, as compared to 2.2±0.9 in those without TRAS treated with conventional medical therapy (p<0.05).

**Conclusions:** The long-term graft and patient survival were as good in TRAS treated patients as those without TRAS, but with particular benefit in superior graft survival post-intervention. Suspected TRAS should be intervened early with PTA/S as initial treatment.

**SA-PO981**

Treatment of New Onset Diabetes after (Renal) Transplantation (NODAT) by Linagliptin and Insulin, a Comparative Analysis

**Authors:** Pratik Das,1 Soumava Gupta.2

**University:** 1Nephrology, RTP, Kolkata, West Bengal, India; 2Nephrology, RTP, Kolkata, West Bengal, India.

**Background:** NODAT has negative impact on renal allograft survival, cardiovascular risk, and patient survival. Adequate glycemic control may alter the outcome. New generation dipeptidyl peptidase-4 (DPP4) inhibitor linagliptin is now increasingly used to treat type2 DM. The present study has evaluated the safety & efficacy of linagliptin monotherapy in renal transplant recipients with NODAT in comparison to insulin.

**Methods:** 200 renal allograft recipients with stable renal function & without past history of diabetes were evaluated for NODAT by routine 2 hrs oral glucose tolerance test. Those having a 2 hours glucose value more than 200mg/dl were randomly selected for either linagliptin monotherapy (15mg single dose) or insulin treatment. Fasting blood sugar was measured at 4 weeks & HbA1c at 12,24,36,48 weeks. Hypoglycemic and/or other treatment related events were noted.

**Results:** 67 patients fulfilled criteria for NODAT were randomly assigned to either linagliptin (n=35) or insulin only (n=32). Mean baseline glomerular filtration rate (GFR) was 50 mL/min/1.73 m2, elderly donor, AR, and higher level of urinary L-FABP at 0hr were found to be significant risk factors. Furthermore, among the patients who did not develop AR, L-FABP showed more strong association with 2-year poor graft function (p=0.006).

**Conclusions:** Our results demonstrate the possibility that urinary L-FABP might be useful in predicting adverse longterm outcome in KT patients.

**SA-PO980**

Urinary Liver-Type Fatty Acid-Binding Protein (L-FABP) Predicts Graft Outcome up to 2 Years after Kidney Transplantation

**Authors:** Myung-kyu Kim, Sang-Kyung Jo, Won-Yong Cho, Hyoung-kyu Kim.

**University:** Internal Medicine, Korea Univ Anam Hospital, Seoul, Republic of Korea.

**Background:** In kidney transplant (KT) recipient, several new biomarkers have been investigated for predicting early tubular injury and our recent study identified day 2 urinary neutrophil gelatinase associated lipocalin (NGAL) to be useful in predicting slow graft function and adverse 1-year outcome. Here in this study, we further investigated the value of urinary NGAL and liver type fatty acid binding protein (L-FABP) in predicting long term graft function up to 2 years.

**Methods:** This was a single-center, prospective observational study. Urinary NGAL and L-FABP levels at 0 hrs, 2 days and 6 days after KT were measured and the clinical outcomes including acute allograft rejection, proteinuria and estimated glomerular filtration rate (eGFR) were collected during the 2-year period after KT.

**Results:** Of the 69 patients investigated, 14 and 7 experienced slow and delayed graft function (SGF and DGF), and urinary NGAL on day 2 after KT was significantly higher in linagliptine group (1.01±0.21 vs 8.76±2.39 episodes, p<0.05).abnormal liver function test in superior graft survival post-KTx in comparison to insulin.

**Conclusions:** Our results demonstrated the possibility that urinary L-FABP might be useful in predicting adverse longterm outcome in KT patients.
SA-PO982

Febuxostat in Renal Transplant Recipients with Hyperuricemia
Youngjoo Jang, Su-Kil Park, Wonseok Yang. Nephrology, Internal Medicine, Asian Medical Center, Seoul, Republic of Korea.

Background: Febuxostat might be an alternative agent for the patient who cannot use allopurinol, because of more selective and less allergenic. However, information concerning the effectiveness and safety of this drug among renal allograft recipients is not well known.

Methods: Seven renal allograft recipients whose eGFR above 30 ml/min/1.73m² and need urate lowering therapy started febuxostat considering side effects or anxiety of using allopurinol. Febuxostat was administered 40mg daily in 6, 20mg daily and tapered on alternate days in 1 who is on Imuran. Uric acid, serum creatinine, hepatic enzyme, and serum cyclosporine or tacrolimus levels were monitored.

Results: The patients mean age was 60 ± 6.05 years. At the first visit after starting febuxostat ( Median duration 1.18 weeks, Range, 0.18 - 3 weeks ), UA levels ( mg/dl ) were lowered from 8.6 ± 1.74 to 4.6 ± 0.64 ( P = 0.018 ) and the other laboratory changes were not significant.

Conclusions: Febuxostat was well tolerated and no adverse effects were noted.

SA-PO983

Cinacalcet Use at the Time of Transplantation Is Associated with a Significant Risk of Delayed Graft Function in Kidney Transplant Recipients
Laurence F. Weekers,1 Stéphanie M.J.G. Grosch,1 Catherine Bonvoisin,1 Olivier Detry,1 Jean-Marie H. Krzesinski,1 François Jouré,1 Nephrology, CHU Ulg, Liege, Belgium; 2Surgery, CHU Ulg, Belgium.

Background: Calcium-sensing receptor (CaSR) has been implicated in the ischemia/reperfusion cascade in cardiomyocytes and neurons. Renal ischemia/reperfusion occurs at the time of transplantation (Tx), with a deleterious impact on early graft function. Here, we retrospectively investigated whether the use of cinacalcet, a CaSR agonist, in kidney transplant recipients (KTR) influences early graft recovery.

Methods: All KTR from 2007 to 2012 were prospectively included in a database. Patients actively treated with cinacalcet on the day of Tx were retrospectively identified and matched with controls on (i) type of donor: living (LD), deceased after brain or circulatory death (DCD); (ii) cold ischemic time (CIT) ± 1 hour; (iii) residual diuresis ± 500 mL; and (iv) donor age ± 5 years. Delayed graft function (DGF) was defined as dialysis requirement in the middle and lowest tertile, respectively. Characteristics of patients and donors were summarized in the table. The UA level under 6.0 mg/dl was achieved in all subjects at first visit and maintained around 6.0 mg/dl (27.35 ± 7.57 weeks, Range 12.7- 36 weeks ).

The UA level under 6.0 mg/dl was achieved in all subjects at first visit and maintained around 6.0 mg/dl (27.35 ± 7.57 weeks, Range 12.7- 36 weeks ).

Conclusions: These retrospective observations suggest that CaSR activation at the time of Tx impairs early graft recovery.

SA-PO984

Urinary Angiotensinogen Levels Are Associated with Graft Survival in Renal Transplant Recipients
Bernhard M.W. Schmidt, Wilfried Gwinner, Irina Scheffner, Mario Schiffer, Hermann G. Haller, Daniel Kayser. Dept of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany.

Background: Intrarenal activity of the renin angiotensin aldosterone system (RAAS) is an important pathophysiological factor for the progression of renal disease. Urinary angiotensinogen (uAGT) levels have been shown to be a measure of intrarenal RAAS activity. We hypothesized that uAGT levels three months after renal transplantation (rTx) may predict long term graft survival.

Methods: We assessed uAGT in patients participating in our rTx protocol biopsy program using a commercially available assay (IIBL, Japan). All samples had been stored at -80°C for at least five years to assure long term follow up of patients. Primary endpoint of our analysis was death censored graft survival. Tertiles of uAGT were built, Kaplan-Meier curves and log-rank test were used for analysis.

Results: The highest tertile of uAGT levels was associated with worse graft survival (figure), p=0.048, log-rank test. Mean graft survival in the highest tertile was 117.0 (95% CI 112.4, 121.6) months vs. 124.3 (95% CI 121.7, 127.3) and 123.8 (95% CI 120.7, 126.9) in the middle and lowest tertile, respectively. uAGT was weakly correlated with donor age (r= −.16, p= .002) and best creatinine (r= −.21, p< .001) but not modulated by treatment with ACE inhibitors or angiotensin receptor blockers.

Conclusions: In conclusion higher uAGT levels reflecting intrarenal RAAS activity are associated with worse graft survival. This reflects a potential pathophysiological role in graft failure e.g. due to profibrotic effects of angiotensin II and aldosterone. Therapeutic strategies to reduce intrarenal RAAS activity e.g. high dose RAAS blockade might be useful to improve long-term graft survival.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
SA-PO986
Adherence and Graft Survival in Pediatric Kidney Transplant Recipients Who Transition to Adult Services
Oleh M. Akchurin,1 Anita V. Tambil,2 Frederick J. Kaskel,1 Rebecca Hashim,3 Marcela Del Rio.1 1Albert Einstein College of Medicine / Montefiore Medical Center; 2Ponce School of Medicine and Health Sciences.

Background: Adoloscent kidney transplant recipients have a high rate of graft loss. Transition of these patients from pediatric to adult care has been proposed as a risk factor for non-adherence and graft failure. However, data about adherence and graft survival after transition are limited and conflicting.

Methods: Retrospective IRB-approved study. Undetectable and/or sub-therapeutic serum tacrolimus levels and their variability were used to measure adherence and were compared between 2 years before and 2 after transition. Graft survival for pediatric patients during the 2 years before and after transition was compared with 4 years before transition and also with post-transplant of young adults starting 1-year post transplant.

Results: Three groups of patients were analyzed: (1) pediatric patients older than 18 years of age prior to their transition to the adult program (n=71), (2) those who were actually transitioned to the adult program (n=22), and (3) young adults 20-25 years of age who received their first transplant in the adult program (n=62). The median age of group 2 at transition was 22.5 [21.7–23.3] years. Overall, there were no significant differences in adherence in group 2 before and after transition. However, patients with lowest tertile of baseline adherence showed improvement of their adherence after transition, which was significantly different from the patients with highest tertile of baseline adherence, p<0.02. The peak graft loss in all pediatric transplant recipients occurred at 18.3±5.7 years. The rate of graft loss was 0.10 in group 1 (19 losses in 185.6 person-years), 0.06 in group 2 (4 losses in 67.9 patient-years), and 0.07 in group 3 (14 losses in 194.7 person-years). The differences in rate of graft loss between the groups were not statistically significant.

Conclusions: Transition of pediatric transplant recipients to the adult program was not statistically associated with worsening adherence and graft loss rate was not significantly different between the groups. Large-scale studies are needed to assess the nationwide impact of transition on adherence and graft loss.

SA-PO987
SHROOM3, a SNP and Renal Allograft Fibrosis
Madhav C. Menon,1 Peter Y. Chuang,2 Zhenghze Li,3 Weiija Zhang,4 Yi Liu,5 Philip O’Connell,7 Robert B. Colvin,6 Bernd Schroppel,1 John C. He,3 Barbara T. Murphy.1 1Icahn School of Medicine, Mount Sinai, NY; 2Harvard Medical School, MA; 3Westmead Clinical School, Sydney.

Background: The Genomics of Chronic Allograft Rejection (GoCAR) is a multicenter study to understand the mechanisms of chronic allograft nephropathy (CAN).

Methods: Serial allograft biopsies were performed on 589 GoCAR participants. To identify molecular drivers of CAN, we examined genes whose expression level varied in the allograft 3 months after transplantation correlated with indices of allograft dysfunction (chronic allograft dysfunction index score (CADI), eGFR) at 12 months after transplantation in 160 participants.

Results: Higher allograft levels of SHROOM3 transcript, antisensed and correlated with CADI and, inversely with eGFR (P<0.01). Genome wide association studies have previously identified an intronic polymorphism (SNP) in SHROOM3 (rs173192) as associated with CKD. G and A are the major and minor alleles at this site respectively. We observed that allograft expression was higher with the G/A or A/A genotypes, compared to G/G in the donor (P<0.02). Recipients who received allografts from A/G or A/A donors were more likely to have a CADI≥2 at 12-mths than recipients of G/G allografts (OR:1.98; P=0.03). The rs173192 locus is located within a consensus binding sequence for transcription factor 4 (TCF4/TCP7L2) downstream of Wnt-βCatenin signaling, and overexpression of TCF4 increased SHROOM3 expression in H2K cells. The A-allele alone had enhancer activity compared to the G-allele with SHROOM3 promoter-enhancer reporter assays. TGF-β up-regulated SHROOM3 expression through TCF4/TCF7 in a TCF4-mediated mechanism, while SHROOM3 facilitated canonical TGF-β-signaling (Smad3 phosphorylation) and Collagen-I production.

Conclusions: In summary, we found that SHROOM3 expression preceded the development of chronic allograft injury and demonstrated that SHROOM3 facilitates TGF-β-signaling. The A-allele of rs173192 exhibited a TCF4-dependent enhancer function, and confers increased risk for CAN at 12-mths. This is the first description of any CKD-associated SNP that modulates gene expression. SHROOM3 may serve as a novel target therapeutic option to both CAN and CKD.

Funding: NIDDK Support, Other NIH Support - NIAID, Private Foundation Support

SA-PO988
A Model to Identify Patients at Risk for Post-Transplant Kidney Disease after Liver Transplantation
Mario Schiffer,1 Christian Lerch,1 Eleni Evangelidou,2 Hermann G. Haller,1 Tobias J. Weismüller.2 1Medicine, Hannover Medical School, Hannover, Germany; 2Dept of Internal Medicine I, Univ of Bonn, Bonn, Germany.

Background: Following liver transplantation (LT) a significant subgroup of the recipients develops chronic kidney disease (CKD) ranging from mild impairment of kidney function to need for chronic hemodialysis treatment. Since CKD after liver transplantation is multifactorial, so far no reliable models exist to predict the development of CKD in liver graft recipients. The goal of this study was the development of a predictive model to estimate the development of renal function after LT based on parameters known before LT. We prospectively evaluated clinical and biochemical parameters of 328 liver recipients transplanted between 2004 - 2008 and developed ordinal logistic regression models which predict CKD stage 3 or CKD stage 4 or worse after LT. The five most important variables of this model were taken to build a more simplified model for clinical use. These variables were diagnosis of PSC, Hepatitis C, Age, GFR before LT and history of diabetes.

Results: The full model allowed with high accuracy the prediction of CKD stage 3 or CKD stage 4 or worse. The simplified model includes 5 parameters (diabetes mellitus, past diagnosis of cholangitis, hepatic fibrosis, donor age, and periprosthetic filtration rate before LT) and showed a good accuracy in the prediction of CKD ≥ stage 3 (AUC =0.739) resp. CKD ≥ stage 4 (AUC = 0.774). To validate these data we performed an external validation and tested the model in a prospective cohort and confirmed an almost similar accuracy for the prediction of CKD ≥ stage 3 (AUC =0.716) resp. CKD ≥ stage 4 (AUC = 0.639).

Conclusions: In conclusion our model allows based on five parameters known before LT the identification of patients at risk to develop CKD Stage 3, 4 or worse after LT. Funding: Government Support - Non-U.S.

SA-PO989
Serum Cystatin C in Renal Transplantation: Beyond GFR Estimation, a Prognosis Marker?
Ingrid Masson, Nicolas Maillard. Nephrology Dialysis Renal Transplantation, Univ Hospital, Saint-Etienne, France.

Background: In renal transplantation, death with a functioning graft remains one of the major causes of graft loss. For many years, renal function impairment is strongly associated with cardiovascular and all cause mortality. Whether this association holds true for kidney transplant recipients (KTR) is unclear. This uncertainty is likely to be due, in part, to the fact that glomerular filtration rate (GFR) estimation based on serum creatinine (SCr) does not always provide an accurate evaluation of the graft function in KTR. As compared to SCR, we have recently shown in a large cohort of KTR that serum cystatin C (SCysC) is a much better marker of GFR.

Herein, we sought to study the ability of the 1-year-post-transplant renal function to predict all cause mortality according to the methods used to assess GFR.

Methods: Three hundred and forty two consecutive KTR for whom a measurement of GFR by inulin clearance was available at 1 year post-transplant were included. SCr and ScysC were measured with standardised methods. The association of the 1-year inulin clearance value with the 1-year MDRD Study equation value and the 1-year CKD-EPI ScysC equation value with all cause mortality was studied by ROC analysis and Cox model.

Results: During a median follow-up of 145 months, 70 KTR died. Mean (±SD) inulin clearance at 1-year-post-transplant was 46 (±19) ml/min/1.73m². Aeras under the ROC curves were similar for inulin and CKD-EPI ScysC equation values (0.564 and 0.550, respectively, NS), and were both significantly superior to that of the MDRD equation (0.483, p<0.01). In Cox analysis, while all types of GFR evaluations were significantly associated to graft loss, only an inulin and a CKD-EPI ScysC equation values below 45 ml/min/1.73m² were associated with an excess risk of mortality (HR of 1.85 vs 1.01 for both inulin and CKD-EPI ScysC vs MDRD, respectively).

Conclusions: We conclude that ScysC-based GFR estimation might better predict KTR outcome as compared to a traditional SCR-based estimation. The one-year post-transplant GFR value given by the CKD-EPI ScysC equation should be further evaluated as a potential surrogate marker for both graft and patient survival.

SA-PO990
The Performance of Cystatin C (CysC) and Creatinine Based CKD-EPI Equations to Estimate GFR in Kidney Transplant (KTx) Recipients
Mira T. Keddis, Hatem Amer, Nick Voskoboiev, Andrew D. Rule, John C. Lieske. Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Performance of Cystatin C- and creatinine-based CKD-EPI equations published in 2012 have not been evaluated in a large cohort of stable KTx recipients.

Methods: A prospective cross-sectional cohort of KTx patients presenting for routine annual visits and who are more than 1 year from transplant were actively recruited. GFR was measured by isothamal clearance (mGFR). Plasma CystC was analysed by particle-enhanced immunnoassay assay, while serum creatinine (Cr) was measured by enzymatic assay, both traceable to international reference materials. eGFR was calculated using published 2012 CKD-EPI equations. Overall bias and accuracy (within 10% and 30%) for each eGFR equation were calculated.

Results: 1151 KTx patients were studied. Mean age was (mean±SD) 56.0 ± 14.2 years; 56.5% were male and 85.6% were Caucasian. mGFR was 55.7 ± 20.7 ml/min/1.73m².

Conclusions: The cystatin-C-based GFR equation performed better than the creatinine-based equation in a large cohort of stable KTx patients. CystC and CystC-Cr equations had significant negative bias.

Funding: Pharmaceutical Company Support - Gentian

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

853A
SA-PO991
Endothelin-1 and Kidney Function in Renal Allograft Recipients
Rupesh Raina,¹ Michael S. Simonson,² Beth A. Vogt,³ Joshua J. Augustine,² Donald E. Hricik,² ¹Dept of Pediatrics, Nephrology, Univ Hospitals Rainbow Babies and Children’s Hospital, Cleveland, OH; ²Dept of Medicine, Nephrology, Univ Hospitals Case Medical Center and Case Western Reserve Univ, Cleveland, OH.

Background: Endothelin-1 (ET-1), a vasoconstrictor and pro-inflammatory peptide, is elevated in chronic allograft nephropathy, and studies in experimental models suggest that ET-1 is a determinant of graft loss. However, whether elevated ET-1 is associated with allograft dysfunction in humans is unclear.

Methods: We examined the association between urinary ET-1, a non-invasive surrogate for ET-1 in kidney cortex, and renal function in an exploratory cross-sectional study of 28 renal allograft recipients 3 to 56 months post-transplant. ET-1 was measured by ELISA in spot urine specimens and corrected for urinary creatinine. Glomerular filtration rate was estimated (eGFR) by the simplified MDRD equation.

Results: ET-1 correlated inversely with eGFR (r = -0.599, P < 0.01) independent of recipient age, sex, and donor age. ET-1 did not correlate with urinary albumin/creatinine ratio nor with IgG/creatinine, a marker of increased glomerular permeability. ET-1 was modestly elevated in patients with posttransplant hypertension (Systolic Blood Pressure > 140 mm Hg) compared to normotensive allograft recipients (5.4 ± 2.6 vs. 3.2 ± 1.5 pg/mg creatinine, P = 0.02). Consistent with findings in experimental models, ET-1 correlated with a urine biomarker of allograft inflammation, macrophage chemotactic protein-1 (r = -0.638, P < 0.01). ET-1 was higher in participants with prior acute rejection (6.5 ± 1.6 vs. 3.9 ± 2.3 pg/mg creatinine, P = 0.002) compared to those without rejection but not in those with prior delayed graft function (4.4 ± 2.5 vs. 4.3 ± 2.2, P = 0.937).

Conclusions: These cross-sectional data are consistent with the hypothesis that elevated ET-1s is associated with low eGFR and inflammation in kidney transplant recipients, particularly in patients with prior episodes of acute rejection.

SA-PO992
Tubular Biomarkers in Serum and Urine of Stable Kidney Transplant Patients – Prospective Observational Study
Bertram Hartmann, Frieder Keller. ¹Internal Medicine I, Nephrology, Univ Hospital, Ulm, Germany.

Background: The surveillance and control of kidney function rely on serum creatinine and glomerular filtration rate (GFR) while interstitial fibrosis and tubular atrophy are leading pathomorphological findings in kidney transplant biopsies.

Methods: This is a prospective observational study in a cohort of 39 stable kidney transplant patients. Lisa Schupp and the authors measured on routine appointments standard (p < 0.01) independent of recipient age, sex, and donor age. ET-1 did not correlate with urinary albumin/creatinine ratio nor with IgG/creatinine, a marker of increased glomerular permeability. ET-1 was modestly elevated in patients with posttransplant hypertension (Systolic Blood Pressure > 140 mm Hg) compared to normotensive allograft recipients (5.4 ± 2.6 vs. 3.2 ± 1.5 pg/mg creatinine, P = 0.02). Consistent with findings in experimental models, ET-1 correlated with a urine biomarker of allograft inflammation, macrophage chemotactic protein-1 (r = -0.638, P < 0.01). ET-1 was higher in participants with prior acute rejection (6.5 ± 1.6 vs. 3.9 ± 2.3 pg/mg creatinine, P = 0.002) compared to those without rejection but not in those with prior delayed graft function (4.4 ± 2.5 vs. 4.3 ± 2.2, P = 0.937).

Conclusions: These cross-sectional data are consistent with the hypothesis that elevated ET-1s is associated with low eGFR and inflammation in kidney transplant recipients, particularly in patients with prior episodes of acute rejection.

SA-PO993
Application of an Established CKD Biomarker Signature to Predict Chronic Renal Impairment after Solid Organ Transplantation
Jens Drube,¹ Eric Schiffer,¹ Harald Mischak,² Christian Lerch,¹ Hermann G. Halter,¹ Mario Schiffer.¹ ¹Pediatrics, Hannover Medical School; ²Mosaiques Diagnostics GmbH, ³Nephrology, Hannover Medical School.

Background: After solid organ transplantation (SOT) some patients develop CKD. This is a serious clinical problem as CKD negatively affects the survival of organs and patients. Momentarily, it is impossible to predict prior to transplantation patients at risk to develop CKD after SOT. Therefore, therapies cannot be adjusted to individual CKD risk profiles. The aim of this study was to test the ability of a CKD biomarker-pattern to detect previously published by Good et al. 2010 to predict CKD after transplantation using prior biomarker data in urine samples. Methods: From the prospective German RECAB registry we generated two groups of transplanted subjects, a case group (lung n=5, heart n=5, liver n=1) and a control group (lung n=7, heart n=3, liver n=2) who had a GFR below 55 or above 70 ml/min/1.73m² three months after transplantation, respectively. We conducted a capillary electrophoresis and mass spectrometry proteome analysis on urine obtained before transplantation. Each proteome profile was compared to the pattern published by Good et al. 2010. Additionally, we analyzed which individual biomarkers of the pattern correlated strongest with CKD outcome after transplantation.

Results: The biomarker-pattern published by >Good et al. was able to predict renal impairment three months after SOT with a sensitivity of 91% and specificity of 67%. The AUC of the ROC analysis was 0.71. Four of the 237 previously defined biomarkers showed a significant correlation with the GFR three months after SOT, another ten showed a significant trend, when P-values corrected for multiple testing.

Conclusions: This study shows that the biomarker-pattern published by Good et al. 2010 can predict the development of CKD three months after SOT from urine obtained before transplantation. These results can be used to refine the biomarker pattern so it can be used in clinical practice.

Funding: Government Support - Non-U.S.

SA-PO995
Urinary Super Saturation in Newly Transplanted Kidney Transplant Recipients: Cause for Concern and Action
Hatem Amar,¹ Elizabeth C. Lorenz,² Dawn S. Milliner,³ Andrew D. Rule,¹ Eric J. Bergstrahl,² John C. Lieske.¹ ¹Nephrology and Hypertension, Mayo Clinic, Rochester, NY; ²Health Sciences Research, Mayo Clinic.

Background: Renal allograft are vulnerable to calcification compared to native kidneys which is a cause for decreased renal allograft function. Risk factors include pre transplant duration of dialysis and secondary hyperparathyroidism. Urinary composition plays a significant role. No systematic evaluation of post-transplant urine supersaturation has been performed.

Methods: Funded by the Rare Kidney Stone Consortium we prospectively enrolled a cohort of 100 consecutive incident kidney only transplant recipients. The study subjects completed a 24-hour urine collection for a super saturation profile 2-4 weeks from transplant.

Results: Age 52±13.3 years, males 61%, Caucasian race 90%, pre-emptive transplantation 57%, deceased donor 74%, mean eGFR 74±20 ml/min/1.73m², serum phosphorus 3.9±2.3 pg/mg creatinine, P=0.002 compared to those without rejection but not in those with prior delayed graft function (4.4 ± 2.5 vs. 4.3 ± 2.2, P = 0.937).

Conclusions: These cross-sectional data are consistent with the hypothesis that elevated ET-1s is associated with low eGFR and inflammation in kidney transplant recipients, particularly in patients with prior episodes of acute rejection.

Funding: NIDDK Support, Other NIH Support - National Center For Advancing Translational Sciences (NCATS)

SA-PO996
Vitamin D Status and Long-Term Outcomes after Kidney Transplantation
Charlotte A. Keyzer,¹ Ineke J. Riphagen,¹ Michel M. Joosten,¹ Gerjan Navis,¹ Charlotte A. Keyzer,¹ Ineke J. Riphagen,¹ Michel M. Joosten,¹ Gerjan Navis,¹

Background: Recent studies linked 25OH but not 1,25OH2 vitamin D deficiency to lower GFR one year after kidney transplantation (KTrx), but whether this discrepancy also holds for long-term hard outcomes is unclear. We investigated the value of circulating 25OH and 1,25OH2 vitamin D levels as risk factors for graft failure and mortality in stable renal transplant recipients (RTR).

Conclusions: For the first time we present a series of urine super saturation profiles in incident kidney transplant recipients. A significant proportion of transplant recipients have urine super saturated above the reference for a variety of crystals putting them at risk for intra graft calcification and crystal deposition.

Funding: NIDDK Support, Other NIH Support - National Center For Advancing Translational Sciences (NCATS)
SA-PO996

Initial Bone Mineral Density Status Predicts the Development of New Vertebral Fractures during Kidney Transplantation
Carlo M. Alifreti, Brigida Brezzi, Fabio Massimo Ulivieri, Maria Meneghini, Riccardo Florenzi, Anna Regalia, Francesco Barretta, Manuela Curreli, Maria Daniela Croci, Maria Pia Rastaldi, Piergiorgio Messa.

Background: Bone disorders and related skeletal fractures are common events during kidney transplantation (KTx). In our study we evaluated: 1) the prevalence of asymptomatic vertebral fractures (VF) at baseline and 1 year after KTx; 2) the factors associated with the occurrence of new VFx during the first year after KTx; 3) the role of bone mineral density (BMD) in the prediction of new VFx.

Methods: 109 consecutive KTx patients (57 M-age range 17-73 years) were evaluated for VF with dual energy X-ray absorptiometry (DXA). A flowchart (Genant et al. Am J Roentgenol 1993 Sep;161:1137-48). In addition to the routine biochemical evaluation, FGF-23, Fetuin, OPG levels were compared with VFx vs nonprogressors.

Results: VFx were present in 22% and 37% of pts at 1st and 12th mth resp. VFx at 12 mths correlated only with serum phosphorus (P) (directly) and PTH (inversely), whereas at 12 mths only with the number of fractures at baseline. Of the studied patients, 25% had one or more new VFx during the first 12 mths of KTx (VFx-PROG). VFx-PROG had lower BMD at baseline, which was a good predictor for new VFx (ROCAU:0.6962), with no difference in PTH, Vit-D status, cumulative steroid doses, FGF-23, Fetuin, and OPG levels compared with VFx nonprogressors.

Conclusions: According to our results: 1) the prevalence of VFx is high in KTx patients and 25% of them have at least one new VFx during the first year after KTx; 2) baseline BMD might be predictive of the occurrence of new VFx; 3) mineral metabolism related parameters do not seem to play a major role in the occurrence of new VFx.

SA-PO997

Can Steroids Be Withdrawn Safely in Routine Practice? Prospective, Four-Year Data from the Mycophenolic Acid Observational Renal Transplant (MORE) Study

V. Ram Peddi, Kimi Ueda Stevenson, Anne Wiland, Kevin M. McCague.

Background: Corticosteroid withdrawal (CSW) after kidney transplantation is widespread. The prospective data are lacking on the long-term implications for acute rejection, graft survival and graft function vs corticosteroid continuation (CSC) in routine clinical practice.

Methods: Prospective data were analyzed from the observational, four-year MORE study of two adult kidney transplant patients receiving mycophenolic acid at 40 centers in the US, managed according to local practice. Cox regression analysis adjusted efficacy outcomes for recipient gender, African vs non-African American, deceased vs living donor, PRA status (>30% vs ≥30%), delayed vs immediate graft function and baseline mycophenolic acid dose (≤2g/day vs >2g/day).

Results: 363 CSW and 509 CSC patients were analyzed. All patients received tacrolimus, with similar trough levels in the CSW and CSC cohorts. The observed four-year incidence of efficacy events in the CSW vs CSC groups was 10.1% vs 14.3% for biopsy-proven acute rejection (BPAR, p=0.05), 13.1% vs 6.3% for graft loss (p=0.030) and 4.8% vs 5.0% for death (p=0.65). Cox regression analysis showed hazard ratios (HR) for CSW vs CSC to be 0.75 (95% CI 0.46, 1.21; p=0.25) for BPAR, 0.35 (0.12, 0.86; p=0.032) for graft loss and 0.82 (0.31, 2.69; p=0.68) for death. Mean estimated GFR (CKD-EPI formula) for
Conclusions: The involvement of txp PharmDs in CV risk factor management led to improved prescribing of medications with compelling indications and lower SBPs. Further studies are warranted to determine the impact of txp PharmD involvement on long-term KTX outcomes.

SA-PO1001
HERAKLES at Month 24: Maintained Superior Renal Function in Patients on an Everolimus-Based Calcineurin Inhibitor Free Regimen Compared to Standard Cyclosporine/Mycophenolate and Low Cyclosporine/Everolimus

Martin G. Zeier,1 Wolfgang Arns,1 F. Lehner,1 Markus Guba,1 Claudia Sommerer,1 Hans-Hellmut Neumayer,1 Johannes Jacobi,1 Peter Weithofer,1 Daniel Baeumer,2 Christoph May,1 Eva-Maria Paulus,1 Oliver Witzke,1 Klemens Budde.1 1HERAKLES Study Group, Germany; 2Novartis Pharma Nuremberg, Germany.

Background: To follow up(FU) on the evolution of renal function(RF) of 3 different immunosuppressive regimen with different calcineurin inhibitor(CNI) exposure at month(Mo)24 post renal transplantation(Tx).

Methods: 802 patients (pts) were included in an 1year, prospective, open-label, randomized(RDZ), controlled multi-center study. After induction with basiliximab pts received cyclosporine A(CsA), enteric-coated mycophenolate sodium(EC-MPS) + steroids. 3Mo post Tx 499 pts were RDZ 1:1:1 to either continue standard(STD) CsA(100-180ng/ml) + EC-MPS(n=166), or to convert to a CNI-free regimen + everolimus(EVR;5-10ng/ml) + EC-MPS(n=171) or to convert to CNI-low regimen + EVR(3-8ng/ml) and reduced CsA(50-75mg/ml;n=162). Mo24 FU visit was performed by 131(96%)STD, 132(96%) CNI-free and 125(93%) CNI-low pts. RF (primary endpoint) was assessed as Glomerular Filtration Rate (cGFR;Nankivell).

Results: Trough levels: CsA 99±32ng/ml in STD, 83±34ng/ml in CNI-low pts; EVR 6.7±3.1ng/ml in CNI-free, 6.2±2.3ng/ml in CNI-low pts. RF was similar at RDZ and had significantly improved at Mo12 by +5.6mL/min/1.73m2(95%CI:[+2.9;+8.3];p<0.001) in favor of CNI-free regimen and remained significantly improved by +4.8mL/min/1.73m2 at Mo24 (ITT;p=0.014). Rejections since RDZ were similar in all 3 groups (12%STD,14%CNI-free,12%CNI-low), safety profile was overall comparable.

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

Underline represents presenting author/disclosure.

856A
SA-PO1002

HERAKLES at Month 24: Follow-Up Results on Efficacy and Safety of Three Different Treatment Regimens in De Novo Renal Transplant Patients Demonstrate Options for Individualized Immunosuppression

Background: To follow-up (FU) on safety and efficacy of 3 different immunosuppressive (IS) regimens (1-3) in 24 months (Mo) after renal transplantation (Tx).

Methods: 802 patients(pts) were included in this 1-year, prospective, open-label, randomized (RDZ), controlled, multi-center study. After induction therapy with basiliximab all pts received cyclosporine A(CsA), enteric-coated mycophenolate sodium(EC-MPS) + steroids. 3 Mo post Tx 499pts were RDZ to 1:1:1 to either continue standard(STD) treatment CsA(100-180ng/ml)=EC-MPS (n=166) or convert to a calcineurin inhibitor (CNI)-free regimen with everolimus (EVR) (5-10ng/ml) + EC-MPS (n=171) or to a CNI-low regimen with EVR (3-8ng/ml) = reduced CsA (50-75ng/ml) (n=162). All pts continued on steroids. Mo24FU visit was performed by 131(96%)STD, 132(96%)CNI-free and 125(93%) CNI-low regimen pts of the FU-population.

Results: From RDZ to Mo24 BPAR was reported in 17/144(12%) STD, 20/146(14%) CNI-free and 17/141(12%) CNI-low pts (ITT). Two (1%) deaths occurred in the CNI-low, none in the other groups. 1 (1%) graft loss was observed in the STD and 3(3%) in the CNI-free group. Premature discontinuation due to AEs occurred in 1/147(1%) STD, 3/148(2%) CNI-free and 1/141(1%) of CNI-low pts (safety-pop) from Mo12 to Mo24. Renal function expressed as cGFR (Nankivell) was significantly improved by +4.8mL/min/1.73m2 for CsA pts, resulting in a difference of 10.6mL/min/1.73m2 in favor of EVR (p=0.007). Mean eGFR of pts who remained to Mo48 on the assigned EVR regimen: +8.7mL/min/1.73m2 (+16.0;+1.4) n=20;p=0.02) over CNI pts (n=31).

Conclusions: Reduced CsA in combination with EVR did not result in better RF compared to STD regimen with EC-MPS. However, CNI-free regimen lead to better RF maintained for 2 years, confirming previous reports.

Funding: Pharmaceutical Company Support - Novartis Pharma Germany

SA-PO1004

Outcome on Renal Function, Efficacy and Safety in Living-Donor Kidney Transplant Recipients after Conversion from a Calcineurin Inhibitor to an Everolimus Based Regimen: Post Hoc Subgroup Analysis from the ZEUS Study

Background: To study renal function and patient outcome in subgroup of living-donation (LD) kidney de novo transplant recipients after conversion from calcineurin inhibitor (CNI) therapy to an everolimus (EVR) based regimen.

Methods: Post hoc subgroup analysis on LD recipients from a prospective, open-label, controlled, multi-center study on renal transplant (Tx) patients that were randomized (RDZ) at month (Mo) 4.5 post Tx to an immunosuppressive regimen consisting of either EVR + entero-coated mycophenolate sodium (EC-MPS) or cyclosporine (CsA) plus EC-MPS.

Results: 300 kidney transplant recipients were RDZ to continue CsA or convert to EVR at 4.5Mo post Tx. Results from 80 LD recipients (EVR: N=42; CsA: N=38) were analyzed post hoc. In this subgroup population, adjusted estimated GFR at Mo12 (Nankivell formula) was 74.2(95%CI [70.5;78.0]) mL/min/1.73m2 for EVR pts vs 63.6(95%CI [59.5;67.8]) mL/min/1.73m2 for CsA pts, resulting in a difference of 10.6mL/min/1.73m2 in favor of EVR group (p<0.001). From RDZ to Mo12, adjusted estimated GFR increased by a mean of 9.9(95%CI [6.2;13.7]) mL/min/1.73m2 with EVR vs 6.6(95%CI [4.8;8.5]) mL/min/1.73m2 in CsA group (p<0.001) in CsA subgroup. Mean trough levels at Mo12: 7.1±2.1mg/mL for EVR vs 11.7±3.2mg/mL for CsA pts. In EVR group 6 Banff EP episodes (5 of them Banff I), occurred vs 1 Banff in CsA group (p=0.109). One graft loss occurred in the CsA group, none with EVR. Discontinuation due to AEs occurred in 6 EVR pts (14.3%) and 5 CsA pts (13.2%) between Mo6 and Mo12.

Conclusions: After 24 Mo IS regimen using EVR with low-dose or without CNI-exposure is an efficacious and safe therapeutic approach offering the opportunity for an individualized IS.

Funding: Pharmaceutical Company Support - Novartis Pharma GmbH Germany
SA-PO1005

Living Renal Donation: Emotional Status of the Donor

Claudia Sommerer 1
Ralf A. Dikow 2
Matthias Schaeler 2
Christian Moutz 2
Vedral Schwenger 2
Martin G. Zeier 2
1 Nephrology, Universitatsklinikum Heidelberg, Germany; 2 Pathology, Universitatsklinikum Heidelberg, Germany

Background: The benefits of living kidney donation for recipients are well-known. Nevertheless, donor safety is of importance at all time. Data on the impact of living donation on the emotional status including depression and anxiety are rare.

Methods: In an open, prospective observational study, renal allograft donors were evaluated with respect to psychosocial and emotional outcome after living donation. Standardized questionnaires (HADS, SF-12) as well as additional questions related to living donation were used.

Results: Altogether, 128 renal allograft donors were evaluated (86 male, median age 49.1 ± 11.4 years, mean age at time after transplantation 3.7 ± 3.8). None of the donors had any serious post-transplant complications and the renal function was stable. 13 donors (13%) assessed general health worse compared to prior to transplantation. Emotional role function was decreased in 8% of the donors. Concerning the emotional status, most of the patients demonstrated normal HADS anxiety scores, with pathological results in 6 patients (5%). Depression scale showed pathological results in 15 donors (13%). Patients with pathological anxiety scores were more likely to be parents, foreign origin and living alone. There was no difference concerning gender, age or renal function. Concerning the HADS depression scale, no difference in the patient cohort with and without depression symptoms could be noticed. Health status was more often judged as worse in patients with pathological results in one of the sub-scales. Renal allograft function or recipient health had no relevant impact on the emotional status of the donor.

Conclusions: A minority of renal donors demonstrated an impact of renal donation on the emotional status or anxiety and depression symptoms. Health status was impacted by pathological results. Parenthood, foreign origin and living alone were identified as risk factors for anxiety symptoms.

SA-PO1006

Evolution of Allograft Fibrosis and Related Markers in Kidney Transplant Patients under Treatment with Cyclosporine and Everolimus

Luís Eduardo Becker 1
Ruediger Walther 2
Martin G. Zeier 2
Claudia Sommerer 2
1 Nephrology, Universitatsklinikum Heidelberg, Germany; 2 Pathology, Universitatsklinikum Heidelberg, Germany

Background: In kidney transplant, protocols to avoid calcineurin inhibitor chronic toxicity are continuously developed in order to prevent allograft fibrosis and function loss. We analyzed the histological evolution of fibrosis and the expression of related markers after conversion from cyclosporine (CsA) to everolimus performed in stable kidney transplant patients.

Methods: Forty patients maintained on prednisone, sodium mycophenolate and CsA were included in our analysis. After 4.5 months of transplantation, patients were randomised to either continue the current CsA regimen (n = 21) or gradually convert from CsA to everolimus (n = 19). Histological sections of kidney biopsies obtained prior to CsA therapy were stained using Sirius red and were analyzed by miles. TGFß tubular expression reduced significantly in the everolimus group compared to the CsA group (p = 0.04). Expression of both PDGF and HIF1A remained stable and was similar in both groups.

Conclusions: A minority of renal donors demonstrated an impact of renal donation on the emotional status or anxiety and depression symptoms. Health status was impacted by pathological results. Parenthood, foreign origin and living alone were identified as risk factors for anxiety symptoms.

SA-PO1007

mTOR Inhibition and Evolution of Urinary Protein Excretion in Non-Renal Transplant Patients – 24 Month Results from 719 De Novo Liver Transplant Patients

G. Junge, Sven Kohler, Ute Eisenberger, Heike Schwende, Wolfgang Arns. HZ304 Study Group

Background: The interplay of glomerular filtration and tubular absorption of proteins with various molecular weights defines pattern/magnitude of urinary protein excretion (UPE). Increased UPE(proteinuria) serves as clinical surrogate for renal injury and progressive damage affecting different parts of the nephron. mTOR inhibitor(i) treatment has also been associated with increased UPE not only in KTx but also non-renal Tx recipients(R).

Methods: Data from study HZ304(NCT00622869), a 24-month(M), randomized, multicenter study in 719 de novo LTxR comparing everolimus(EVR 3-8ng/mL) plus reduced tacrolimus(TAC 3-5ng/mL) to standard TAC(TAC C 6-10ng/mL). Total daily UPE, measured as U/PUC ratio, as well as a set of different urinary proteins is described to allow a more detailed investigation of the origin/course of UPE in de novo LTxR receiving EVR.

Results: UPE was higher with EVR+TAC compared to TAC with highest values at M6 (290mg/d) followed by decrease to M12 and M24 (194mg/d) compared to 158mg/day in TAC at M24. UPE ~500mg/d occurred in 18.1% of TAC-C vs 23.6% in EVR+TAC (18.9% when EVR C0 was 3-8ng/mL). Analysis of urinary protein electrophoresis and levels of b2MG(12kDa), a1MG(26 kDa), Alb(70 kDa), Tf(80 kDa), and IgG(150 kDa) suggested mixed glomerular/tubular UPE for TAC while patients on EVR with new proteinuria showed incomplete partial micro-molecular UPE (tubular type).

Conclusions: Clinical observations suggest that mTOR inhibition might be associated with increased UPE, potentially due to enhanced cell wall permeability and podocyte dysregulation. However, in case of mTORi facilitated CNI reduction the improvement in glomerular blood flow and consequently higher overall protein filtration in combination with mTOR-dependent reduction in tubular protein reabsorption may also contrive to increased UPE.
SA-PO1009
The Risk Factors for mTOR Inhibitors Associated Proteinuria in Kidney Transplant Recipients  Hung-Tien Kuo, Hung-Chun Chen. Nephrology, Kaohsiung Medical Univ Hospital, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

Background: The use of mammalian target of rapamycin inhibitor (mTORI) after kidney transplantation has been associated with an increased risk of proteinuria. The purpose of this study is to investigate the risk factors for proteinuria after mTORI treatment in kidney transplant recipients in a Taiwan medical center.

Methods: A total of 55 adult (46.7±10.6 years old) deceased donor kidney transplant recipients who received mTORI treatment (sirolimus/everolimus 47/8, started at 351 days post-transplant in median) were enrolled. They had no overt-proteinuria before the initiation of mTORI treatment. The risk factors for mTORI-associated proteinuria were investigated using multivariate logistic regression analysis. The impact of mTORI-associated proteinuria on overall graft survival was investigated using multivariate Cox-regression analysis.

Results: Median follow-up after the initiation of mTORI treatment was 1603 days. During this time, there were 15 outcomes of new-onset proteinuria (27.3%) and 2 outcomes of overall graft failure (3.6%). After adjusting for major confounding factors in the logistic regression model, the independent risk factors for mTORI-associated proteinuria included renal function impairment (initial eGFR<30 vs. ≥60ml/min, odds ratio=91.7, P<0.01; 30-60 vs. ≥60ml/min, 3.1, P=0.20) and high body mass index (BMI≥25 vs. <25 Kg/m², 7.84, P=0.05). In the multivariate Cox regression model, mTORI-associated proteinuria was not significantly associated with the risk of overall graft failure.

Conclusions: In our study cohort, renal function impairment and obesity at the initiation of mTORI treatment were strong predictors for proteinuria. However, the impact of mTORI-related proteinuria on overall graft survival in kidney transplantation cannot be supported in the current analysis.

SA-PO1010
Medication Safety: The Next Big Challenge to Improving Long-Term Outcomes in Kidney Transplantation? David J. Taber, Justin Spivey, Nicole A. Pilch, John McGillicuddy, Kenneth Chavin, Frank Treiber, Prabhakar Baliga, Titte Srinivas. MUSC, Charleston, SC.

Background: Immunosuppressant regimens have significantly decreased acute rejection, but have potentially increased the risk of graft loss driven by infections, over-immunosuppression, adverse drug reactions, and medication errors.

Methods: This was a post-hoc analysis of a prospective randomized controlled trial that included adults that had a solitary renal transplant between 3/09-7/11. Data collection and analysis included sociodemographics, medications, adverse drug reactions, and medication errors. Patients were divided into groups based on the development of a clinical significant medication error, defined as a significant or severe medication error contributing to hospitalization, and analyzed for post-transplant clinical outcomes.

Results: 200 patients were included in this analysis; 233 medication errors were identified, with 64% of the cohort having at least one error. Immunosuppressant medications were associated with 48% of these errors. There was a total of 327 significant adverse drug events. Patients that experienced at least one med error had 1.8 times the risk of developing an adverse drug event (90% vs. 82%, p=0.128). 28 patients (12%) experienced a clinically significant medication error (CSME). Patients that experienced CSMEs had a statistically significant or severe medication error contributing to hospitalization and analyzed for post-transplant clinical outcomes.

Results: 200 patients were included in this analysis; 233 medication errors were identified, with 64% of the cohort having at least one error. Immunosuppressant medications were associated with 48% of these errors. There was a total of 327 significant adverse drug events. Patients that experienced at least one med error had 1.8 times the risk of developing an adverse drug event (90% vs. 82%, p=0.128). 28 patients (12%) experienced a clinically significant medication error (CSME). Patients that experienced CSMEs had a statistically significant or severe medication error contributing to hospitalization and analyzed for post-transplant clinical outcomes.

Results: 200 patients were included in this analysis; 233 medication errors were identified, with 64% of the cohort having at least one error. Immunosuppressant medications were associated with 48% of these errors. There was a total of 327 significant adverse drug events. Patients that experienced at least one med error had 1.8 times the risk of developing an adverse drug event (90% vs. 82%, p=0.128). 28 patients (12%) experienced a clinically significant medication error (CSME). Patients that experienced CSMEs had a statistically significant or severe medication error contributing to hospitalization and analyzed for post-transplant clinical outcomes.

Conclusions: Clinically significant medication errors occur in one out of every eight kidney transplant recipients and lead to an increased risk hospital readmissions, cost of care and graft loss.

SA-PO1011
Are Thiazide Diuretics Safe and Effective Antihypertensives in Kidney Transplantation?  David J. Taber, Titte Srinivas, Nicole A. Pilch, Boje S. Thomas, Maria N. Salazar, Kenneth Chavin, Prabhakar Baliga, Leonard Egge. MUSC, Charleston, SC.

Background: There is limited data assessing the safety and efficacy of thiazides as antihypertensives in kidney transplant (KTX) recipients.

Methods: This was a longitudinal retrospective cohort study of all KTX recipients transplanted between 2000-08 with follow-up through 2012. Patients were grouped based on receiving thiazide therapy. Safety and efficacy comparisons were made within thiazide patients and between groups.

Results: 1,093 KTX were included in this study (thiazide group: 108, control group: 985). KTX that received thiazides had a more aggressive HTN phenotype, demonstrated by being older (53±11 vs 48±13 yrs, p<0.001), more pre-KTX hypertension (97% vs 88%, p=0.004), diabetes (36% vs 27%, p=0.035), more post-KTX HTN medications (2.1±0.9 vs 1.4±1.0, p<0.001) and more HTN medication changes (10.9±4.4 vs 5.7±3.4, p<0.001, see Table 1). Despite this, means BPs were similar between thiazide and controls (139/77 vs 136/77) while receiving thiazide therapy. Safety analysis revealed thiazide patients were more likely to be readmitted to the hospital (70% vs. 53%, p<0.001), develop hyperkalemia (56% vs. 38%, p<0.001) or hypokalemia (28% vs. 18%, p=0.010), but had similar rates of hypotension, eGFRs, graft loss and death. After controlling for age and comorbidity differences, hospital readmissions were fairly similar between groups (OR 1.49, 95% CI 0.92–2.40). Within the thiazide cohort, paired repeated measures analysis demonstrated SBP (147±17 to 139±18, p<0.001) and DBP (79±9 to 77±11, p<0.001) were reduced after thiazide initiation.

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

Underline represents presenting author/disclosure.

859A
Conclusions: Based on long-term outcomes, thiazides appear to be safe and effective antihypertensives in kidney transplantation; in the short-term, thiazides may increase the risk of hospitalization and potassium disturbances. Prospective RCT are warranted to confirm results.

SA-PO1012

Improving or Maintaining Renal Function over 5 Years with Belatacept or Cyclosporine (CsA): Insights from the BENEFIT and BENEFIT-EXT Long-Term Extension (LTE) Studies F. Vincenti,1 L. Rostaing,2 A. Durrbach,3 K. Rice,4 L. Pupim,5 J. Grinyo.6

1UCSF, USA; 2Univ Hosp Toulouse, France; 3Bicêtre Hosp, France; 4Baylor Univ Med Ctr, USA; 5Bristol-Myers Squibb, USA; 6Univ Hosp Bellvitge, Spain.

Background: In BENEFIT and BENEFIT-EXT, the early renal function benefit observed in belatacept(bela)-treated patients (pts) was maintained over 3 years with a consistent safety profile. Here we report renal function outcomes over 5 years in the LTE cohort of both studies.

Methods: In both Phase III studies, adult kidney transplant recipients (living or SCD in BENEFIT; ECD in BENEFIT-EXT) were randomized to a more or less intensive (LI) regimen of bela or CsA. Pts entered the LTE after 3 years. GFR stages at Months (Mos) 12 and 60 are shown in the Figure. Post hoc analyses reported here assessed shifts in cGFR stage between Mos 12 and 60 in the LTE cohort, with the approved LI regimen vs. CsA. To be analysis eligible, patients in the LTE had to have a GFR value at Mo 12 and Mo 60. In BENEFIT, 139 of 165 pts in bela LI and 102 of 136 in CSA were eligible; in BENEFIT-EXT, 103 of 113 LI and 79 of 87 CSA were eligible.

Results: In BENEFIT, from Mo 12–60, 77 of 85 LI pts and 21 of 43 CsA pts in Stage 2 maintained or improved their GFR stage. Among Stage 3 pts, 33 of 35 LI and 40 of 52 CsA maintained or improved their GFR stage. Among Stage 4 pts, 3 of 4 LI and 7 of 12 CsA maintained or improved their GFR stage.

Conclusions: Despite modest sample sizes, these results suggest that patients treated with belatacept were more likely than CsA-treated patients to maintain or improve renal function over 60 Mos in both studies.

SA-PO1013

A Decade of Treatment with Belatacept in Renal Transplantation: Final Results from the Long-Term Extension (LTE) of the Phase 2 Study F. Vincenti,1 C. Larsen,2 J. Grinyo,3 F. Mühlbacher,4 G. Blanco,5 Y. Vanrenterghem,6 F. Lehner,7 C. Jones-burton,8 B. Charpentier.9

1UCSF, USA; 2Emory Univ; 3Univ Hospital of Bellvitge, Spain; 4Medical Univ of Vienna, Austria; 5Univ Hospital, Nantes, France; 6Univ Hospital Gasthuisberg, Belgium; 7Medizinische Hochschule Hannover, Germany; 8Bristol-Myers Squibb, USA; 9Univ Hospital of Bicêtre, France.

Background: Results of the Phase 2 LTE of belatacept in kidney transplantation demonstrated a favorable safety profile & improved renal function vs cyclosporine (CsA) at 5 years (Vincenti F et al, JASN 2010;21(9):1587–96). Here we report the safety & efficacy of belatacept in the LTE up to study closure (9–13 years).

Methods: 218 patients were randomized to receive a more or less intensive regimen of belatacept (n=145) or CsA (n=73), with belatacept patients receiving treatment at 4- or 8-week intervals (5 mg/kg after 6 months). Only 9 CsA patients remained at the end of the study. 44 belatacept patients completed the study, their results are presented here.

Results: Mean belatacept treatment duration for these 44 patients was 9.7± 0.4 years. Mean(SD) MDRD cGFR was 70(21) mL/min/1.73m2 at Month 3 and 72(17) mL/min/1.73m2 at the end of the study (Figure). There was 1 acute rejection episode in Year 9 (8-week dosing interval), there were no deaths or graft losses. From randomization to study end, 82% of belatacept patients had serious AEs, 36% had serious infections, 18% had malignancies (with no cases of PTLD). From randomization to end of study, 30% of patients missed no infusions, 16% missed only 1 infusion.

Conclusions: While the sample sizes are limited in this self-selecting cohort, data suggest that the profile of belatacept is consistent over nearly a decade. Patients maintained renal function over ~10 years with no new safety findings & high treatment compliance.
SA-PO1014

Accuracy of Kidney Failure Risk Equations among Kidney Transplant Recipients

Brad C. Astor,1,2 Brenda L. Muth,3 Arjang Djamiel.1,3 1Dept of Medicine, Univ of Wisconsin School of Medicine and Public Health, Madison, WI; 2Dept of Population Health Sciences, Univ of Wisconsin School of Medicine and Public Health, Madison, WI; 3Dept of Surgery, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: Accurate prediction of graft failure among kidney transplant recipients may identify patients at greatest risk and allow improved management and preparation for return to dialysis. Kidney failure risk equations have recently been developed and validated in native chronic kidney disease (CKD), but their utility in transplant recipients is unknown.

Methods: We tested the accuracy of the 3-variable (age, sex, estimated glomerular filtration rate) and 4-variable (urinary protein:creatinine ratio) to predict 3-year and 5-year graft failure. The cohort included a cohort of 1,073 patients who received a kidney transplant at the University of Wisconsin from 1990-2009 and had survived one year post-transplant. C-statistic, net reclassification index (NRI) and integrated discrimination improvement (IDI) are reported. The NRI was calculated for risk groups of <5%, 5-10% and >10% for 3-year survival and <10%, 10-20%, and >20% for 5-year survival.

Results: A total of 91 grafts failed within 3 years and 134 failed within 5 years. The 4-variable model resulted in a significantly positive NRI for 3-year survival, but the C-statistics did not significantly differ between models for 5-year survival.

Conclusions: The accuracy of both kidney failure risk equations was substantially lower in this population of kidney transplant recipients (C-statistics ≤ 0.80) than reported for native CKD populations (C-statistics > 0.90). While the 4-variable equation, with the addition of urinary protein:creatinine ratio, significantly improved risk prediction, additional factors must be considered to provide accurate risk prediction in kidney transplant recipients.

SA-PO1015

Effect of Mycophenolate Mofetil Dose on Long-Term Kidney Allograft Function

Karol K. Mihovilovic, Matija Pavlovic, Bojana Maksimovic, Mladen Knotek. Clinical Hospital Merkur, Zagreb, HR, Croatia.

Background: Studies have reported significant improvement in kidney function in patients on MMF with lower exposition to calcineurin inhibitors. The optimal long-term MMF dosing in patients maintained on contemporary low-dose calcineurin inhibitors is still underestimated. The aim of our study was to determine effect of MMF dose on kidney function over five years post-transplant.

Methods: A cohort of 171 transplant patients with kidney, kidney-pancreas and kidney-liver transplantation was included. Immunosuppression consisted of anti-IL2 or antithymocyte immunoglobulin induction with MMF, calcineurin inhibitors ± steroids. Estimated creatinine clearance (eCrCl) was calculated using Cockcroft-Gault formula. MMF dose at 1, 2, 3, and 4 years were correlated with eCrCl at respective time point. Univariate and multiple regression analyses were done to test relationship between independent variables and eCrCl. Data were analyzed as means±SD or median with range.

Results: 105 patients had kidney transplantation and 58 kidney-pancreas transplantation. Recipients were a mean of 42±12.03 years old at the time of transplantation, 63 percent of them were male and all were Caucasians. Donors were a mean of 42.8±16.2 years old. There were 46 living donor transplants.

Conclusions: Higher MMF dose with lower calcineurin concentration is associated with better long-term renal function and may increase long-term survival of transplanted kidney.

SA-PO1016

Are We Reducing Tacrolimus Exposure Adequately after Kidney Transplantation? A 3-Year Analysis of the Mycophenolic Acid Observational REAL Transplant (MORE) Study

Najlaa S. Shihab,1 Ali Olaya,2 Anne Wiland,3 Kevin M. McCague,2 Larry Chan.1 1Univ of Utah School of Medicine, Salt Lake City, UT; 2Oregon State Univ and Oregon Health & Science Univ, Portland, OR; 3Novartis Pharmaceuticals Corporation, East Hanover, NJ; 4Univ of Colorado School of Medicine, Aurora, CO.

Background: It is unclear if tapering of tacrolimus (Tac) exposure in routine practice after kidney transplantation is adequate to minimize calcineurin inhibitor-related nephrotoxicity.

Methods: MORE was a prospective, observational study of de novo kidney transplant recipients receiving mycophenolic acid (MPA) at 40 US centers, and managed according to the individual Tac levels and estimated GFR (eGFR) at each time point. Tac and eGFR were analyzed up to 3 years post-transplant. Tac C0 was graded as low, moderate or high (<6, 6-8 or >8ng/mL) and eGFR analyzed as <60 or ≥60mL/min/1.73m2. Risk of eGFR <60 at 1, 2 or 3 years was analyzed by Cox multivariate model, adjusting for delayed graft function, recipient age, PRA, HLA mismatch, expanded criteria donor, MPA dose at month 1 and CMV serology.

Results: 904 patients were analyzed. The 5% of patients with low/moderate/high Tac C0 was 29%/36%/34% at year 1, 37%/36%/27% at year 2 and 39%/35%/27% at year 3. Incidence of biopsy-proven acute rejection at month 12 was 8.5%, 8.3% and 6.5% respectively. A total of 91 grafts failed within 3 years and 134 failed within 5 years. The adjusted odds ratio (AOR) for eGFR <60 at years 1, 2 and 3 in patients with low vs high Tac C0 was 1.28 (95% CI 1.83-1.96; p=0.263), 1.75 (1.05-2.92; p=0.033) and 1.69 (0.83-3.25; p=0.115), respectively. AORs for eGFR<60 at years 1, 2 and 3 in the high vs moderate Tac C0 groups were 1.24 (0.84-1.84; p=0.282), 1.13 (0.71-1.81; p=0.605) and 1.14 (0.62-2.08; p=0.680).

Conclusions: Over a quarter of patients were exposed to high Tac C0 (>8ng/mL) up to 3 years after kidney transplantation, resulting in a lower eGFR at 2 years. Risk of low eGFR may be adversely affected by maintenance of unnecessarily high Tac exposure.

Funding: Pharmaceutical Company Support - Novartis

SA-PO1017

Pregnancy Outcomes in Kidney Recipients Who Discontinued Mycophenolic Acid Products prior to Conception

Serban Constantinescu,1 Peter Axelrod,1 Lisa Coscia,2 Michael J. Moritz,3 Vincent T. Armenti.2 Temple Univ School of Medicine, Philadelphia, Pennsylvania, PA; 3Gift of Life Institute, Philadelphia, Pennsylvania, PA; Lehigh Valley Health Network, Allentown, PA.

Background: The FDA changed the pregnancy category for mycophenolic acid products (MPA) from C to D in 2007. Transplant centers report discontinuing MPA in female kidney recipients anticipating pregnancy.

Methods: Data were collected by the National Transplantation Pregnancy Registry (NTPR) via questionnaires, phone interviews and medical records.

Results: 114 pregnancies were conceived on MPA, and in 163 pregnancies MPA was discontinued preconception (69% switched to another agent).

Conclusions: Women who discontinued MPA preconception had significantly longer transplant to conception intervals and lower eGFR before, during and after pregnancy. Pregnancy resulted in significantly higher rate of livebirths and lower incidence of birth defects. Rejection rate during pregnancy and graft loss within 2 yrs of delivery were similar between groups.


SA-PO1018

Differences in Long-Term Kidney Transplantation Outcomes between Hispanic and Non-Hispanic Whites in the United States

Maria Cristina Arce,1 Colin R. Lenihan,1 Maria E. Montez-Rath,2 Wolfgang C. Winkelmayer.1 1Div of Nephrology, Stanford Univ, Palo Alto, CA; 2Div of Medical General Disciplines, Stanford Univ, Palo Alto, CA.

Background: For most patients who develop kidney failure, kidney transplantation offers the greatest promise for restoring a healthy, productive life. It is widely known that disparities in long-term outcomes persist among racial and ethnic minorities in the United States, but little is known about the Hispanic minority population.

Methods: Using the U.S. Renal Data System, we identified 105,250 Caucasian patients who received their first kidney transplant between 1/1/1996-12/31/2010 and investigated long-term kidney graft survival by Hispanic ethnicity. Death and death-censored graft failure were analyzed using Cox proportional hazards model, stratified by year of transplant, to estimate unadjusted and adjusted cause-specific hazard ratios (HRCS) and subdistribution (competing risk analysis) hazard ratios (HRs) with corresponding 95% confidence intervals (CI).

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

Underline represents presenting author/disclosure.

861A
Results: A total of 11,003 (10.5%) patients experienced kidney graft failure during 544,257 person-years of follow-up. In the unadjusted analysis, the incidence rate of death-censored graft failure was 2.25/100 person-years in Hispanics versus 4.17/100 person-years in non-Hispanics. The incidence rate of death occurred in 3.04/100 person-years in Hispanics versus 4.13/100 person-years in non-Hispanic whites. In the adjusted analysis, we found that Hispanics undergoing kidney transplantation experienced improved survival (adjusted HR=0.85; 95%CI 0.66-0.72) but similar death-censored graft survival (HRr=0.96; 95%CI 0.91-1.01) compared to non-Hispanic whites. When accounting for competing risks, the graft survival by ethnicity remained similar (HRr=0.95; 95%CI 0.94-1.05). The presence of diabetes and level of education did not modify this association.

Conclusions: Few studies have described long-term transplantation outcomes in this rapidly growing minority population burdened with not only socioeconomic challenges but cultural and language barriers as well. Overall, Hispanics were found to have similar kidney graft survival compared to non-Hispanic whites.

Funding: Other NIH Support - T32 DK007357-26

SA-P01019

Changes in Graft Survival among Pediatric and Young Adult Recipients, 1992-2010
Bethany J. Foster,1 Mourad Dahhou, 1 Xun Zhang, 2 Susan M. Samuel.2 1McGill Univ Health Centre, Montreal, Canada; 2 Albertina Children’s Hospital, Calgary, Canada.

Background: Adult kidney transplant recipients had significant improvements in graft survival from the late 1980s to mid-1990s, but only very modest changes thereafter. We aimed to determine if graft failure rates among pediatric recipients changed between 1992 and 2010.

Methods: Using United States Renal Data System (USRDS) data, we studied individuals who received a 1st kidney transplant at ≤5 years old between 1992 and 2010. We used Cox models to compare graft failure (death or graft loss) rates in individuals transplanted in 1992-1997 with those transplanted in 1998-2005, and 2006-2010. Models were stratified by age at transplant, and adjusted for sex, race, donor source, age, primary disease, socioeconomic status, and duration of dialysis before transplant.

Results: Graft failure rates were significantly lower in more recent time periods compared with 1992-1997. Improvements over time were significantly larger for those <5 years at transplant (interaction p<0.001).

Conclusions: Graft failure rates have decreased substantially over calendar time among young recipients.

Funding: Clinical Revenue Support

SA-P01020

Renal Transplantation in the Older Populations: 5 Years Single Centre Experience
Asmus Y.M. Al-Chidadi, Mark Harber. Centre for Nephrology, Royal Free Hospital Univ College London, Hampstead, London, United Kingdom.

Background: Elderly patients are increasingly being considered for renal transplantation due to the aging population. However there may be associated short term morbidity and mortality that is more apparent in the elderly. Transplantation due to the ageing population. However there may be associated short term morbidity and mortality that is more apparent in the elderly.

Methods: We reviewed the course of 47 recipients, 65 years or older transplanted between the 1st of January 2008 and the 31st of December 2010. One year patients and graft survival were compared with 367 patients aged 64 years or younger transplanted during the same period.

Results: Survival was significantly higher in the younger group at 97.55% vs. 91.67%, p=0.028. Graft loss was not significantly different between the two cohorts (4.17% vs. 4.17% in the older group, p=0.819). Initial hospitalization was not significantly different between the two groups as well as hospital stay in the first 3 months and the number of admissions in the first year. E-GFR on discharge was significantly higher among the younger cohort (38.4 ± 22.1 vs. 22.0 ± 13.0, p=0.03). E-GFR at one year however did not achieve significance: 52.35±22.25 vs. 46.06 ±21.28 in the older cohort, p=0.077. Delayed graft function was indicated in 60% in the older versus just over 30% in the younger group, p<0.001. On bivariate analysis the mean number of rejection episodes was nearly identical in the 2 cohorts (0.26±0.80 Vs. 0.25±0.48).

Conclusions: Perhaps surprisingly the initial length of hospitalization in the first year among the older cohort was only a little different from younger recipients, however there was a significant higher rate of mortality and delayed graft function in the older cohort. The slightly poorer eGFR among the older cohort although it wasn’t statistically significant at one year might have been a reflection of allocating more marginal and significantly older donors compared to younger cohort. The significant increase in mortality is an important consideration when listing older patients for transplantation.

Funding: Government Support - Non-U.S.

SA-P01021

Long Term (Visit to Visit) Instability Is an Independent Predictor of Progressive Renal Function Loss in Transplant Patients

Background: Hypertension is an established risk factor for renal function loss in transplant pts but it is unknown whether BP instability is an independent risk factor for the same outcome.

Methods: We tested the relationship between long term, visit-to-visit BP variability [expressed in terms of standard deviation (SD)] and the evolution of the GFR over-time (eGFR slope) in an unselected series of 154 clinically stable renal transplant patients followed up for a median time of 3.2 years (IQ range: 2.2-4.9 years). In a sub-sample of 86 pts, we also investigated the association between short term (24h) BP variability (assessed by ambulatory BP monitoring, ABPM) and the same renal outcome.

Results: Office BP was on average 131±10/78±7 mmHg and the visit to visit variability (SD) was 7.1±1.5/2.1±2.2 mmHg. Visit to visit systolic BP variability was inversely related to baseline eGFR (rho=-0.21, P=0.07) but was independent of average BP and other classical risk factors. During the follow-up, the eGFR decreased in 64 pts (2.8±3.4 ml/min/1.73m2/year, range: -20.6 to -0.01) and increased in the remaining 90 pts (3.7±3.2, ml/min/1.73m2/year, 0.01 to 15.6). Overall, there was an inverse relationship between visit to visit SBP and DBP variabilities and renal function deterioration over time (rho=-0.17, P=0.035 and rho=-0.19, P=0.02) and these associations held true also after data adjustment for the average BP and baseline eGFR (partial rho=-0.19, P=0.02 and partial rho=-0.19, P=0.02). Short term systolic and diastolic BP variability was largely unrelated to eGFR slope.

Conclusions: Visit to visit BP systolic variability predicts GFR loss over-time in transplant pts. Such an effect is independent of underlying average BP and other risk factors. In contrast short term (24h) variability does not predict renal outcomes. These observations have prognostic and therapeutic implications. Trials aimed at minimizing visit to visit BP variability are needed to establish whether attenuation of visit to visit variability may improve renal outcomes in transplant pts.

Funding: Government Support - Non-U.S.

SA-P01022

Communication between Community Nephrologists and the Transplant Centers: A Survey of Nephrologists
Sreedhar Devathi, Ahmad Aswad, Shahed Abbasi, Nasrollah Ghahramani. Dept of Medicine, Div of Nephrology, PennState Hershey Medical Center, Hershey, PA.

Background: Interactive communication between the primary nephrologist and the transplant center (TC) is crucial to the optimal care of the patient pre- and post- kidney transplant (KT). Ideally, the TC and the nephrologist should discuss the plans for transition of care prior to KT. We examined nephrologists’ current practice and experience regarding patient-related communication with the TC.

Methods: Invitations were sent to 3180 nephrologists in the eastern US. 822 expressed interest, and 250 were randomly invited to complete a questionnaire about demographics, practice characteristics, and their communication with TC. A total of 216 surveys with complete responses were analyzed. Univariate analysis and stepwise logistic regression were performed.

Results: 90% indicated access to an attending physician in the TC to discuss patient-related issues; 50% call the TC about patients they are referring; 57% call to provide updates if more than half of their patients are not employed (OR:0.43; p=0.02). Practice updates on listed patients (OR:3.25; p=0.0005). Nephrologists are less likely to call with the care of patients post-KT (OR:3.35; p=0.002). Nephrologists who attended more than one transplant-related CME was associated with higher likelihood to call the TC to refer patients (OR:3.77; p<0.0001) and to discuss the care of patients post-KT (OR:3.35; p=0.002). Nephrologists who attended more than 2 national nephrology meetings in a 5-year period were more likely to call to provide updates on listed patients (OR:2.25; p=0.0005). Nephrologists are less likely to call with updates if more than half of their patients are not employed (OR:0.43; p=0.02). Practice updates in groups of more than 10 increased the likelihood that a nephrologist will call the TC to refer patients (OR:2.30; p=0.0005). Fewer studies or patients for transplanted patients (OR:0.06; p=0.02).

Conclusions: The majority of nephrologists are satisfied with the communication with the TC. The likelihood of communication is related to participation in continuing educational meetings, the overall composition of the patients and the number of nephrologists in the practice.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author/disclosure.
SA-PO1023
Red Cell Distribution Width Is Associated with Obstructive Sleep Apnea in Kidney Transplant Recipients
Miklos Zsolt Molnar,1,2 Akos Ujjaszsi,1 Katalin Fornadi,1 Marta Novak,1 Istvan Mucsi,1 1Univ of Toronto, Toronto, Canada; 2Nephrology and Hypertension, Univ of California, Irvine, Irvine, CA; 3Semmelweis Univ, Budapest, Hungary; 4McGill Univ Health Centre, Montreal, Canada.

Background: Red cell distribution width (RDW), a marker of heterogeneity in the size of circulating erythrocytes. It is associated with mortality in various patient populations. We assess the association between Obstructive Sleep Apnea (OSA) and RDW in stable kidney transplant recipients to demonstrate if RDW is associated with intermittent hypoxemia generated by OSA.

Methods: Cross-sectional study of 100 kidney transplant patients who underwent polysomnography. Socio-demographic information and data about medication, comorbidity and laboratory parameters were collected.

Results: The mean age was 51±13 years, 43% were women, and the prevalence of diabetes was 19%. The mean RDW was 14±1%, and the median (interquartile range) Apnoe-Hypopnoe Index (AHI) was 3 (13). We found an incremental linear association between the AHI and RDW in unadjusted (B=0.027, 95%CI:0.012-0.04; p<0.001) linear regression models.

After adjustment for relevant factors, such as age, gender, eGFR, comorbidity, abdominal circumference, serum albumin, serum CRP, blood hemoglobin and soluble transferrin receptor levels, AHI was still associated with RDW (B=0.022, 95%CI:0.007-0.037; p=0.005).

Conclusions: RDW is associated with the apnoe-hypopnoe index, the objectively assessed measure of the severity of OSA. It is tempting to speculate RDW is increased in response to intermittent hypoxemia (a hallmark of OSA). Further studies will need to unravel if the link between RDW and mortality is a reflection of underlying OSA.

SA-PO1024
Prevalence of Primary Hyperaldosteronism in Renal Transplantation Is More Common Than Reported
Mahendra V. Govani, Cara Crone, Russell A. White, Alvin Wei, Islam A. Ghitheim, Joseph Wheelan, Jay H. Weiss. Kidney and Pancreas Transplantation, St. Vincent Hospital, Indianapolis, IN.

Background: Despite several case reports of primary Hyperaldosteronism (PHA) diagnosed after renal transplantation, prevalence of this condition has not been studied in detail.

Methods: Between 1/1/2009 and 4/31/2013, 186 kidney alone transplants (146DD and 40LD) were performed at our center in 184 patients. On longitudinal follow-up, 7 patients were found to have refractory hypertension (≥3 antihypertensive drugs) and refractory hypokalemia (no potassium (K) restriction and supplemental K>40 mEq/day) without any obvious non-urinary K loss. Plasma aldosterone to renin ratio (PARR) was performed if the link between RDW and mortality is a re

Results: Mean blood pressure did not differ between before and after KT (124±19/81±13 vs 121±10/83±19 mmHg, P=0.05), but the number of anti-hypertensive medication was significantly decreased (1.7±1.2 vs 0.6 ±0.9, P <0.05). Before KT, 41 out of 48 patients (85%) showed abnormal circadian rhythm (non-dipper) and reverse dipper was only 13% (7/54). At 1 year from KT, the abnormal circadian rhythm did not improve in most patients. The proportion of non-dipper did not change compared to before KT and reverse dippers showed increasing pattern (27% (13/48) to 31%(15/48)). However, the proportion of dipper showeddecreasing pattern (15%(7/48) to 10%(4/48)). In individual analysis, 27 out of 28 non-dippers before KT still showed abnormal circadian rhythm (18 non-dippers and 9 reverse dippers at 1 year after KT) and only 1 changed to dipper. In 13 reverse dippers before KT, only 2 patients converted to dipper and 11 patients still showed non-dipper(n=6) and reverse diper(n=5). In 7 dippers before KT, only 2 patients remained in dipper, and another 5 showed abnormal circadian rhythm after KT (4 non-dippers and 1 reverse dipper).

Conclusions: In conclusion, overall status of blood pressure improved, but circadian rhythm showed deteriorating pattern at 1 year after transplantation.

SA-PO1026
Initial Stabilization in Pulse Wave Velocity Is Followed by Rapid Worsening One Year after Kidney Transplantation
Fadi Tohme, Eduard Cruz, Harald M. Stauss, Roberto S. Kaili. Univ of Iowa Hospitals and Clinics, Iowa City, IA.

Background: Cardiovascular (CV) disease is the leading cause of mortality in advanced CKD and after kidney transplantation (KT). Pulse wave velocity (PWV) is a highly sensitive and non-invasive predictor of CV risk. Our aim was to identify factors associated with a significant change in PWV after KT.

Methods: Kidney transplant recipients at an academic center were recruited between 2009 and 2012. Visits occurred at 3, 12, 24 or 36 months after transplant. Patients who did not have at least 2 sequential measurements of PWV were excluded. Data collected at each visit included age, gender, eGFR, blood pressure (BP), weight and carotid-femoral PWV , measured using the SphygmoCor system. Correlations were calculated using nonparametric Spearman’s coefficient. Visits at 11-14 months and 21-37 months after transplant were compared using ANCOVA.

Results: 56 visits corresponding to 25 patients were included. Mean age was 50 [36-64] years and 72% were males. The absolute value of PWV had a positive correlation with age, SBP and weight (p<0.001) but not with gender (p=0.37), eGFR (p=0.7) or time elapsed from transplant (p=0.154). Sequential change of PWV (Δ-PWV) correlated with the time elapsed from transplant (p=0.01), but not with the change in SBP,eGFR or weight. ANCOVA analysis (using time between sequential measurements as a covariate) showed a significantly lower Δ-PWV in the 11-14 months group compared to the 21-37 months group (p=0.049).

Conclusions: Prevalence of PHA (definite and probable) is 3.3% in our cohort. All posttransplant patients with both refractory hypertension and hypokalemia (especially when patients are on tacrolimus) need to be tested for PHA.

Funding: Clinical Revenue Support

SA-PO1025
The Change of Circadian Rhythm of Blood Pressure after Successful Kidney Transplantation in End Stage Renal Disease
Myung Hyun Lee, Cheol Whee Park, Yong-Soo Kim, Chul Woo Yang. Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary’s Hospital, Seoul, Republic of Korea.

Background: The change of circadian rhythm after kidney transplantation (KT) is not fully studied. In this study, we prospectively investigated circadian rhythm before and after KT.

Methods: We performed 24 hour ambulatory blood pressure monitoring (ABPM) in 48 patients before KT and at 1 year after KT. Circadian rhythm was presented as dipper (ASBP ≥10%), non-dipper (0 ≤ ASBP <10%), and reverse dipper (SBP nocturnal rise) according to the nocturnal reduction of systolic blood pressure (ASBP). We evaluated the pattern of circadian rhythm and mean blood pressure before and 1 year after KT.

Results: Mean blood pressure did not differ between before and after KT (124±19/81±13 vs 121±10/83±19 mmHg, P=0.05), but the number of anti-hypertensive medication was significantly decreased (1.7±1.2 vs 0.6 ±0.9, P <0.05). Before KT, 41 out of 48 patients (85%) showed abnormal circadian rhythm (non-dipper) and reverse dipper was 27% (13/48) and dipper was only 13% (7/54). At 1 year from KT, the abnormal circadian rhythm did not improve in most patients. The proportion of non-dipper did not change compared to before KT and reverse dippers showed increasing pattern (27% (13/48) to 31%(15/48)). However, the proportion of dipper showeddecreasing pattern (15%(7/48) to 10%(4/48)). In individual analysis, 27 out of 28 non-dippers before KT still showed abnormal circadian rhythm (18 non-dippers and 9 reverse dippers at 1 year after KT) and only 1 changed to dipper. In 13 reverse dippers before KT, only 2 patients converted to dipper and 11 patients still showed non-dipper(n=6) and reverse diper(n=5). In 7 dippers before KT, only 2 patients remained in dipper, and another 5 showed abnormal circadian rhythm after KT (4 non-dippers and 1 reverse dipper).

Conclusions: In conclusion, overall status of blood pressure improved, but circadian rhythm showed deteriorating pattern at 1 year after transplantation.
Arterial Stiffness and Changes in QTc Interval in Renal Transplantation

Patients: Mehtap Erkenm, Uyar,1 Ugur Bal,2 Zeynep Bal,1 Emre Tutal,1 Burak Sayın,1 Orhan Guliyev,1 Begum Erdem,1 Siren Sezert.1

Methods: 100 kidney transplant recipients from our renal transplant outpatient clinic were enrolled into the study. All patients were evaluated for clinical and biochemical parameters. Anthropometric and body composition analyses were performed for all patients. Body compositions were analyzed by using the Body Composition Analyzer (Tanita BC-420MA). PWV was determined from pressure tracing over carotid and femoral arteries using the Sphygmocor system. Pre- and post-transplant electrocardiographic (ECG) evaluations were performed. Each QT interval was corrected for the patient’s heart rate using Bazett’s Formula.

Results: A total of 125 RTRs were reviewed for diagnosis of de novo skin lesions in nurse led clinics between Sep 2010 and Nov 2011. Immunosuppressive regimen, age, gender, and skin type were looked as potential risk factors. Spearman’s correlation was used for data analysis.

Results: 2 of the 3 MN relapses were positive before transplantation, maintaining high titles of anti-PLA2R in the 3rd month and when the biopsies confirming the relapses were done (11 and 13 months respectively). The test became negative after the administration of rituximab in both, with no correlation with proteinuria or clinical outcomes. The 3rd MN relapse was negative before and in the 3rd month after transplantation but became positive after five years, at the moment of histological diagnosis. Only 3 of the 10 patients who did not relapse had positive pretransplant anti-PLA2R, although at low titles, and they became negative in the first months after grafting.

Conclusions: Persistent high titles of anti-PLA2R after kidney transplantation are a good predictor of MN relapse. Monitoring after using rituximab is somewhat uncertain, because of no correlation with proteinuria or clinical outcomes.

SA-PO1029

The Natural History and Risk Factors Identified for Development of Skin Cancer in Renal Transplant Recipients

Rosa M. Montero,1 Donald Choi,2 Christopher Harland,1 Mona Wahba.1

Background: No consensus regarding the guidance and recommendations of skin cancer surveillance in Renal Transplant Recipients (RTRs). In this cross-section observational study all RTRs attending skin surveillance clinic were reviewed to determine the natural history of skin lesions occurring in RTRs and identify risk factors associated with development of these lesions.

Methods: A total of 125 RTRs were reviewed for diagnosis of de novo skin lesions in nurse led clinics between Sep 2010 and Nov 2011. Immunosuppressive regimen, age, gender, and skin type were looked as potential risk factors. Spearman’s correlation was used for data analysis.

Results: 13 Non Melanoma Skin Cancer (NMSC) and 17 Premalignant lesions (PMLa) were found in this cohort. Increasing age significantly correlated with the development of Bowen’s disease (BD) (p=0.03,r=0.20). Basal cell carcinoma (BCC) had a predilection for male RTRs (p=0.01). A bimodal distribution appeared in both NMSC and PMLa at ~5yrs (mode for BCC: 3 yrs) and 10yrs post 1st renal transplant (RT). RTRs on Prednisolone (P+) Cyclopisin correlated with development of PMLa (BD: p=0.01,r=0.246). The combination of P+ Tacroleximus (FK) + Mycophenolate Mofetil correlated with the development of BCC (p=0.03,r=0.17). FK + Azathioprine developed cases of BCC (p=0.03,r=0.194) and Acinitic Keratosis (AK) (p=0.03,r=0.19). All of the skin lesions found occurred in those with skin types I-V with BCC; AK and BD predominantly in the lower skin type (Spearman’s correlation p<0.001,p<0.001,p=0.01, respectively). NMSC and PML develop before 5 yrs and rise steadily with a similar rate of growth by 20yrs post 1st RT.

Conclusions: Early screening is recommended in view of high detection rates <5yrs of NMSC and PMLa in RTRs post 1st RT. The high incidence of BCC in <5yrs post 1st RT suggests a role for rigorous pre-transplant screening as BCC are slow growing lesions. Risk factors for NMSC include skin types I-V; length and combination of immunosuppression. We recommend skin surveillance from 3 years to 20 years should occur as a minimum in RTRs post 1st RT.

SA-PO1030

Clinical and Genetic Predictors of Cutaneous Squamous Cell Carcinoma in Kidney Transplant Recipients

M. Leo Sanders, Jason Karnes, Joshua Denny, Dan M. Roden, T. Alp Ikizler, Kelly A. Birdwell. Vanderbilt Univ Medical Center.

Background: Cutaneous squamous cell carcinoma (cSCC) occurs 100 times more frequently in kidney transplant recipients (KTRs) compared to the general population with more aggressive metastasis, a higher rate of recurrence, and an increased morbidity and mortality. We set out to identify clinical and genetic predictors which confer an increased risk for cSCC in this patient population.

Methods: We retrospectively identified 78 cSCC cases and 246 controls among Caucasian KTRs using a DNA biobank linked with de-identified electronic medical records (EMRs). We performed a genome wide association study (GWAS) for cSCC with 711,021 single nucleotide polymorphisms (SNPs) using the Illumina OMNI1 and OMNI platforms. Logistic regression was used to determine adjusted odds ratios for clinical predictors and SNP effects in a dominant model using SAS and PLINK.

Results: Age (OR 1.11 [1.08-1.13], p=0.0001), months of immunosuppression (OR 1.02 [1.01-1.04], p=0.0001) and inhaled tobacco use (OR 2.10 [1.07-4.09], p=0.030) were significant clinical predictors of cSCC development while gender and duration of dialysis were not. No SNPs reached nominal genome-wide significance (p<10 -8). The two top associations were rs2139796 in TRPC3, previously associated with glomerulonephritis and proteinuria (OR 9.13, p=7.04x10^-10) and rs373610, a nonsynonymous SNP in OBSCN previously associated with tobacco addiction (OR 5.90, p=1.58x10^-4). The 3rd MN relapse was negative before and in the 3rd month after transplantation but became positive after five years, at the moment of histological diagnosis. Only 3 of the 10 patients who did not relapse had positive pretransplant anti-PLA2R, although at low titles, and they became negative in the first months after grafting.

Conclusions: Persistent high titles of anti-PLA2R after kidney transplantation are a good predictor of MN relapse. Monitoring after using rituximab is somewhat uncertain, because of no correlation with proteinuria or clinical outcomes.

SA-PO1027

Results: PWV, a good marker of CV risk, initially stabilizes after KT but rapidly increase within a year of transplant. Those changes seen in PWV can not be explained by changes in SBP, GFR or weight after transplant. Persistent elevated PWV after 1 year from transplant may play a role in high rates of CV events post KT.

Funding: Other NIH Support - NHLBI

SA-PO1028

Anti-PLA2R Monitoring in Relapsing Membranous Nephropathy after Kidney Transplantation

Miguel Segars,1 David San Segundo,2 Marcos Lopez-Hoyos,2 Emilio Rodrigo,1 Juan Carlos Ruiz,1 Gema Fernandez-Fresnedo,1 Angel Luis M. De Francisco,1 Manuel Arias-Rodriguez.1

Background: Idiopathic membranous nephropathy (MN) is an important cause of chronic kidney disease with relatively high incidence of relapse after transplantation. The antibodies against the phospholipase A2 receptor (anti-PLA2R) seem to play a key role in the pathogenesis and diagnosis of idiopathic MN. The aim of our study was to know the posttransplant evolution of anti-PLA2R in patients with MN.

Methods: We selected 13 transplanted patients from our database with histological diagnosis of MN before transplantation and biopsies done under clinical suspicion of relapse or other pathologies after transplantation: 3 of them had histological confirmation of MN relapse, 2 in the first year and one after 5 years. We analyzed the sera of the 13 patients (from a prospectively updated sera bank) with indirect immunofluorescence for anti-PLA2R, on the day before transplantation, after 3 months and on the day of the confirmatory biopsy. We also analyzed the sera of 2 out of 3 MN relapsed cases after the administration of rituximab.

Conclusions: PWV, a good marker of CV risk, initially stabilizes after KT but rapidly increase within a year of transplant. Those changes seen in PWV can not be explained by changes in SBP, GFR or weight after transplant. Persistent elevated PWV after 1 year from transplant may play a role in high rates of CV events post KT.
SA-PO1031
Six Years Posttransplant Follow-Up of the First Case Who Underwent Partial Bladder Transplantation with En Bloc Kidney Transplant in a Human Noriko Sugawara,1 Tatsu Asano,1 Kei Nishiyama,1 Shoichiro Kanda,1 Kiyonobu Ishizuki,1 Masataka Hisano,1 Hiroko Chikamato,1 Yuko Akioka,1 Rie Yagi,1 Motoshi Hattori,1 1Dept of Pediatric Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan; 2Dept of Urology, Tokyo Women's Medical Univ, Tokyo, Japan.

Background: We have reported a 12-month-old girl who underwent partial bladder transplantation with en bloc kidney transplant (Kato et al. Am J Transplant 8: 1060, 2008). Because her native bladder was extremely small, bilateral kidneys were transplanted en bloc with their ureters connected to a patch of the donor bladder, which encompassed the bilateral ureterovesical junction (bladder patch technique). That was the first case report of transplanting a vasculared segment of the human urinary bladder. Although this technique has several potential benefits including preserving the normal anti-reflux mechanism, there are some concerns. One potential concern is the inadequacy of blood supply to the donor bladder wall. Another concern is that the donor bladder wall may be less susceptible to income disparities. That was the bloc

Methods: Surgical complications (20% in PD vs 13.3% in HD), DGF (8.8% in PD vs 11% in HD). Comorbidities was more in the PD patients but they had better residual renal function.

Results: 45 patients on PD and 52 on HD were included in the study. Both groups were similar in terms of recipient’s age & gender, diabetic & non diabetic status of the recipients & different blood groups. Immunosuppression protocol was similar in both groups. Duration of dialysis was significantly longer in PD patients. In the pretransplant period the infectious complications similar (15.4% in PD vs 17.8% in HD). Comorbidities was more in the PD patients but they had better residual renal function. The mean eGFR values at 1 month (86.1±23.8 vs 79.9±15.3;p=0.22) and at last follow up (60.9±23.5 vs 60.3±18.8;p=0.94) was similar in both groups. Post transplant infections were similar. The mean cumulative patient survival was similar (PD: 84 months vs HD: 85 months). The 1, 2, 5, & 8 year patient survival in PD patients was 98%, 93%, 86% & 80% and in HD patients was 100%, 95%, 85% & 80% respectively. The overall mean cumulative death censored graft survival was similar (PD: 83 months vs HD: 84 months). The 1,2,5 & 8 years death censored graft survival of PD patients was 98%, 90%, 85% & 75% and in HD patients was 100%, 93%, 84% & 79% respectively.

Conclusions: The short & long term outcomes, AR & DGF of renal allograft recipients do not differ with modality of dialysis in living donor renal transplantation.

SA-PO1034
Mortality in Patients with a Failed Transplant after a Return to Dialysis Zhiwar Abdulrahman, Nassim Kamar, Lauren Espoisto, F. Sallusto, I. Cardeaus-desangles, Arnaud Dell Bello, Lionel Rostaing. Dept of Nephrology, Dialysis, Transplantation, Toulouse Univ Hospital, Toulouse, France.

Background: It is not clear whether mortality increases among those with kidney-allograft failure relative to those who start dialysis but have never received a transplant. METHODS: We compared mortality rates and its causes among 136 patients with a failed kidney allograft who returned to dialysis (between January 2006 and December 2012 at Toulouse University Hospital, France) with 532 de novo hemodialysis patients who had never received a transplant. Within failed-allograft patients, we also compared mortality rates of those who had lost their graft before or after the end of the first year post transplant, and those who were or were not on a waiting list for a kidney transplant.

Results: Overall mortality was comparable between failed-allograft patients (22.8%) and de novo hemodialysis patients (24.1%; p=0.79). Mortality rates were also similar between patients who lost their allograft within 1 year post transplant (22.9%) and those who lost their allograft after 1 year (p=0.86). Failed-allograft patients who were not relisted for a kidney transplant had the highest mortality rate (40.8%) when compared to those patients who had been relisted (12.6%; p=0.0002) and hemodialysis-transplant-naive patients (24.1%, p=0.001). The lowest mortality rate (6%) was observed in failed-allograft patients who had re-transplant when compared to those patients who were still on a waiting list (21.6%) and those who were not relisted (40.8%; p=0.0002). The major causes of mortality in the failed-allograft group (n=31) were cardiovascular (29%), others are cancer, gastrointestinal complications, and sepsis caused equal mortality rates (13% each). Causes of mortality in de novo hemodialysis patients (n=128) were similar. Conclusions: Patients with a failed kidney allograft and transplant-naive patients undergoing de novo hemodialysis had equivalent mortality risks and the causes of mortality were similar, the most frequent being cardiovascular. Failed-allograft patients who underwent re-transplantation had the lowest mortality rate regardless of their status vis-à-vis kidney transplantation.

SA-PO1035
Elevated Fibroblast Growth Factor 23 Levels Are Associated with Chronic Rejection and Declining Kidney Transplant Function Michael E. Seifert,1 2 Aftab S. Chishti,1 Myra L. Chiang,2 David T. Selewski,3 Debbie S. Gipson,1 Keith A. Hruska,2 1Southern Illinois Univ; 2Washington Univ; 3Univ of Kentucky; 4West Virginia Univ; 5Univ of Michigan.

Background: Chronic rejection (CR) is characterized by cumulative vascular injury that leads to kidney transplant failure. Chronic kidney disease-mineral bone disorder (CKD-MBD) contributes to vascular injury in native CKD, but its importance in CR is unknown. The relationship of CKD-MBD factors such as fibroblast growth factor 23 (FGF23) and Dickkopf-related protein 1 (Dkk1) have not been associated with remote transplant loss and mortality but not directly with CR. We hypothesized that FGF23 and other biomarkers of CKD-MBD would serve as non-invasive biomarkers of CR.

Methods: Preliminary analysis of 26 pediatric kidney transplant recipients enrolled in an ongoing multicenter, case-control study of biomarkers of vascular injury in native CKD, but its importance in CR is unknown. The relationship of CKD-MBD factors such as fibroblast growth factor 23 (FGF23) and Dickkopf-related protein 1 (Dkk1), and sclerostin (SOST) levels in the CR group but the mean plasma FGF23 was significantly higher vs. No CR (p=0.001). The lowest mortality rate (6%) was observed in failed-allograft patients who had re-transplant when compared to those patients who were still on a waiting list (21.6%) and those who were not relisted (40.8%; p=0.0002). The major causes of mortality in the failed-allograft group (n=31) were cardiovascular (29%), others are cancer, gastrointestinal complications, and sepsis caused equal mortality rates (13% each). Causes of mortality in de novo hemodialysis patients (n=128) were similar. Conclusions: Patients with a failed kidney allograft and transplant-naive patients undergoing de novo hemodialysis had equivalent mortality risks and the causes of mortality were similar, the most frequent being cardiovascular. Failed-allograft patients who underwent re-transplantation had the lowest mortality rate regardless of their status vis-à-vis kidney transplantation.

Methods: Pediatric (<18 yrs old) renal transplant recipients from 1997-2006 were identified from United States Renal Data Service files and follow-up data through 2009 were available. Subjects were linked by zip code to median family income from the 2000 U.S. Census. Median family income was stratified by quartiles. Primary outcomes were death, graft loss due to rejection and all causes. Proportional hazards regression and Kaplan-Meier curves modeled risk based on income. Covariates included considered race, etiology of ESRD, age, race, gender, and donor type (deceased-donor vs. living-related).

Results: There were 7,781 pediatric renal transplant identified. Maximum follow-up was 11.7 years. 59% were male, 19% black, and congenital/urologic conditions accounted for 50% of ESRD etiologies. Mean age at transplant was 11.4 ± 5.1 yrs. 85% had living-related donors. Median annual household income was $38,131 vs $51,101 (p<0.05). Of 951 (25%) lost their graft and 442 (5.6%) died. Of graft loss, (4.6%) were due to rejection. In unadjusted regression with the highest income group as the reference, there was a 17% increased risk of mortality (HR 1.17 [95%CI 1.09-1.25; p<0.001]) and a 13% increased risk of graft loss (HR 1.13 [95%CI 1.1-1.17; p=0.001]) for each successive decrease in income quintile. There was no relationship between graft loss due to rejection and meda family income [HR 0.98 [95%CI 0.85-1.14; p=0.78].

Conclusions: Those with the lowest income had increased risk of death and graft loss compared those with the highest income. Differences in rates of graft rejection are not the primary mediators of this relationship. Policy makers should consider the effect of income when determining benefits for pediatric kidney transplant recipients.
Conclusions: Plasma FGF23 is inversely correlated with eGFR and is a better non-invasive biomarker for CR. These findings will be further validated as we complete enrollment and analysis for this study. We speculate that FGF23 is a modifiable risk factor for CR that must be explored in a prospective study.

Funding: Other NIH Support • NIH UL1 TR000448; NIH KL2 TR000450

SA-PO1036

The Fall in FGF-23 Levels at One Year following Kidney Transplantation Ameliorates Acute Allograft Rejection Risk Monique E. Cho,1 William H. Chong,2 Michael S. Ring,1 Xiaogee Zhao.3

Methods: In all 163 kidney and kidney/pancreas transplants performed in our center from 1999-2007, 82 stored serum samples taken 0-3 months prior to tx (baseline) were available for analysis. Sixty of the 82 samples had repeat serum samples at one yr. We hypothesized that the greater decline in FGF23 levels during the first yr is associated with decreased risk of allograft rejection and favorable allograft function. Because of non-parametric distribution of the data, Kruskal-Wallis test was used to investigate the relationship between FGF23 and renal allograft outcome.

Background: Although increased serum levels of fibroblast growth factor 23 (FGF23) predict progression of CKD and increased mortality risk, no published studies have described the role of FGF23 in incident renal transplant (tx) population.

Results: The median (IQR) baseline intact FGF23 was 4873 (589, 16041) pg/mL. At one-yr post tx, it decreased to 53 (36, 85) pg/mL, with a median reduction of 3305 (215, 15453) pg/mL. During the mean follow-up of 5.7±2 yrs, there was a total of 31 rejections (77% 1A/B, 23% 2A/B) in 24 patients (87% in the 1st yr). Of the 31 rejection episodes 18 were included in the analysis (6/24 patients did not have FGF23 decline data and those with multiple rejections were treated as one episode). The 5-yr median serum Cr was 1.5 (1.2, 1.8) mg/dL in 70 patients. Patients who experienced rejection had a median FGF23 decline of 1022 pg/mL while those without rejection had a median FGF23 decline of 4804 pg/mL, P=0.037. The baseline or 1-yr FGF23 level was not associated with the rejection risk. Those with greater reduction in FGF23 levels at 1 yr showed a trend for lower serum Cr at 5 yrs. There was no difference in the baseline serum PTH or phosphorus levels in the rejection vs. non-rejection group.

Conclusions: While greater FGF23 fall in the 1st yr may be associated with decreased allograft rejection risk, a larger study is needed to determine if FGF23 change independently predicts renal allograft outcome.

Funding: NIDDK Support

SA-PO1037


Methods: Four groups of pigs (n=7 each) after 6 weeks of ARAS or sham were treated for 4 additional weeks with SC injections of Bendavia (0.1mg/kg diet) or control, pigs were treated for another 4 weeks with Bendavia (0.1mg/kg SC, 5d/week) or vehicle (n=7 each). Single-kidney hemodynamics and function were studied using fast-CT, and microvascular architecture (micro-CT), oxidative stress (DHE), and fibrosis (trichrome) ex-vivo. Renal endothelial function (responses to acetylcholine [Ach]) was studied in vivo (CT) and ex-vivo (renal arteries, organ bath).

Results: All ARAS pigs developed hypertension (mean arterial pressure=137.4±13.2mmHg). Renal blood flow (RBF) and glomerular filtration rate (GFR) were blunted in ARAS+Vehicle, but improved in ARAS+Bendavia. Loss of small outer cortical microvessels, oxidative stress, and fibrosis were ameliorated in Bendavia-treated pigs. Furthermore, Bendavia normalized renal endothelial function both in vivo and in vitro.

Conclusions: Chronic treatment with Bendavia in ARAS pigs improved stenotic kidney hemodynamic and function, and normalized vascular endothelial function in-vivo and ex-vivo. Microvascular loss, oxidative stress, and fibrosis were attenuated in ARAS+Bendavia, uncovering a unique therapeutic potential for Bendavia in restoring renal function in chronic experimental ARAS.

Funding: Pharmaceutical Company Support • Stealth Peptides Inc.

SA-PO1038


Methods: After 6 weeks of ARVD (unilateral renal artery stenosis and high-cholesterol diet) or control, pigs were treated for another 4 weeks with Bendavia (6 1mg/kg SC, 5d/week) or vehicle (n=7 each). Single-kidney and cardiac function were assessed by multidetector CT, and myocardial fibrosis by trichrome. Renal vein and inferior vena cava levels of interleukins (II1-α, II1, and 8) were measured by ELISA, and their net release calculated from their gradient.

Results: Blood pressure was similarly elevated in both ARVD groups, yet glomerular filtration rate (GFR), left ventricular muscle mass (LVMM), E/A ratio, and myocardial fibrosis normalized only in Bendavia-treated pigs (Table). Release of inflammatory IL was higher in the ARVD+Vehicle and correlated with myocardial fibrosis and diastolic dysfunction, but decreased in ARVD+Bendavia pigs (Figure).

Conclusions: Chronic treatment with Bendavia improved stenotic kidney function, and prevented myocardial hypertrophy, fibrosis, and diastolic dysfunction. These effects might be mediated partly by ameliorating renal dysfunction and inflammatory cytokines release, underscoring ubiquitous protective properties of Bendavia in chronic experimental ARVD.
SA-PO1039

Renal and Vascular Safety after Renal Denervation Using the Symplicity Catheter in a Porcine Preclinical Model

Stefan Tunev, Robert J. Melder.

Methods: The renal and vascular safety following RDN by RF energy was evaluated quantitively in normal swine at 7, 14, and 28 days by histological morphometric analysis and blood biochemistry. The success of RDN was confirmed by the significant drop in tissue norepinephrine values measured in the renal cortex. Naïve animals were used as controls for all time points.

Results: Historically, the average circumferential extension of the RF lesion in the arterial media at 7 days was estimated at 28%. Quantitative morphometric analysis of the medial lesion extension confirmed this observation and yielded an average value of 26% (N=415 histological sections). Endothelialization was scored for each histological section semi-quantitatively and showed scores of 4 (~95% of the luminal surface covered by endothelium) for all sections at 7, 14 and 28 days. Quantitative morphometric analysis of endothelialization confined to the areas of RF lesions was performed using CD31 immunohistochemistry and demonstrated that the average percent endothelialization of the lesion area only at 7 days is ~99%. Thin caged mural thrombi (completely endothelialized) were noted histologically in 5 out of 54 vessels at day 7 whereas none of the vessels at day 14 of 28 contained any thrombi. Histological assessment of serial kidney sections from all time points (N=1260 sections) failed to demonstrate presence of renal thrombo-embolization, infarction, foreign bodies, hemorrhage, microgranulomas and fibrosis. Furthermore, blood chemistry analysis showed that the treated animals did not developed significant deviations in renal physiological blood parameters (BUN, Creat, Ca, P, Na, K, Cl, BUN/Creat).

Conclusions: The data demonstrated that RDN via the Symplicity catheter results in consistent RF lesions with no compromise in vascular integrity, followed by a rapid vascular healing with no downstream anatomical or physiological consequences to the kidney.

Funding: Pharmaceutical Company Support - Steltis Peptides Inc.

SA-PO1040

Angiotensin-(1-7) Modulates Renal Vascular Resistance through Inhibition of Mitogen-Activated Protein Kinase p38 in Apolipoprotein E Deficient Mice

Arkadiusz Lubas, Robert Ryczek, Jerzy Smoszna, Stanislaw Niemczyk.

Background: Angiotensin II (AngII) plays a key role in the regulation of renal vascular resistance (RVR). AngII acts as a stimulator of MAPKs, with p38-MAPK and ERK1/2 playing key roles in the development of hypertension.

Methods: Male Wistar rats were either saline or AngII infused at a dose of 1 mg/kg/day via osmotic minipumps for 7 days. Blood pressure (BP) was measured using tail-cuff method prior to and after AngII infusion. Renal vascular resistance (RVR) was measured using an isolated rat kidney preparation. p38-MAPK activation was assessed using an antibody against phospho-p38 (p-p38).

Results: AngII infusion significantly increased BP and RVR, compared to saline-infused rats. p-p38 levels were increased in the AngII-infused group compared to saline-infused controls. Inhibition of p38-MAPK using SB203580, a specific inhibitor, significantly reduced AngII-induced increases in BP and RVR.

Conclusions: These results suggest that p38-MAPK plays a key role in regulating renal vascular resistance in response to AngII infusion. Inhibition of p38-MAPK may provide a novel therapeutic strategy for the treatment of hypertension.

Funding: NIH Support - NHLBI/NIH, R01 DK071767
Renal injury as renal hypertension is poorly understood. The purpose of this study was to examine the renin release and correlate the renin release, but the relationships between tissue in hypertensive patients (NTNBPN, n=32) during induction when serum creatinine levels were increased significantly. The renin release was significantly associated with left ventricular mass index (LVMI) (r=-0.43) and NTBPBN (r=-0.45). In multiple stepwise regression analysis model (TNl, NTBPBN; CCKDPKI, CDDKI-PDI, EF, LVEF, LVMI, LSVS, LVD, LVCI, IMP, MAP, NPBPBN, LVCO and CS-CDDKI-PDI independently significantly lower than PCP and TCP (0.071 ±0.66 cm/s vs 0.46 ±0.33 cm/s and 0.273 ±0.188 cm/s; p<0.001). 

Results: 

Conclusions: 

Renal cortical perfusion is significantly associated with cardiac function in CKD patients. Ultrasound measurement of renal perfusion should be considered as a new tool in diagnosing cardio-renal interactions.

Funding: Clinical Research Support

SA-PO1043
Beraprost Sodium Suppresses Progression of Chronic Renal Failure by Protecting Renal Capillary Endothelial Cells and Improving Renal Hypoxia in Glomerulonephritis Rats Shinichi Yamaguchi, Yasufumi Goto, Naohako Sato, Hajimu Kurumatani, Mitsuko Miyamoto, Masateru Yamada. Pharmaceutical Research Laboratories, Toray Industries Inc., Kanagawa, Japan.

Background: Beraprost sodium (BPS), a chemically stable prostacyclin analog, has been reported to suppress the progression of chronic renal failure (CRF) in glomerulonephritis (GN) rats (Kidney Week 2012). Also, an international P/lernl/ll study of BPS using a renal composite endpoint is ongoing in Asia (China, Hong Kong, Japan, Malaysia, Singapore, Taiwan, and Thailand). In order to clarify the mechanism of the suppression of CRF progression, we examined whether BPS protects renal capillary endothelial cells and improves renal hypoxia in GN rats.

Methods: GN was induced to rats by injecting anti-glomerular basement membrane antibody. BPS administration (0.6mg/kg/day, p.o.) was started from day 15 after GN induction when serum creatinine levels were increased significantly. Glomerular flow rate (GFR) was measured by inulin clearance method. The number of renal capillary endothelial cells was quantitatively measured by immunohistochemistry with anti-aminopeptidase P antibody (AAP-1) and anti-angiotensin II type 1 antibody (AT1). The renal hypoxic region was evaluated by immunohistochemistry with anti-pimonidazole antibody-positive area.

Results: At day 15 after GN induction, GFR in GN rats was significantly decreased to 57% of normal rats, and further decreased to 11% at day 50. In BPS-treated GN rats, the decrease in GFR was completely inhibited until day 50. Anti-aminopeptidase P antibody-positive area in GN rats was decreased to 60% of normal rats at day 15, and further decreased to 44% at day 50. The decrease in the number of renal capillary endothelial cells was significantly prevented in BPS-treated GN rats. Furthermore, the anti-pimonidazole antibody-positive area was also increased in GN rats at day 50. And, the increase in renal hypoxic region was also prevented by BPS administration.

Conclusions: In this study, BPS inhibited the decrease of GFR, protected renal capillary endothelial cells and improved renal hypoxia associated with CRF in GN rats. Therefore, it is suggested that the improving effect of BPS on renal hypoxia contributes to the suppression of CRF progression.

SA-PO1044
Renal Venous Inflammatory and Injury Biomarkers Are Associated with Net Renin Release and Persist Despite ACE/ARB Therapy in Human Atherosclerotic Renal Artery Stenosis (ARAS) Sandra Herrmann, Ahmed Saad, Alfonso Eirin, Lilach O. Lerman, Stephen C. Tektor. Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: ARAS is known to reduce renal blood flow (RBF) and induce renin release, but the relationships between tissue inflammation and injury and renin release are largely unclear. The purpose of this study was to examine the relationships of renal injury as reflected by systemic and renal vein (RV) levels of the neutrophil gelatinase associated lipocalin (NGAL) and the inflammatory cytokines TNF-α and MCP-1 which are induced in inflammation and ischemia.

Methods: Inpatient studies were performed in ARAS (n=39), with more than 60% occlusion, or in essential hypertensive patients (n=32), measured NAG and RV levels of NGAL, MCP-1 and TNF-α. Plasma renin activity (PRA) was measured and net contribution of renal vein renin (RVR) was determined as follows: PRA (RA-IVC/RA+IVC) x 100%. RVB was measured with multidetector CT and GFR by iohexol clearance.

Results: Renal blood flow, perfusion, and GFR were reduced in the STK. Renal vein levels of NGAL, TNF-α and MCP-1 were higher in ARAS than RV (Table). Net renin contribution of the STK and co-ordinated with RV was correlated with RV NGAL (r=0.5, p<0.02) and MCP-1 (r=0.4, p<0.02) levels in the STK but not with TNF-α.

Conclusions: Oclusive renovascular disease triggers pressor mechanisms including renin release. These results demonstrate an association of net renin contribution of the STK and activation of inflammatory and injury pathways, despite therapy with renin-angiotensin system (RAAS). We interpret these data to indicate that RAAS blockade alone fails to inactivate inflammatory injury in this condition that likely requires additional anti-inflammatory measures to restore post-stenotic kidney function.

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

Underline represents presenting author/disclosure.

SA-PO1045
Contrast-Enhanced Ultrasound Using Perfluobutane Microbubble Agent Is Useful to Evaluate the Degree of Tubulointerstitial Injury Kavoy Tourouka, Takashi Yasuda, Tsutomu Sakurada, Sayuri Shrai, Yugo Shibagaki, Kenjiro Kimura. Div of Nephrology and Hypertension, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan.

Background: Although we evaluate kidney function mostly by glomerular filtration rate, the degree of tubulointerstitial injury (TII) is more predictable of renal prognosis, but is harder to assess. We have reported that kidney contrast-enhanced ultrasound (CEUS) using perfluorbutane is useful to evaluate renal microcirculation in patients with chronic kidney disease (CKD). To evaluate the possibility of assessing TII by CEUS, we examined the results of our previous study, by comparing CEUS parameters with kidney functional and histological findings.

Methods: We examined the parameters of CEUS in total of 23 CKD patients who underwent kidney biopsy. We first obtained the data of PSV (peak systolic velocity), EDV (end diastolic velocity), RV (resistive index) using color Doppler. For CEUS, we administered bolus i.v. (0.0075mg/kg) of perfluorbutane from median vein, then flushed with saline and recorded the data for ten minutes. We evaluated the contrast intensity using image analysis software, and drew a time intensity curve (TIC). Peritubular kidney biopsy was obtained within one month after a CEUS and calculated the degree of tubulointerstitial injury.

Results: In patients with CKD, the time to reach the peak was delayed, peak intensity was low, intensity decreased earlier, and TIC was gentile, compared to those in patients with normal renal function. Because the change in the first 3 seconds from the start of cortical enhancement was remarkable, we assessed the slope of the TIC during this 3 seconds (CS-3 slope) that represents the intensity of the rising gradient. CS-3 slope had a strong correlation with the degree of tubulointerstitial injury (r=-0.70, p<0.0001), and a mild correlation with eGFR (r=0.45, p<0.02). By multivariate analysis, CS-3 slope had significant correlations with RV, PSV, EDV.

Conclusions: Contrast-enhanced ultrasonography with perfluorbutane may be a useful tool to assess the degree of tubulointerstitial injury.

SA-PO1046
Involvement of ACE and ACE2 in Kidney and Cardiac Dysfunction in Rats with Heart Failure Ravit Cohen, Hoda Awad, Niroz Abu-salhe, Zaher Armaly. Physiology, Faculty of Medicine, Technion, Haifa, Israel; Nephrology, EMMS, Nazareth Hospital, Nazareth and Galilee Medical School-Bar Ilan Univ, Zafad, Israel; Rambam Medical Center, Haifa, Israel.

Background: The role of Angiotensin II (Ang II) in the pathogenesis of CHF has been well established. However, the involvement of Angiotensin 1-7 (Ang 1-7) and ACE2 in this phenomenon is largely unclear. This study examined (a) Expression of ACE and ACE2 in the renal and cardiac tissues of CHF rats, and (b) Acute and chronic renal and cardiac effects of Ang 1-7, AVE0991 (Ang 1-7 agonist), and A779 (Ang 1-7 antagonist) in these rats.

Methods: CHF was induced by surgical creation of aorto-caval fistula. ACE and ACE2 immunoactivities were determined in the renal and cardiac tissues of CHF rats and their sham controls. In the acute protocol, the effects of incremental doses of Ang 1-7, Ang II, AVE0991, or A779 on glomerular filtration rate, cardiac output, and cardiac dysfunctions.

Results: ACE and ACE2 immunoactivities were determined in the renal and cardiac tissues of CHF rats, and their sham controls. In the acute protocol, the effects of incremental doses of Ang 1-7, AVE0991, or A779 on glomerular filtration rate, cardiac output, and cardiac dysfunctions.

Conclusions: This study demonstrates that ACE and ACE2 are activated in CHF. Ureapapulation of Ang 1-7 and A779 with their beneficial actions may cause a compensatory response in face of the deleterious classic RAAS to prevent worsened renal and cardiac dysfunctions.
SA-PO1047
Long-Term Administration of Type-I Interferon Leads to Premature Atherosclerosis
Yanpeng Diao, Pui Lee, Rajesh Mohandas, Mark S. Segal. Medicine, Univ of Florida, Gainesville, FL.

**Background:** Disease states such as SLE, CMV, and HIV are associated with elevated type I interferon (IFN-I) and increased cardiovascular risk. We have demonstrated that IFN-I has detrimental effects on endothelial progenitor cells that could contribute to the atherosclerosis (AS). However, the relationship between IFN-I and smooth muscle progenitor cells (SMPC), cells derived from the bone marrow that can differentiate into mature SMC, has not been determined. We hypothesized that IFN-I could induce premature AS by increasing the number of SMPC in the bloodstream and increasing the number of immature SMC within the vasculature.

**Methods:** In vitro, SMPC isolated from wild-type (WT) and IFN receptor knock-out (IFNR-KO) animals, were cultured in medium plus or minus IFN-I. In vivo, two mice models of long-term IFN-I exposure (electroporation of an IFN-I plasmid, or Q 3 day IFN-I i.p. injection for 3 months) were studied and the number of SMPC and degree of AS were analyzed.

**Results:** The number of SMPC from WT mice was significantly increased when cultured in medium plus IFN-I. However, IFN-I had no effect in the SMPC from IFNR-KO mice. Increased SMPC numbers were also observed in mice treated with or that expressed IFN-I. In addition, atherosclerotic-like lesions were found in the arterial wall in WT mice expressing IFN-I. Within the lesions we observed CD34+/SM-α-actin+ expressing cells.

These cells did not express SM myosin heavy chain, suggesting that they were immature SMC.

**Conclusions:** For the first time we demonstrated that elevated IFN-I levels could lead to an atherosclerosis-like lesion. In concert with our previous work, this work suggests a complex interplay between the bone marrow, circulating cells, and the vessel wall leading to IFN-I mediated atherosclerosis. This has profound implications for cardiovascular disease in a number of disease states.

SA-PO1048
Aryl Hydrocarbon Receptor Plays a Crucial Role for Uremic Toxin-Induced Vascular Inflammation
Shunsuke Ito,1,2 Yoshiharu Itoh,3 Masayuki Yoshida.1 1Tokyo Medical and Dental Univ; 2Kureha Corporation.

**Background:** Indoxyl sulfate has been known as one of the major components of uremic toxin in chronic kidney disease patients. The aryl hydrocarbon receptor (AhR) is a ligand-inducible transcription factor known to mediate the toxic effects of numerous environmental toxin in chronic kidney disease patients. The aryl hydrocarbon receptor (AhR) is a ligand-inducible transcription factor known to mediate the toxic effects of numerous environmental toxin in chronic kidney disease patients. The aryl hydrocarbon receptor (AhR) is a ligand-inducible transcription factor known to mediate the toxic effects of numerous environmental toxin in chronic kidney disease patients. The aryl hydrocarbon receptor (AhR) is a ligand-inducible transcription factor known to mediate the toxic effects of numerous environmental toxin in chronic kidney disease patients.

**Methods:** In vitro, SMPC isolated from wild-type (WT) and IFN receptor knock-out (IFNR-KO) animals, were cultured in medium plus or minus IFN-I. In vivo, two mice models of long-term IFN-I exposure (electroporation of an IFN-I plasmid, or Q 3 day IFN-I i.p. injection for 3 months) were studied and the number of SMPC and degree of AS were analyzed.

**Results:** The number of SMPC from WT mice was significantly increased when cultured in medium plus IFN-I. However, IFN-I had no effect in the SMPC from IFNR-KO mice. Increased SMPC numbers were also observed in mice treated with or that expressed IFN-I. In addition, atherosclerotic-like lesions were found in the arterial wall in WT mice expressing IFN-I. Within the lesions we observed CD34+/SM-α-actin+ expressing cells.

These cells did not express SM myosin heavy chain, suggesting that they were immature SMC.

**Conclusions:** For the first time we demonstrated that elevated IFN-I levels could lead to an atherosclerosis-like lesion. In concert with our previous work, this work suggests a complex interplay between the bone marrow, circulating cells, and the vessel wall leading to IFN-I mediated atherosclerosis. This has profound implications for cardiovascular disease in a number of disease states.

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

869A
Reproducibility of Renal Perfusion Measurements Using Arterial Spin Labelling MRI – A Healthy Volunteer Study. Keith Gillis, Christie McComb, Scott Morris, Christian Delles, Patrick B. Mark. Glasgow Renal and Transplant Unit, Western Infirmary Glasgow, Glasgow, United Kingdom; 2Univ of Glasgow, Glasgow, United Kingdom.

Background: Accurate assessment of renal perfusion is a crucial part of measuring kidney function and allows assessment of renal hemodynamics in health and disease. Arterial spin labelling magnetic resonance imaging (ASL MRI) is a novel non invasive method of measuring renal function using paramagnetic properties of blood as endogenous contrast. We studied the reproducibility of ASL MRI in normal volunteers.

Methods: ASL MRI was performed in 12 healthy volunteers on 2 occasions 4-28 days apart on a 3 Tesla MRI scanner along with measurement of routine serum biochemistry. A flow sensitive alternating inversion recovery perfusion and true fast imaging with steady precession sequence (FAIR True-FISP) was utilised to obtain 5 kidney images on each occasion. Cortical and whole kidney perfusion was then calculated on 24 kidneys on 2 visits using automated analysis software.

Results: All subjects (5 male, mean age 44 years) completed 2 ASL MRI studies. Mean estimated glomerular filtration rate was 98.3 ml/min by CKD-EPI formula. Mean cortical perfusion (CP) on visit 1 was 321 ml/min/100g whilst on visit 2 was 336ml/min/100g. Whole kidney perfusion (WKP) was 227ml/min/100g on visit 1 and 230ml/min/100g on visit 2. There was no significant difference between perfusion values measured in visit 1 and visit 2 (CP p=0.167; WKP p =0.659). Bland Altman plots showed no systematic bias for n-Ficoll20-45Å or a-Ficoll20-45Å, and thus had no effect on glomerular charge selectivity. Furthermore, contrary to PS, Hyase did not affect glomerular charge selectivity.

Conclusions: ASL MRI provides a repeatable method of measuring renal perfusion in healthy volunteers. Further research is required to determine if this is also the case in renal impairment, and if findings correlate with renal function.

Funding: Private Foundation Support

SA-PO1051

Influence of Klotho Gene Polymorphisms on Vascular Klotho Expression and Cardiovascular Disease. Javier Donato, Rafael Martinez, Ernesto Martin, Carmen Mora, Mercedes Muros, Violeta Cazaña, Juan F. Navarro-González,1,4 1Research Unit, Univ Hospital Ntra. Sra. de Candelaria, Santa Cruz de Tenerife, Spain; 2Cardiac Surgery Service, Hospita Universitario de Canarias, La Laguna, Spain; 3Clinical Analysis Service, Univ Hospital Ntra. Sra. de Candelaria, Santa Cruz de Tenerife, Spain; 4Nephrology Service, Univ Hospital Ntra. Sra. de Candelaria, Santa Cruz de Tenerife, Spain.

Background: Klotho protein has been associated with beneficial effects on cardiovascular (CV) health. The aim of our study was to analyze the relationship between Klotho gene polymorphisms, mRNA expression levels in the vascular wall and the presence of vascular disease.

Methods: We analyzed three single nucleotide polymorphisms (SNPs) of Klotho locus [rs3804067 (exon 2), G-395A (rs1207568) (promoter) and C1818T (exon4)] in 111 patients undergoing coronary or valve replacement surgery. Gene expression studies were performed in fragments of thoracic aorta.

Results: G-395A polymorphism is related to Klotho levels in vascular tissue: Klotho mRNA levels were significantly lower in homozygous carriers of the G allele [0.19 ± 0.1 vs. 0.97 ± 0.17 (log relative units), P<0.0001]. These differences were not observed for the other two polymorphisms. When comparing the vascular klotho expression levels with clinical characteristics of patients, we observed a higher incidence of coronary artery disease (CAD) in subjects with lower mRNA Klotho expression (P=0.06). However, the G-395A polymorphism was not related with the incidence of CAD. By contrast, CAD and atherosclerotic disease were more frequent in patients carrying the minor allele of the F352 polymorphism (77.9%, P=0.08 and 89.8%, P<0.01, respectively). Finally, the incidence of valve calcification was higher in homozygous carriers of the C allele of C1818T polymorphism compared to carriers of the T allele (43% vs 19%, P<0.01).

Conclusions: Polymorphisms of the Klotho gene may influence tissue expression levels of this protein as well as be related to the incidence of atherosclerotic vascular disease and valvular calcification.

SA-PO1052

Protamine Sulfate and Hyaluronidase Reduce the Size-Selectivity, but Not the Charge-Selectivity, of the Rat Glomerular Filtration Barrier In Vivo. Kristinn Sverrisson, Josef Axellson, Anna Rippe, Bengt Rippe. Dept of Nephrology, Clinical Sciences, Lund, Sweden.

Background: The proteinuric actions of protamine sulfate (PS) have classically been, at least partly, attributed to alterations of the negatively charged glomerular endothelial glycoalyx (GC). To investigate whether the charge-selective properties of the glomerular filtration barrier (GFB) would be altered by PS we assessed the glomerular sieving of conformationally intact, anionic (carboxymethylated) Ficoll (n-Ficoll) compared to charge modified, conformationally intact, anionic (carboxymethylated) Ficoll (a-Ficoll) before and after systemic infusions of PS in rats. For comparison we also investigated the impact of systemic infusions of PS in rats. For comparison we also investigated the impact of systemic infusions of PS in rats.

Results: As reported previously, we found a significant glomerular charge selectivity for Ficoll molecules of radius 20-45Å (Ficoll20-45Å). PS infusions increased 0.2 for Ficoll20- 45Å markedly, and partly reversibly, for both n-Ficoll and a-Ficoll. For a-Ficoll, 0 the increase was less pronounced, and thus had no effect on glomerular charge selectivity. Furthermore, contrary to PS, Hyase did not affect 0 for a-Ficoll, whereas it caused a moderate increase in 0 for large n-Ficoll molecules.

Conclusions: Systemically administered PS and Hyase decreased the size-selectivity of the rat GFB, but did not affect its charge selectivity, as indicated by the unaltered 0 for a-Ficoll20-45Å after PS or Hyase infusions.

Funding: Government Support - Non-U.S.
SA-P01056
Quantitative Measurement of Vascular Occlusion Is Associated with Tissue Hypoxia and Inflammatory Cytokines in Human Atherosclerotic Renal Artery Stenosis
Ahmad Saad, Sandra Herrmann, Alfonso Eirin, John A. Crane, Michael A. McKusick, James Glocner, Lilach O. Lerman, Stephen C. Textor. Mayo Clinic.

Background: Atherosclerotic renal artery stenosis (ARAS) reduces renal blood flow (RBF) and amplifies kidney hypoxia, but the relationship of degree of arterial stenosis and RBF reduction and renal injury remains poorly understood. We tested the hypothesis that RBF reduction and renal injury as reflected by renal vein levels of neutrophil gelatinase associated lipocalin (NGAL) would be magnified with more severe occlusive vascular disease in humans with ARAS.

Methods: Inpatient studies were performed in patients with ARAS (r=40, 71.3±11% (Range 48, 89) occlusion by quantitative CT angiography) or essential hypertension (EH) (n=30), during fixed Na+ intake and ACE/ARB Rx. Single-kidney(SK) cortical/medullary perfusion, volume and RBF were measured using multidector CT, and glomerular filtration rate (GFR) by isothalamic clearance. Tissue deoxyhemoglobin levels (R2+) and fractional kidney hypoxia (% of axial area with R2+≥20) were measured by BOLD-MRI at 3T.

Results: SK-RBF, volume, cortical and medullary perfusion were reduced in the post-stenotic kidney, as was GFR. Renal vein NGAL and fractional hypoxia were higher in patients with ARAS than EH. The degree of arterial stenosis correlated directly with NGAL levels (r = 0.49, P=0.0004) and fractional hypoxia (r = 0.33, P=0.01) and inversely with the RBF, GFR, and kidney volume (r = −0.59, P<0.0001; r = −0.66, P<0.0001, and r = −0.54, P=0.0001).

Conclusions: Our results demonstrated that elevated renal venous markers of kidney injury (NGAL) and RBF in ARAS are correlated with the severity of arterial stenosis measured by CT. Therefore, although moderate blood flow reduction is often tolerated, severe stenosis is associated with active inflammatory injury in renovascular disease.

SA-P01057
Early Detection of Renal Hemodynamic Dysfunction Using Sonographic Analysis in Drug-Induced Nephrotoxicity Rat Models
Tromeshi Lu,1 Vivian Y. Chan,2 Li-Li Hsiao.1
1Renal Div, Brigham and Women’s Hospital, Boston, MA; 2Harvard College, Cambridge, MA.

Background: Drug-induced nephrotoxicity consists 19-25% of all cases of acute kidney injury (AKI). Conventional metrics such as serum creatinine (sCr) has been shown inadequate to detect nephrotoxicity before significant renal function loss and there is no robust method to accurately early detect hemodynamic in the course of drug-induced nephrotoxicity. To detect drug-induced kidney hemodynamic dysfunction in the early discovery phase would provide great benefit for better decision-making about candidate compounds and dose selection, as well as better design for clinical trials that will provide clear information about product benefit and safety. Real-time sonography combined with Color-Doppler imaging technique is the most advanced non-invasive tool to evaluate kidney status, and it is particularly useful for detecting early vascular occlusions and arterial stenosis in renal function analysis.

Methods: Rats were treated with Cisplatin (5 mg/kg b.w., single dose, i.p.) to induce AKI. Nephrotoxicity was assessed 6 days after Cisplatin treatment by measuring sCr and histopathology of kidney. Hemodynamic evaluation using Sonography combined with Color-Doppler imaging via Vevo2100 system (VisualSonrc, Toronto, Canada).

Results: Our data showed successful drug-induced proximal tubular kidney injury by histological examination. Color-Doppler ultrasound study of AKI rats showed that resistive index (RI) and pulsatile index (PI) were increased; and peak-systolic velocity (mm/s), end-diastolic velocity (mm/s), and arterial stenosis correlated directly with GFR and it is particularly useful for detecting early vascular occlusions and arterial stenosis in renal function analysis.

Conclusions: These observations suggest that RI, PI, VTI, peak-systolic velocity and end-diastolic velocity may serve as hemodynamic parameters to evaluate early phase of kidney injury. We suggest that this technical advance will provide an unprecedented opportunity for a non-invasive and sensitive method. Furthermore, the combination of these parameters with histopathology and sCr suggest their potential utility to study drug-induced dysfunction and nephrotoxicity.

Funding: Private Foundation Support

SA-P01058
Measurement of flow-mediated dilation (fMD) in the femoral artery of anesthetized rats by using a high-resolution ultrasound system. FMD was calculated from the change in diameter of the femoral artery (relative to baseline diameter) following reperfusion after 5 min ischemia of the iliac artery.

Results: Urinary protein (uTP) and blood pressure (BP) were increased in Nx rats. Femoral blood velocity instantaneously increased (i.e. reactive hyperemia) at reperfusion after 5 min of hind limb ischemia. Following reactive hyperemia, maximum arterial dilation (i.e. FMD) was observed at 0.5–1 min after reperfusion. FMD tended to negatively correlate with uTP and BP. In Nx rats treated with C.E.R.A., Hb increased to within the normal range, but at 4TP and BP did not show any significant change. C.E.R.A. significantly increased FMD in the femoral artery without changing reactive hyperemia. C.E.R.A. significantly decreased nitrotyrosine (a marker of peroxynitrite) in the femoral artery. In addition, C.E.R.A. enhanced phosphorylation of endothelial nitric oxide synthase (eNOS) in the femoral artery.

Conclusions: These results demonstrated that, in Nx rats, C.E.R.A. improved endothelial function with reduction of oxidative stress and improvement of eNOS activity.

SA-P01054
Klotho Is Not Expressed Endogenously in Healthy and Uremic Vascular Tissue
Rien Meeneke,1 Joyce Struijk,1 Joris van Ark,1 Melissa Verkaik,1 Martin H. De Borst,2 Marc G. Vervloet,1 Jan- luuk Hillebrandts.1
1Pathology, UMC, Netherlands; 2Physiology, VUmc, Netherlands; 3Internal Medicine - Nephrology, VUmc, Netherlands; 4Internal Medicine - Nephrology, UMC, Nethelands.

Background: Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD), a disease state that is strongly associated with loss of renal klotho. Reversely, murine klotho deficiency also causes marked medial calcification. It is thought that klotho conveys a vasoprotective effect, inhibiting calcification and the development of atherosclerosis. Klotho expression in the vessel wall itself, however, is still disputed.

Methods: We assessed klotho expression in healthy renal donor arteries (N=6), CKD (renal transplant recipient) arteries (N=10), carotid endarterectomy specimens (N=4), healthy vascular tissue, and human cells whose serum level is a stronger predictor of the risk of cardiovascular events.

Results: Using anti-klotho antibody KM2076, we detected strongly positive staining in healthy renal donor arteries, and human cells whose serum level of CysC and markers of vascular dysfunction, including the renal RI, ankle-brachial index (ABI), in healthy donor and CKD arteries, nor by immunohistochemistry and immunofluorescence, Western blotting (WB), qRT-PCR, and mass spectrometry. We extensively validated antibody specificity, using multiple antibodies to compare staining patterns, and comparison assays and WB with recombiant human klotho (RhKlotho).

Conclusions: In contrast to recently published data, using several independent and validated methods, we conclude that klotho is not expressed in healthy or atherosclerotic vascular tissue, nor in cultured HASMcs. The putative vasoprotective effect of klotho most likely results from circulating klotho levels.

Funding: Private Foundation Support

SA-P01055
Serum Cystatin C Is a Significant Diagnostic Marker of the Renal Resistive Index Detected on Doppler Ultrasound in Patients with Chronic Kidney Disease
Ayu Ogawa, Hitoshi Sugiyama, Masashi Kitagawa, Hiroshi Morinaga, Toshio Yamanari, Akifumi Onishi, Yoko Kikumoto, Shinji Kitamura, Yohei Maeshima, Hirofumi Makino. Okayama Univ Graduate School of Medicine, Okayama, Japan.

Background: Cystatin C (CysC) is a cysteine protease inhibitor produced nearly by all human cells whose serum level is a strong predictor of the risk of cardiovascular events than that of creatinine. The resistive index (RI) on renal Doppler ultrasoundography is a good indicator of renal vascular resistance as well as renal outcomes in patients with chronic kidney disease (CKD). However, it is unclear whether the serum CysC level is associated with signs of vascular dysfunction, such as renal RI in CKD patients.

Methods: We determined the levels of serum CysC in 73 CKD patients (median age: 57.0 years, male: 67.1%, diabetes: 9.6%) and investigated the relationship between the level of CysC and markers of vascular dysfunction, including the renal RI, ankle-brachial pulse wave velocity (baPWV), a marker of arterial stiffness, and intima-media thickness (IMT), a marker of atherosclerosis.

Results: The serum CysC level was significantly correlated with the renal RI (P = 0.0001), mean IMT (P = 0.0499) and baPWV (P = 0.0001). The serum CysC level was a significant determinant of the renal RI (P = 0.0281), but not the baPWV or mean IMT, in a multivariate regression analysis using a biomarker model. The multivariate odds ratio of the serum CysC level for a renal RI of 0.70, a level that predicts worse renal outcomes, was 4.04 (P = 0.0030); however, the odds ratios for the baPWV and mean IMT were not significant. The area under the receiver-operating characteristic curve comparing the serum CysC level for predicting the RI 0.70 was 0.526 (P < 0.0001) (cutoff value: 2.04 mg/L). The serum CysC level was significantly correlated with the level of albuminuria and inversely correlated with the eGFR, as previously reported.

Conclusions: The serum CysC level is independently associated with signs of vascular dysfunction, such as the renal RI, in patients with CKD. The study suggests that the serum CysC level serves as a significant marker of the renal RI in CKD patients.
**SA-PO1058**

Proteinuria in Zucker Diabetic Fatty Rat Predicted by Small Renal Artery Function at Young Age


**Background:** Severity of chronic kidney disease varies considerably among patients with similar risk profiles, such as obesity, diabetes (DM) and also be dependent on intrinsic factors. Early occurrence of vascular dysfunction in progressive renal disease has led us to question whether renal vascular function might condition the susceptibility of obese individuals to renal damage.

**Methods:** Obese Zucker diabetic fatty (ZDF) rats (n=10) at pre-DM state were subjected to unilateral nephrectomy (UNx) and followed for development of proteinuria until 10 weeks thereafter. At the moment of UNx, intrarenal arteries were isolated from extirpated kidneys and individually studied for endothelium-dependent relaxation (EDR) to acetylcholine and pressure-induced myogenic constriction (MC) responses. Linear regression analysis was performed of baseline EDR and MC (both expressed as AUC in arbitrary units) with increase in proteinuria (mg/24h).

**Results:** At the end, ZDF-UNx rats showed DM - i.e. increased blood glucose (18.5±3.2 mmol/L), HbA1c (5.9±0.6 %), cholesterol (5.4±0.6 mmol/L) and urinary glucose leakage (2.6±1.1 mmol/24h) and associated renal injury including marked urinary protein excretion (190±25 mg/24h). Proteinuria was significantly predicted by renal artery function such that individuals with low EDR and/or high MC at baseline showed a higher increase in proteinuria during DM-development thereafter.

**Conclusions:** Proteinuria in ZDF rat is predicted by intrarenal artery function at young age. This seems of relevance as our society is becoming increasingly obese and developing associated health problems, such as diabetic nephropathy. Hence, tools that help to monitoring intrarenal vascular function could be useful to identify the individuals prone to the renal damage.

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

**SA-PO1059**

Far-Infrared Induces Autophagy to Inhibit Advanced Glycation End Product-Induced Apoptosis in Vascular Endothelial Cells

Yung-Ho Hau, Tso Hsiao Chen, Cheng-Hsin Chen. Div of Nephrology, Dept of Internal Medicine, St. John's Hospital, Taipei Medical Univ, Taipei, Taiwan; Div of Nephrology, Dept of Internal Medicine, Wan Fang Hospital, Taipei Medical Univ, Taipei, Taiwan.

**Background:** Diabetic vascular complication accounts for disabilities and high mortality rates in diabetic patients. The accumulation of advanced glycation end products (AGEs) in diabetic patients can trigger apoptotic changes in vascular endothelial cells and involves in the development and progression of micro- and macroangiopathy. Far-infrared radiation (FIR) therapy has been proved to be effective in increasing patency of dialysis vascular access.

**Methods:** Our study is to investigate the biological effects of FIR on AGEs-induced apoptosis in human umbilical vein endothelial cells (HUVECs).

**Results:** We found FIR exposure for 30 min significantly inhibited AGE-bovine serum albumin (BSA)-induced apoptosis in HUVECs. FIR exposure inhibited AGE-BAS-induced apoptotic signals, including cleaved caspase-3 increase and Bcl-xL decrease. We found that FIR exposure induced nuclear translocation of p38 mitogen-activated protein kinase (p38MAPK) and phosphatidylinositol-3 kinase (PI3K) class III expression. PLZF siRNA transfection inhibited FIR-induced p38MAPK and PI3K expression.unts. The maximal arteriolar contraction was significantly larger in Shb-/- (87 %; n=8) than in Shb+/+ (54 %; n=8) mice. Low-dose Ado alone contracted arterioles in both genotypes (6 % in Shb-/- and 7 % in Shb+/+). Ado significantly enhanced Ang II constriction in arterioles in both genotypes (to 93 % in Shb-/- and to 72 % in Shb+/+).

**Conclusions:** Low-dose adenosine augments Ang II arteriolar constriction effectiveness, which indicates Ado-Ang II interaction in both Shb-/- and Shb+/+ mice. The absence of Shb increases GFR. The underlying mechanisms remain to be resolved.

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

**SA-PO1060**

Src Homology 2 Domain-Containing Protein B Deficient Mice Display an Increased Glomerular Filtration Rate and Augmented Renal Arteriolar Contractions to Both Adenosine and Ang II

Xiang Gao, 1 Medical Cell Biology, Uppsala Univ, Uppsala, Sweden; 2Karolinska Institute, Stockholm, Sweden.

**Background:** Src homology 2 domain-containing protein B (Shb) is an adapter protein which regulates several signal transduction cascades and endothelial cell functions. The adenosine-angiotensin II (Ado-Ang II) interaction plays an important role in the regulation of glomerular filtration rate (GFR), vascular resistance and tubuloglomerular feedback. We used Shb-knockout (Shb-/-) and wild-type (Shb+/+) mice to investigate their GFR and effectiveness of Ado and Ang II to constrict renal resistance vessels.

**Methods:** GFR was measured in conscious Shb-/- and Shb+/+ mice using FITC-inulin. Isotonic contractions were measured in isolated and perfused renal afferent arterioles from Shb-/- and Shb+/+ mice.

**Results:** Concentration responses to Ang II (10-11 to 10-6 M; 2 minutes each) doses or low-dose Ado (10-10 M; 15 min) alone, as well as Ado (10-6 M) in combination with cumulative application of Ang II (10-10 to 10-6 M; 2 minutes each) were studied in both genotypes. There was a significantly increased GFR (371 ± 12 μl/min, n=11) in Shb-/- compared to Shb+/+ (321 ± 11 μl/min, n=8) mice. The maximal arteriolar contraction to Ang II was significantly larger in Shb-/- (87 %; n=8) than in Shb+/+ (54 %; n=8) mice.

**Conclusions:** Our data suggest that FIR therapy induces autophagy to inhibit AGE-BSA-induced apoptosis in HUVECs.
Several distinct features of the response varied among the groups as shown in the figure. Transient peaks and/or damped oscillations are consistent with simple negative feedback control with intrinsic delay and gain exceeding some threshold. Peaks at Lag<15s and >25s presumably owe to myogenic and TGF responses, respectively. Most of the difference among Sham LS, Sham HS, and STN LS can be explained by quantitative adjustments of the TGF gain. Unique to STN HS was a 3s vasodilatory phase followed by sluggish autoregulatory response.

**Conclusions:** Simple systems analysis revealed distinct components to the autoregulatory response that are individually affected by STN and dietary salt. Overall, the autoregulatory response is slower and salt-sensitive in STN.

**Funding:** Veterans Affairs Support

**SA-PO1064**

**Diffusion Tensor Imaging: A Useful Tool in the Evaluation of Renal Artery Stenosis**

Emiliana Ferrarossac,1 Laura Patregnanci,1 Caterina Gaudion,1 Fiorenza Busato,2 Valeria Centicic,1 Rita Gollferi,1 Antonio Santorod,1,2


**Background:** Diffusion Tensor Imaging (DTI) is an MR imaging technique used to show molecular diffusion. The apparent diffusion coefficient (ADC) combines the effects of capillary perfusion and water diffusion in the extracellular space. Fractional Anisotropy (FA) is a quantitative value that provides information on direction of water molecules flow within a tissue. DTI provides information on diffusion and perfusion simultaneously.

Aim of this study was to evaluate feasibility of DTI in detecting unilateral kidney alteration in pts with renal artery stenosis (RAS).

**Methods:** We studied 13 patients (pt) with RAS and 15 control subjects without any kidney disease. All subjects underwent morphological MRI followed by DTI sequence. Mean ADC and FA values of cortical and medullary Regions of Interest were calculated. The reference range for ADC and FA on cortex and medulla in the control group was defined as mean±2SD. For each kidney in the pt with RAS the corresponding parameters were compared with the reference range.

**Results:** Reference ranges on controls were: 2.55±0.18-10^{-3} mm²/s for cortical ADC, 2.25±0.24 ×10^{-3} mm²/s for medullary ADC, 0.308±0.071 for cortical FA and 0.389±0.067 for medullary FA.

In 7 pt DTI parameters confirmed the unilateral alteration showed by the CE-MRI. In 1 pt DTI confirmed the bilateral alteration showed by the CE-MRI. In the other 5 pt DTI parameters suggested functional alterations but not corresponding to the side involvement showed by the CE-MRI.

**Conclusions:** DTI of the kidneys is a new application that allows us to study renal alterations. Previous studies demonstrated the feasibility of DTI in pt with CKD, showing lower ADC than in control subjects. This preliminary results suggest to increase the number of data to investigate the DTI ability to measure the functional alteration of each kidney, also by adding percentage of RAS and kidney volume data. Based on these data DTI could be useful on RAS study by evaluating functional alteration of each kidney.

**Funding:** NIDDK Support

**SA-PO1065**

**Interferon-Gamma Increases Connexin-40 Expression and Affects Electrical Properties of Renal Cell Types:**

Brancko Braun,1 Wenqing Zhuang,1 Steve Hopper,2 Amanda Alexander,2 William Todd,2 William Cuppers,1 Medicine/Nephrology, Univ of Alberta; 1Physiology, Univ of Alberta; 2Pediatrics, Univ of Alberta, Edmonton; 3Physiology and Kinesiology, Simon Fraser Univ, Vancouver, Canada.

**Background:** Connexin (Cx)-37, -40 and -43 are part of the gap junctions between and participate in the electrochemical coupling of endothelial cells (EC). These properties have been implicated in vascular regulation, since the EC seem to form the ‘electrical cable’ for axial signal transmission in the microvasculature. We investigated whether CX expression responds to stimuli known to be involved in endothelial dysfunction.

**Methods:** Interferon-gamma (IFNγ) strongly induced Cx-40 expression and subsequently was tested with respect to transcellular impedance. Human microvascular EC-1 (HMEC-1, CDC) in culture were subjected to partial vs. full confluence, normal vs. high glucose (5 vs 25 mM), IL-6; IFNγ; TNFα; Ang II and DETA-NONOate. After 4h and 24h cells were harvested for RNA isolation, DNA degradation and RT-qPCR with specific primers.

**Results:** Of all stimuli, IFNγ (1-30 ng/ml) consistently induced Cx-40 expression at 4h and 8h dose dependently to 10-20 fold when corrected for the control (HPRT). TNFα and IL-6 resulted in a small, significant depression of Cx-37 expression at 4h. The induction of Cx-40 by IFNγ was reproduced in HUVEC (less pronounced) and glomerular EC in culture. All other stimuli did not change expression of Cx-37, Cx-40 or Cx-43. Two JAK inhibitors, EGCG (100-250 uM) and A-490 (100-250 uM) dose-dependently inhibited the induction of Cx-40 expression by IFNγ. Subsequently, HMEC-1 were subjected to 10-30 ng/ml IFNγ for up to 48h and transcellular cell impedance monitored by cell-substrate impedance sensing (EICS, Applied Biosciences). IFNγ dose-dependently increased cell impedance significantly after 24h and this was blunted by A-490 (25 uM).

**Conclusions:** These experiments point to an important role of IFNγ to induce CYX40 expression. IFNγ also seems to increase EC electrical impedance, which could ‘insulate’ the electrical cable. Experiments testing intercellular conductance are ongoing.

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

**SA-PO1066**

**Comparison of Combination Therapy with Irbesartan/Amlodipine and Irbesartan/Cilnidipine for Attenuation of Albuminuria in Rats with Streptozotocin-Induced Diabetic Nephropathy:**

Minoru Satoh, Yuko Nishi, Hiroyuki Kadoya, Tamaki Sasaki, Naoki Kashihara, Dept of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.

**Background:** Managing hypertension is important for decreasing the risks of cardiovascular and renal diseases. Calcium channel blockers (CCBs) have been shown to have suppressive effects on urinary albumin excretion. However, it is unknown whether this effect differs in combination therapy with angiotensin receptor blockers (ARBs). This study aimed to compare the efficacy of the combination therapy of irbesartan/amlopidine and irbesartan/cilnidipine on diabetic nephropathy.

**Methods:** Male Sprague-Dawley rats with streptozotocin–induced diabetes were treated with CCBs, amlopidine (2.0 mg/kg/day) or cilnidipine (2.0 mg/kg/day), with or without the ARB, irbesartan (20.0 mg/kg/day). In the acute protocol, changes in the diameters of glomerular afferent and efferent arterioles were examined by charge-coupled device video microscope. In the chronic protocol, urinary albumin excretion, glomerular reactive oxygen species, and endothelial surface layer were evaluated.

**Results:** In the acute protocol, cilnidipine monotherapy caused a greater dilation in glomerular afferent arterioles than amlopidine monotherapy. In both groups, combination therapy with irbesartan induced comparable dilation in the glomerular efferent arterioles. In the chronic protocol, cilnidipine monotherapy suppressed albuminuria more than amlopidine monotherapy. However, the addition of irbesartan reduced the albumin excretion in both groups. In a group initiated on irbesartan monotherapy, addition of cilnidipine or amlopidine had no further effect on albuminuria reduction.
Conclusions: Cilnidipine monotherapy suppressed increased albuminuria more than amloidipine monotherapy. However, combination therapy with irbesartan led to a greater reduction in albuminuria in both treatment groups and with equal effectiveness. The combinations of irbesartan with cilnidipine or amloidipine are equally effective in reducing albuminuria in diabetic nephropathy.

**Funding:** Pharmaceutical Company Support - Dainippon Sumitomo Pharma, Private Foundation Support

SA-PO1066

Comparison of Central Venous Pressure with Cardiac Output Measured by Non-Invasive Cardiac Output Monitoring during Anesthesia for Kidney Transplant Surgery

Joon Seok Oh, Jin Ho Lee, Seong Min Kim, Yong Hun Sin, Yong Ki Park, Joong Kyung Kim.

**Div of Nephrology, Internal Medicine, Bong Seng Memorial Hospital, Busan, Korea; Div of Nephrology, Internal Medicine, Dongnagae Bong Song Hospital, Busan, Korea.**

**Background:** Patients with end-stage renal disease (ESRD) can be hemodynamically unstable because of frequent changes in peripheral resistance and blood volume during kidney transplant surgery. Cardiac output (CO) is a key variable when describing and treating the cardiovascular system. Thermodilution via a pulmonary artery catheter is the most frequently used method, but it lacks accuracy. Non-invasive cardiac output monitoring (NICOM) measures CO based on chest bioreactance. Validated data of NICOM in patients with kidney transplant surgery are lacking. So we compared central venous pressure (CVP) with cardiac output monitored via NICOM system during anesthesia for renal transplant surgery.

**Methods:** Stroke volume (SV) values using NICOM were recorded during anesthesia in patients with renal transplant surgery and CVP values were measured at the same time. The difference between measured and average values of SV (ACVP) and SV (ASCVP) were calculated in each subject, because SV values may be different depending on the person who measured. Correlation analysis was performed for SV with ASV and ACVP.

**Results:** Twenty subjects were enrolled and the SV and CVP values were measured 100 times. There was a positive correlation with ASV and ACVP (R = 0.61, p < 0.001).

**Conclusions:** Stroke volume measured by NICOM and CVP showed a positive correlation. NICOM may be effective as non-invasive method for circulating volume monitoring in patients with renal transplant surgery.

SA-PO1067

Angiotensin II Type 2 Receptor Activation Counteracts Angiotensin II-Induced Loss of Glomerular Permeselectivity – A Multiphoton Microscopy Study

Ina Maria Schiessl, Hayo Castrop.

**1Div of Nephrology, Internal Medicine, 2Division of Nephrology and Dept of Medicine, Duke University Medical Center, Durham, NC; 3Dept of Medicine, Univ of California, San Francisco, CA; 4Univ of Manchester, United Kingdom; 5Amgen, Thousand Oaks, CA.**

**Background:** The extracellular calcium-sensing receptor (CaSR) is expressed in the vasculature, but the roles of the CaSR in vascular pathophysiology still remain unclear.

**Methods:** We studied the phenotype of a mouse model of vascular smooth muscle cell (VSMC) targeted CaSR deletion by breeding exon 7 LoxP-CaSR mice with SM22a-Cre mice.

**Results:** CaSR wild-type (WT) and knock-out (KO) mice showed no difference in weight, lifespan or reproductive capability. However, compared to WT control, 9 month old KO mice were hypotensive (90 ± 2.8 vs. 95 ± 2.8 mm Hg, p < 0.05, N=6-11). Wire myography showed reduced phenylephrine-induced contraction and increased acetylcholine-induced relaxation of isolated KO aortae compared to WT control, suggesting a role for vascular CaSR in the control of arterial tone and hence blood pressure. Ca 2+ and FGF23 levels were significantly elevated in KO mice compared to WT (Ca 2+: 3.05 ± 0.27 vs. 2.28 ± 0.09 mM; FGF23: 384.4 ± 83.5 vs. 145.0 ± 11.0 pg/ml, p<0.01, N=6-11) indicating an indication of the vascular CaSR on Ca 2+/Pi homeostasis, a notion supported by the observation that KO mice showed significantly impaired bone mineral density. In vitro, VSMC cultured from KO mice – which show a ~60% reduction of CaSR staining intensity compared to WT (quantitative immunofluorescence) – exhibited a significantly greater predisposition to calcify in mineralising conditions (3 mM Pi and 1 mM Ca 2+) compared to WT control (24.60 ± 0.99 AU, alizarin red densitometry, p<0.001, N=6-8).

**Conclusions:** These data point to an important physiological role for the vascular CaSR in blood pressure regulation and electrolyte homeostasis and to a possible protective role against vascular calcification in pathophysiology.

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

SA-PO1068

The Vascular Smooth Muscle Cell Calcium-Sensing Receptor Is Involved in Blood Pressure Regulation, Calcium-Homeostasis and Protection from Calcification


**Cardiff Univ, United Kingdom; Astra Zeneca, Macclesfield, United Kingdom; Dept of Medicine, Univ of California, San Francisco, CA; Univ of Manchester, United Kingdom; Aungst, Thousand Oaks, CA.**

**Background:** The Extracellular Calcium-Sensing Receptor (CaSR) is expressed in the vasculature, but the roles of the CaSR in vascular pathophysiology still remain unclear.

**Methods:** We studied the phenotype of a mouse model of vascular smooth muscle cell (VSMC) targeted CaSR deletion by breeding exon 7 LoxP-CaSR mice with SM22a-Cre mice.

**Results:** CaSR wild-type (WT) and knock-out (KO) mice showed no difference in weight, lifespan or reproductive capability. However, compared to WT control, 9 month old KO mice were hypotensive (90 ± 2.8 vs. 95 ± 2.8 mm Hg, p < 0.05, N=6-11). Wire myography showed reduced phenylephrine-induced contraction and increased acetylcholine-induced relaxation of isolated KO aortae compared to WT control, suggesting a role for vascular CaSR in the control of arterial tone and hence blood pressure. Ca 2+ and FGF23 levels were significantly elevated in KO mice compared to WT (Ca 2+: 3.05 ± 0.27 vs. 2.28 ± 0.09 mM; FGF23: 384.4 ± 83.5 vs. 145.0 ± 11.0 pg/ml, p<0.01, N=6-11) indicating an indication of the vascular CaSR on Ca 2+/Pi homeostasis, a notion supported by the observation that KO mice showed significantly impaired bone mineral density. In vitro, VSMC cultured from KO mice – which show a ~60% reduction of CaSR staining intensity compared to WT (quantitative immunofluorescence) – exhibited a significantly greater predisposition to calcify in mineralising conditions (3 mM Pi and 1 mM Ca 2+) compared to WT control (24.60 ± 0.99 AU, alizarin red densitometry, p<0.001, N=6-8).

**Conclusions:** These data point to an important physiological role for the vascular CaSR in blood pressure regulation and electrolyte homeostasis and to a possible protective role against vascular calcification in pathophysiology.

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

**SA-PO1069**

Tubular Vegfa Is Required for Renal Microvascularization and Oxygen Sensing

Henrik Dinkme, Matthew A. Sparks, Sebastian Frische, Thomas M. Coffman, Susan E. Quaggin.

**1Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Canada; 2Div of Nephrology and Dept of Medicine, Duke Univ, Durham, NC; 3Dept of Biomedicine, Univ of Aarhus, Aarhus, Denmark; 4Northwestern Univ, Feinberg School of Medicine, Chicago, IL.**

**Background:** Adequate renal oxygenation is pivotal for maintaining essential functions of the kidney. Vascular endothelial growth factor A (VEGFA) plays a key role in vascular formation and maintenance, processes that are critical for sufficient tissue perfusion and oxygenation.

**Methods:** Using a range of targeted transgenic mice models we determined the intrarenal localization of the VEGF system and the functional consequences of Vegfa ablation in renal tubules.

**Results:** Here we show that Vegfa is expressed in select tubular epithelial cells, while expression of its receptor (Kdr/Vegfr2) is restricted largely to capillary beds. Early genetic ablation of tubular Vegfa allows the formation of a grossly normal kidney. However, microvascular density is markedly reduced, leading to increased renal hypoxia. As a consequence the mice develop pronounced polycythemia, elicited by an augmented renal production of erythropoietin. In kidney, expression of classical hypoxia-inducible factor-1 responsive transcripts remains unaltered; suggesting that erythropoiesis partly compensates the capillary rarefaction. An increase in diastolic blood pressure (112 ± 3.7 vs. 104 ± 1.6 mmHg) is present in mice lacking tubular Vegfa maintained on a normal diet, while systolic blood pressure (139 ± 2.8 vs. 135 ± 2.8 mmHg) does not change. The difference in diastolic pressure is ablated when dietary NaCl content changed or when angiotensin II is infused. Moreover, renal electrolyte excretion remains unperturbed by reductions in tubular Vegfa.

**Conclusions:** Tubular Vegfa is required for normal renal microvascularization and oxygen sensing.
SA-PO1070
Role of MicroRNA-126 in Asymmetric Dimethylarginine Induced Endothelial Dysfunction 
Filippo Martino,1 Jan T. Kielstein,2 Thomas Thum,3 Johan M. Lorenzen.2 1Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Hannover, Germany; 2Dept of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany.

Background: Asymmetric Dimethylarginine (ADMA), an endogenous inhibitor of NO, is elevated in patients with chronic kidney disease and is known to contribute to endothelial dysfunction. It remains unclear if microRNAs have an impact on these detrimental effects. We investigated the role of microRNA-126, which is essential for endothelial biology in ADMA induced endothelial dysfunction.

Methods: We measured ADMA-Plasma levels in 39 patients with coronary artery disease (CAD) by ELISA assay and correlated them with circulating miR-126 levels assayed by qRT-PCR. We infused ADMA into healthy rats (250μg/Ml ADMA/kg/day) and healthy human volunteers (0.1mg ADMA/kg/min, 40 minutes) and quantified plasma levels of different microRNAs. We investigated the underlying molecular mechanisms in vitro by using HUVECs. Stimulating them with ADMA, we quantified extra- and intracellular levels of miR-126. Transcriptional activation was assessed by electrophoretic mobility shift assay (EMSA).

Results: Plasma Levels of ADMA in CAD patients correlated inversely with levels of circulating miR-126 (r=-0.52, p<0.001). ADMA infusion reduced circulating levels of miR-126 in rats. Levels of circulating miR-126 in healthy human volunteers were significantly decreased after ADMA infusion (p<0.05), whereas other microRNAs were not significantly altered. We could detect a time dependent alteration of extracellular and intracellular levels of miR-126 (extracellular: decreasing 24h p<0.05; intracellular: increasing 2p<0.05) in vitro. Changes of intracellular levels of miR-126 were not related to transcriptional activation by ETS-1, which is known to regulate miR-126.

Conclusions: We were able to show, that miR-126, which is known to convey alarm signals to injured endothelium and thereby contribute to repair mechanisms and cellular survival, is regulated by ADMA. Therefore, detrimental effects of ADMA on endothelial function might be partly mediated by miR-126. These effects are rather a consequence of altered miR-126 trafficking (e.g. through exosomes/microvesicles) than transcriptional regulation.

SA-PO1071
Angiopoietin-2 Induced Arterial Stiffness in Chronic Kidney Disease 
Fan-Chi Chang,1,2,3 Yu-Bai-Siang Chou,4 Szu Yu Pan,1 Yi-Ting Chen,1,2,5 Wen-Chih Hsu,1 Shuei-Liong Lin.5 1Renal Div, National Taiwan Univ Hospital, Taipei, Taiwan; 2Dept of Internal Medicine, National Taiwan Univ Hospital Chu-Tung Branch, Hsin-Chu, Taiwan; 3Graduate Institute of Physiology, College of Medicine National Taiwan Univ, Taipei, Taiwan; 4Dept of Internal Medicine, National Taiwan Univ Hospital Yun-Lin Branch, Yun-Lin, Taiwan; 5Dept of Internal Medicine, E-DA Hospital, Kaohsiung, Taiwan.

Background: Arterial stiffness is recognized detrimental to cardiovascular outcome. Given increased arterial stiffness in chronic kidney disease (CKD), we hypothesized that abnormal endothelial cell growth factor is implicated. 

Methods: The cohort of CKD patients and animal models of CKD were studied. 

Results: In the cohort of 416 CKD patients, plasma level of angiopoietin-2 was independently correlated with the severity of arterial stiffness assessed by pulse wave velocity. Using murine CKD models induced by 5/6 subtotal nephrectomy or unilateral ureteral obstruction, we demonstrated the increase of plasma angiopoietin-2. Angiopoietin-2 expression markedly increased in tubular epithelial cells of fibrotic kidney but decreased in other tissues including aorta and lung. Expression of collagen and pro-fibrotic genes in aortic vascular smooth muscle cells was increased in CKD mice or mice producing human angiopoietin-2. Angiopoietin-2 stimulated endothelial expression of monocyte chemokines and adhesion molecules, increased Ly6C+ macrophage in aorta. Pro-fibrotic cytokine transforming growth factor β1 was increased in aortic endothelial cells and Ly6C+ macrophages by angiopoietin-2. Angiopoietin-2 blockade not only attenuated expression of monocyte chemokines, pro-fibrotic cytokines, and collagen in aorta, but also decreased pulse pressure of mice after 5/6 subtotal nephrectomy.

Conclusions: This study identifies a link between fibrotic kidney and arterial stiffness through angiopoietin-2. Targeting angiopoietin-2 to attenuate inflammation and collagen expression may provide a novel therapy for cardiovascular disease in CKD.

Funding: Government Support - Non-U.S.
**Methods:** Blood pressure, arterial stiffness, heart rate variability (HRV) and circulating adrenergic mediators were measured during clamped euglycemia and hyperglycemia in 40 normotensive patients with T1D (NCT01392560). Studies were repeated after 8 weeks of empagliflozin (25 mg daily).

**Results:** During clamped euglycemic conditions, empagliflozin reduced systolic blood pressure (111±9 to 109±9 mmHg, p<0.0187), and augmentation indices at the radial (+52±16 to -57±17%, p<0.0001), carotid (+1.3±17.0 to -5.7±17.0%, p<0.0001) and aortic positions (+0.1±13.4 to -6.2±14.3%, p<0.0001) declined. Similar effects on arterial stiffness were observed during clamped hyperglycemia; however, blood pressure effects were not significant. Carotid-radial pulse wave velocity decreased significantly under both glycemic conditions (p<0.0001), while declines in carotid-femoral pulse wave velocity were only significant during clamped hyperglycemia (5.7±1.1 to 5.2±0.9 m/s, p=0.0017). HRV, plasma noradrenaline and adrenaline remained unchanged under both glycemic conditions.

**Conclusions:** Empagliflozin reduces arterial stiffness in patients with uncomplicated T1D. The mechanisms responsible for this decline in arterial stiffness require further study and may relate to pleiotropic actions of SGLT2 inhibition, including glucose lowering, antihypertensive and weight reduction effects.

*Funding:* Pharmaceutical Company Support - Boehringer-Ingelheim

SA-PO1075

**Differential Effects of Indoxyl Sulfate and Inorganic Phosphate in Murine Cerebral Endothelial Cells**

Andréa Marques Stinghen,1,2 Jean-marc Chillon,1 Ziad Massy,1,3 Agnès Boullier.1,3 Inserm U1088, UPJV, Amiens, France; 1UPPR, Curitiba, Brazil; 3A.Paré Hospital, Paris, France.

**Background:** Endothelial dysfunction, partly due to nitric oxide (NO) unavailability and increased oxidative stress, plays a key role in stroke in CKD patients. To explore the mechanisms, we evaluated the effects of two uremic toxins on cerebral endothelium function.

**Methods:** A murine cerebral endothelial cell line (bEnd.3) was treated with various concentrations of indoxyl sulfate (IS) and inorganic phosphate (Pi). Cell viability was assessed by MTT. NO, ROS and O$_2^-$ productions were measured using DAF-FM (0.1 μM), DCFH-DA (1 μM) and DHE (10 μM), respectively. N-acetyl-L-cysteine (NAC, 10mM) and vitamin E (10 μg/mL) were added prior to IS or Pi treatment. Peroxynitrite (ONOO$^-$) involvement was evaluated using ebselen, a peroxide scavenger. eNOS uncoupling was analyzed by adding 10μM tetrahydrobiopterin (BH$_4$).

**Results:** Cell viability decreases after 24h of IS or Pi treatment (P<0.01). Both toxins significantly reduce NO production (IS, P<0.05; Pi, P<0.001). IS dose-dependently induces ROS production in treated cells (P<0.001). Pi mediates a significant oxidative stress with an highest effect at 3mM (P<0.001). Antioxidants pretreatments significantly reduce ROS levels in cells treated with either IS or Pi (P<0.05 and P<0.001 respectively). IS reduces O$_2^-$ production in a dose-dependent manner compared to control cells (P<0.001). This effect is also observed with 2mM Pi (P<0.001). Both antioxidants decrease O$_2^-$ production compared to control cells with a greater effect in Pi-treated cells (P<0.001) than in IS-treated cells (P<0.05). Ebselen reduces ROS production induced by both toxins (P<0.001) suggesting a role of ONOO$^-$ in this process. Whereas BH$_4$ addition has no effect on O$_2^-$ and NO levels in IS-treated cells, it significantly reduces O$_2^-$ and increases NO production in Pi-treated cells (P<0.001) suggesting an eNOS uncoupling induced by Pi.

**Conclusions:** This study shows for the first time that 2 uremic toxins induce cerebral endothelial dysfunction by two different mechanisms. They both decrease NO levels by inducing an oxidative stress. However, Pi seems to be more deleterious since it also induces eNOS uncoupling.

*Funding:* Government Support - Non-U.S.
Effect of Adipose-Derived Stem Cells Cultured with Auralosadine IV on the Cisplatin-Induced Renal Tubular Cells
Huiling Wang, Div of Nephrology, Jinlin Hospital, Shanghai, China.

Background: To investigate the role and possible mechanisms of human adipose-derived mesenchymal stem cells (hADSCs) cultured with Auralosadine IV (Ast) to human renal tubular epithelial cells line (HIKC) induced by cisplatin in vitro.

Methods: HIKC cells were induced by different concentrations of cisplatin for 24 hours. The proliferation activity and apoptosis of HIKC were evaluated with CCK-8 and Flow Cytometer assay respectively. The influence of hADSCs on HIKC was detected by transwell culture system, which was used to co-culture for 48 hours. After that, the apoptosis rate and proliferating rate of HIKC was detected by TUNEL and PCNA assay respectively. Transwell culture system was used to test the migration effect of hADSC. The number of migrating cell was counted under a fluorescence microscope.

Results: & δ/29; As the increasing of concentrations of cisplatin, the number of HIKC was decreasing, meanwhile the apoptosis and necrosis proportion of HIKC was enhancing. When the density of cisplatin was smaller than 10μmol/L, compared to model group (no co-culture), the apoptotic rates of HIKC co-cultured with hADSCs were decreased and the cell number increased obviously (P<0.05). The effects on HIKC were even more pronounced when hADSC cultured with 20mg/L Ast. When the density of cisplatin was bigger than 10μmol/L, the proliferation activity and apoptotic rates of HIKC were no significant difference between co-cultured group and model group (P>0.05). Crystal violet staining show that hADSCs cultured with 20mg/L Ast can increase the number of cells crossing the membrane in the transwell culture system (P<0.05) after co-cultured.

Conclusions: As the increasing of concentrations of cisplatin, the degree of HIKC injury was increasing. Cisplatin-inuced HIKC can facilitate the migration of hADSC in vitro and hADSCs cultured with 20mg/L Ast can increase the number of cells crossing the membrane. The HADSCs could lessen the apoptosis of HIKC induced by cisplatin, especially cultured with 20mg/L Ast, when the density of cisplatin was smaller than 10μmol/L. However, when the density was bigger than 10μmol/L, it had no obvious effect on HIKC.

Funding: Government Support - Non-U.S.

PUB004
The Role of Autophagy in Radiocontrast Induced Nephropathy
Gang Jee Ko, So Yeon Bae, Mi-yeon Jung, Yu ah Hong, Heui-jung Pyo, Young-Joo Kwon. Dept of Internal Medicine, Korea Univ College of Medicine, Seoul, Korea.

Background: Radiocontrast induced nephropathy (CIN) is the third common cause of acute renal failure among inpatients. Although the number of patients taking the exams using radiocontrast is increasing, little has been progressed in the treatment for CIN. The pathophysiology of CIN was known as tubular injury with toxic effect of radiocontrast. Autophagy, which regulates cell death in physiological as well as in pathological conditions with various stress, was known to have a role in tubular injury of acute kidney injury related to cisplatin and ischamia. We investigated the role of autophagy in radiocontrast induced nephropathy.

Methods: Radiocontrast nephropathy was induced with male C57BL/6j mice by intraperitoneal injection of iohexol (Omnipaque). Prostaglandins and nitric oxide (NO) synthesis was inhibited prior injection of ioxeol with indomethacin and NO synthase inhibitor. Cis-induced tubular injury by radiocontrast. Mannitol was used for osmotic control of ioxel, and 3-methylenedine (MA) was used as an autophagy inhibitor. Tubular injury caused by ioxel was also examined in vitro model using rat tubular cells (NRK-52E).

Results: Increased autophagy after ioxel administration was demonstrated with increased LC3 II expression in damaged tubules of kidney. Serum creatinine and tubular injury measured in PAS staining were significantly increased at 24hrs after ioxel administration compared to controls, and they were worsen with autophagy inhibition by 3MA (Creatinine: saline vs 3MA, 0.26±0.01 vs 0.36±0.04; LC3: saline vs 3MA, 0.26±0.01 vs 0.36±0.04) in NRK-52E. Increased caspase 3 and 9 expression after ioxel administration was also examined in vitro model using rat tubular cells (NRK-52E). Increased caspase 3 and 9 expression after ioxel administration was augmented by autophagy inhibition.

Conclusions: Autophagy was associated with radiocontrast induced nephropathy.

PUB005
Evaluation of Ischemic Renal Injury after Neprhon-Sparing Surgery Using Dynamic Renal Scintigraphy and L-FABP
Korea.

Background: Renal scintigraphy is an established method to quantitatively assess split renal function. L-type fatty acid binding protein (L-FABP) is a novel urinary biomarker of acute renal failure among inpatients. Although the number of patients taking the exams using radiocontrast is increasing, little has been progressed in the treatment for CIN. The pathophysiology of CIN was known as tubular injury with toxic effect of radiocontrast. Autophagy, which regulates cell death in physiological as well as in pathological conditions with various stress, was known to have a role in tubular injury of acute kidney injury related to cisplatin and ischamia. We investigated the role of autophagy in radiocontrast induced nephropathy.

Methods: Radiocontrast nephropathy was induced with male C57BL/6j mice by intraperitoneal injection of ioxel (Omnipaque). Prostaglandins and nitric oxide (NO) synthesis was inhibited prior injection of ioxeol with indomethacin and NO synthase inhibitor. Cis-induced tubular injury by radiocontrast. Mannitol was used for osmotic control of ioxel, and 3-methylenedine (MA) was used as an autophagy inhibitor. Tubular injury caused by ioxel was also examined in vitro model using rat tubular cells (NRK-52E).

Results: Increased autophagy after ioxel administration was demonstrated with increased LC3 II expression in damaged tubules of kidney. Serum creatinine and tubular injury measured in PAS staining were significantly increased at 24hrs after ioxel administration compared to controls, and they were worsen with autophagy inhibition by 3MA (Creatinine: saline vs 3MA, 0.26±0.01 vs 0.36±0.04; LC3: saline vs 3MA, 0.26±0.01 vs 0.36±0.04) in NRK-52E. Increased caspase 3 and 9 expression after ioxel administration was augmented by autophagy inhibition.

Conclusions: Autophagy was associated with radiocontrast induced nephropathy.

Evaluation of Ischemic Renal Injury after Neprhon-Sparing Surgery Using Dynamic Renal Scintigraphy and L-FABP

Yoong Tokunori Yamamoto, Hideki Mizuno, Norihisa Matsukawa, Momokazu Gotoh. Urology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

Background: Renal scintigraphy is an established method to quantitatively assess split renal function. L-type fatty acid binding protein (L-FABP) is a novel urinary biomarker to reflect acute kidney injury and may play a role in predicting the extent of ischemic renal injury following nephron-sparing surgery. We evaluated ischemic renal injury after nephron-sparing surgery using dynamic renal scintigraphy and urine level of L-FABP in treated kidney.

Methods: We performed open and laparoscopic nephron-sparing surgery for 7 patients with small renal mass and inserted ureteral catheter into the treated renal pelvis. Ischemic renal injury of the treated kidney was evaluated by comparing effective renal plasma flow (ERPF) estimated by radioisotope scintiscan Te 99m-methacetylglycylglycine (99mTc-MAG-3) scintigraphy before and 1 week after the operation. We calculated a previously described variable called baseline weighted differential (b-wd) of ERPF that represents the percentage of loss of kidney function, comparing the baseline value with b-wd of ERPF=1 week Postoperative ERPF - baseline ERPF/ baseline ERPF. Urine was obtained from the ureteral catheter 4 hours and 24 hours after de-clamping of the renal artery. We defined induction rate of L-FABP by dividing the 24-hour level by the 4-hour level. The correlation between b-wd of ERPF and induction rate of L-FABP obtained from the ureteral catheter was assessed.

Results: There was a strong correlation(R2=0.633) between b-wd of ERPF and the logarithm of induction rate of L-FABP. The proximal tubul was stained by L-FABP.

Conclusions: The results of the present study suggest that L-FABP is an effective urinary biomarker to predict the extent of ischemic renal injury following nephron-sparing surgery.

Methods: Renal proximal tubule (PT) S1PR1KO (PEPCK-Cre S1pr1 KO) and control mice (PEPCK-Cre) received cisplatin (Cis-27 mg/kg, 20mgCM) and renal injury was assessed on day 3 by monitoring plasma creatinine (Cr), inflammatory cell infiltration (by flow cytometry) and changes in pro-inflammatory cytokines (by real time RT-PCR). TKPTS cells were used for over-expression of S1P1.

Results: Compared to control mice (Cr 0.79±0.02 mg/dL) C induced more kidney injury in PT S1P1 KO mice (1.22±0.13, p<0.05) and FTY720 reduced injury in control mice (0.47±0.06, p<0.01) but not in PT S1P1 KO mice (1.32±0.22, n.s.). Control or PT S1P1 KO mice treated with Cis had significantly higher levels of pro-inflammatory cytokines (CXCL1, MCP-1, TNF-α and IL-6) and increased neutrophil and macrophage infiltration in kidneys compared to vehicle-treated mice on day 3. FTY720 attenuated the increased immune cell infiltration and expression of cytokines in control but not PT S1P1 KO mice. Over-expression of S1P1 in TKPTS cells rendered cells resistant to Cis-induced cell death compared to empty vector controls. S1P1-overexpressing TKPTS cells had higher Mt respiratory capacity, Mn superoxide (MitoSOX/JC-1/Mitotracker) and more Mt fusion compared to control cells after Cis.

Conclusions: In summary, activation of S1P1 expressed in PT attenuates C-induced AKI by preserving Mt function. We conclude that FTY720 administration or increasing S1P1 expression might represent a novel strategy in the prevention of C-induced AKI. We are currently examining the mechanism of Mt control by S1P1 activation.

Funding: NIDDK Support

877A

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

Underline represents presenting author.
The Expression of Canonical Transient Receptor Potential Channels 6 in Renal Cortex and Hippocampus of Rats after Intraportal Injection of Silver Nanoparticles

Ye Liu, Zhiuo Yang.
Medical College, Nankai Univ, Tianjin, China.

Background: The canonical transient receptor potential channels (TRPC) are members of a large channel family known as TRP channels. TRPC6 serves a variety of functions in both brain and kidney. Recent years, the discovery that the TRPC6 mutation causes familial focal segmental glomerulosclerosis (FSGS) has drawn great attention to the investigation of this ion channel. The aim of the present study was to observe the expression of TRPC6 in renal cortex and hippocampus during early postnatal development of normal rats, and after exposure to silver nanoparticles.

Methods: A dosage of 1mg/kg Ag-NPs was applied to 16 post weaning rats through intraperitoneal injection (Ag-NPs treated group). Other 16 rats of the same age were the same group and served as control. Eight rats from each group were randomly chosen and executed at the end of the first week, and then the kidneys and hippocampus were removed. Other rats kept on with the treatment of either Ag-NPs or normal saline until the end of the fourth week. Then the rats were executed and the samples were removed as before. Immunofluorescence and Western blotting methods were used to detect the expression alteration of TRPC6 in rats.

Results: Results showed that the expression of TRPC6 was detected in glomerulus and tubules of both control group and Ag-NPs treated group. A stable expression was detected in the rat renal cortex during postnatal maturation in control group, while in Ag-NPs treated group, the expression of TRPC6 was increased in rat kidney cortex, and this increased tendency was getting more obvious in rats, which exposed to Ag-NPs for 4 weeks. The expression of TRPC6 didn’t show an obvious variation in hippocampus between control group and Ag-NPs treated group.

Conclusions: These in vivo experiments suggested that the expression of TRPC6 underwent very little change with the development of kidney and hippocampus in normal post weaning rats, while an increased expression of TRPC6 was found in Ag-NPs exposure group. More research will be needed to further exploration of this ion channel.

PUB007

In Vitro and In Vivo Study of Necroptosis in Renal Tubular Epithelial Cells

Xinling Liang, Jialun Luo, Yuan Han Chen, Fen Jiang. Div of Nephrology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China.

Background: Recently research show that there are 4 but not 3 major morphologies of cell death: apoptosis, autophagy, necrosis and a new way described recently: necroptosis which was our major concern that may lead us to a new target point of protecting tubular epithelial cells. Necroptosis death receptor signaling with receptor-interacting protein 1 or 3 (RIp1 or RIP3) activation, with or without caspase 8 activation can be inhibited by necrostatins or genetic alteration of RIP1 and RIP3.

Methods: We have used a human HK-2 renal tubular epithelial cell line to investigate the necroptosis phenomenon in vitro. HK-2 cells were subjected to TNF-α followed by ATP depletion, and benzoylloxycarbonyl-Val-Ala-Asp-fluoro-methylketone (zVAD–fmk) was added to block the activity of caspase-8. And tried to interfere the process. Based on the in vitro result, we made a further research with SD mouse. We used a unilateral nephrectomy+ischemia-reperfusion model (I/R model) and pretreated the mouse with nec-1, NSA and mdivi respectively and combined in different groups, along with parallel control groups were sited. Blood and tissue samples were drawn after the model conducted.

Results: We have used a human HK-2 renal tubular epithelial cell line to investigate the necroptosis phenomenon in vitro. HK-2 cells were subjected to TNF-α followed by ATP depletion, and benzoylloxycarbonyl-Val-Ala-Asp-fluoro-methylketone (zVAD–fmk) was added to block the activity of caspase-8. And tried to interfere the process. Based on the in vitro result, we made a further research with SD mouse. We used a unilateral nephrectomy+ischemia-reperfusion model (I/R model) and pretreated the mouse with nec-1, NSA and mdivi respectively and combined in different groups, along with parallel control groups were sited. Blood and tissue samples were drawn after the model conducted.

Conclusions: By this research we establish a way to build a necroptosis cell line model which may lead us to a new target point of protecting tubular epithelial cells. Necroptosis death receptor signaling with receptor-interacting protein 1 or 3 (RIp1 or RIP3) activation, with or without caspase 8 activation can be inhibited by necrostatins or genetic alteration of RIP1 and RIP3.

PUB008

Trps1 Promotes Kidney Repair following Ischemia-Reperfusion Injury by Regulating Proliferation and Re-Differentiation of Renal Tubular Epithelial Cells

Keohong Chen, Junlong Yi, Yani Li, Ning Ye, Nephrology, Daping Hospital, Third Military Medical Univ, Chongqing, China.

Background: Renal tubular epithelial cells (RTECs) are the main victims of acute kidney injury (AKI). Tubule repair following AKI involves epithelial de-differentiation followed by cell proliferation and re-differentiation. Trps1 is a transcription factor which plays a crucial role in the regulation of mesenchymal-epithelial transition in early stage of embryonic kidney development. The purpose of this study is to investigate the role of Trps1 in kidney repair following AKI.

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

878A
Conclusions: We have shown that renal outcomes following AKI on CKD is a spectrum of a continuum from quick complete recovery through to the rapid, unpredictable and precipitate progression to irreversible ESRD without any renal recovery ever. The latter pattern is the syndrome of rapid onset end-stage renal disease (SORO-ESRD), a previously unrecognized syndrome, that we first described in 2010. Undeniably, the variable renal outcomes following AKI on CKD is best described as the several colors of the rainbow.

PUB011
Quadruple Whammy – A New Preventable Syndrome of Peri-Operative AKI on CKD in Patients on Concurrent Combination Triple Whammy Medications
Macaulay A. Onuigbo,1,2 Belmarie P. Roman-maradiaga,3 Ngozi J. Achebe,4 1Medicine, Mayo Clinic, Rochester, MN; 2Nephrology, Mayo Clinic Health System, Eau Claire, Eau Claire, WI; 3Hospital Medicine, Mayo Clinic Health System, Eau Claire, Eau Claire, WI; 4Internal Medicine, Capital Medical Center, Olympia, WA.

Background: The potential nephrotoxicity from combination diuretics-ACEIs-NSAIDs, the ‘triple whammy’, is often unrecognized. In early 2013, we described accelerated post-operative AKI in patients on triple whammy, named ‘quadruple whammy’, in the British Medical Journal.

Methods: Case reports.

Results: 1. A 59-year old morbidly obese Caucasian male, hypertension, serum creatinine (SCr) 1.42 mg/dl (eGFR 54), developed accelerated oliguric AKI after elective right nephrectomy, peri-operative hypotension and anemia. He was on Lisinopril-Hydrochlorothiazide 20/25, Naturetone (NSAID) 1000 mg daily. Within 24-hours, Scr more than doubled to 3.2 mg/dl (eGFR 22) with metabolic acidosis and hyperkalemia (Figure 1a). He was transfused; hypotension corrected. He was discharged on Amlodipine and Furosemide. Scr was 0.99 mg/dl (eGFR 85), one month later.

Conclusions: ‘Quadruple Whammy’, a new syndrome of preventable AKI with ‘triple whammy’, due to superimposition of peri-operative stressors especially hypotension is preventable, not uncommon, and calls for more pharmacovigilance.

PUB012
Contrast Induced Nephropathy after Transcatheter Arterial Chemoembolization in Hepatocellular Carcinoma
Kenichi Ishizawa,1 Takamasa Ohki,2 Takafuni Kanemitsu,1 Tomoko Honda,1 Masatomo Chikamori,1 Ayako Tsuchiya,1 Rika Miura,1 Mai Sugahara,1 Nobuo Toda,2 Naobumi Misc.1 1Dept of Medicine, Div of Nephrology, Mitsui Memorial Hospital, Tokyo, Japan; 2Dept of Medicine, Div of Gastroenterology, Mitsui Memorial Hospital, Tokyo, Japan.

Background: The aim of this study was to determine the incidence and risk factors for contrast induced nephropathy (CIN) after transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC) and coexisting chronic liver disease.

Methods: We retrospectively investigated 126 patients (97 male, age 70±9 years, estimated glomerular filtration rate (eGFR) 78±21 ml/min with HCC who underwent TACE between January 2003 and January 2011. The first TACE treatment session of each patient was examined. CIN was defined as an increase in serum creatinine of ≥ 0.5 mg/dl or ≥ 25% over baseline within 72 hours after TACE. Low-osmolality contrast medium, iopamidol, was administered in all patients.

Results: CIN developed in 4 patients (3.2%) and all recovered without renal replacement therapy. In a univariate analysis, age (P<0.05), HCC diameter more than 5-cm (P<0.05) and total bilirubin (P<0.05) influenced the development of CIN. Multivariate analysis including these 3 variables demonstrated that HCC diameter more than 5-cm (P<0.05) was a significant predictor of CIN. Between patients with and without CIN, the prevalence of chronic kidney disease (eGFR less than 60 ml/min/1.73 m², 50% vs. 18%, P<0.11) and diabetes (50% vs. 20%, P<0.14) was comparable. The mean dose of contrast medium was 100±45 ml.

Conclusions: CIN after TACE was associated with HCC size, but not with underlying kidney dysfunction. In the present study, the incidence rate of CIN was lower than previously reported (9 – 24%).

PUB013
M13-796 Study Design – A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Safety and Efficacy Trial of Multiple Dosing Regimens of ABT-719 for Prevention of Acute Kidney Injury in Patients Undergoing High Risk Cardiac Surgeries
Samina Khan,1 Peter A. McCullough,2 Lakhmir S. Chawla,3 Thomas M. Beaver,4 Elliott Bennett Guerrero,5 Deli Wang,4 Mark T. Houser.1 1AbbVie, IL; 2Providence Park Hospital, MI; 3George Washington Univ Medical Center, Washington, DC; 4Univ of Florida, FL; 5Duke Univ Medical Center, NC.

Background: Prevention and treatment of acute kidney injury (AKI) is a significant unmet medical need. Patients undergoing high risk major surgeries are at increased risk for ischemia reperfusion (I/R)-induced AKI. ABT-719 is a novel melanocortin receptor agonist in development for prevention and treatment of AKI. In a Phase 2 study (CS007), 800 µg/kg of ABT-719 reduced the incidence of AKI defined by AKIN and RIFLE criteria, as well as

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
the 90 day composite outcomes. We describe the study design of M13-796 (ClinicalTrials.gov Identifier NCT01771765), a Phase 2b trial of ABT-719 in patients undergoing high risk on-pump cardiac surgeries.

Methods: This is a double-blind, placebo-controlled study. Subjects will be randomized at a 1:1:1:1 ratio into 4 treatment groups: placebo and ABT-719 at 800, 1600 or 2100 μg/kg (3, 5 or 6 bolus infusions, respectively). AKI will be evaluated according to the AKIN, RIFLE and KDIGO criteria with additional clinical outcomes of interest.

Results: The primary efficacy endpoint is the proportion of subjects developing AKI based on the AKIN criteria. The key secondary efficacy endpoint is the proportion of subjects developing at least one of the composite events: death, need for renal replacement therapy, or having a ≥25% reduction in eGFR at 90 days.

Conclusions: M13-796 is designed to further evaluate the efficacy of ABT-719 and optimal dosing strategy for prevention of AKI in patients undergoing high risk on-pump cardiac surgeries.

Figure 1: Study Schematic

Funding: Pharmaceutical Company Support - AbbVie

PUB014

Pseudo-Acute Renal Failure after Abdominal Hysterectomy

Muhammad K. Shakeel. Nephrology and Internal Medicine of Anderson, Anderson, SC.

Background: Intrapерitoneal urinary leak from either urinary bladder or ureteral perforation should be considered in the diagnosis of acute kidney injury after gynaecological surgery.

Methods: I present a case of reversible acute renal failure after total abdominal hysterectomy. Patient developed intraperitoneal urinary bladder perforation. Subsequently she was noted to have elevated BUN and creatinine after 48 hours of surgery. Elevated creatinine occurred as a result of intraperitoneal urine leak and reabsorption through the peritoneum. Patient was taken to the OR and the leak was repaired.

Results: There was a prompt recovery of the serum biochemistry. Early recognition and surgical repair as opposed to dialysis therapy are warranted in such clinical setting. Nephrologist and gynaecologist should be aware of this diagnosis since pseudo-renal failure which may resolve without dialysis.

Conclusions: Early recognition and surgical repair as opposed to dialysis therapy are warranted in such clinical setting. Nephrologist and gynaecologist should be aware of this diagnosis as this condition may resolve without dialysis.

PUB015

ANA Negative Patient with Lupus Nephritis

Muhammad K. Shakeel. Nephrology and Internal Medicine of Anderson, Anderson, SC.

Background: I present a case of a 44-year-old male who presented with acute kidney injury and nephrotic syndrome.

Methods: Patient underwent a native kidney biopsy which showed immune complex mediated focal proliferative glomerulonephritis with 10% crescents consistent with lupus glomerulonephritis. Initial serology including ANA, complement levels and double stranded DNA antibodies were negative. Patient was treated with monthly pulse cyclophosphamide and corticosteroids. Patient failed Cyclophosphamide and a repeat kidney biopsy was done which again showed crescentic glomerulonephritis consistent with lupus nephritis. Repeat serology including ANA complements were again negative. Patient was treated with rituximab two times doses. Patient remained nephrotic and there was no improvement in kidney function. Patient was started on haemodialysis and is doing well.

Results: The diagnosis of a SLE depends on patient’s clinical and laboratory abnormalities. ANA is a diagnostic hallmark of SLE having a frequency of 95% in SLE patients. There are previous case reports of patients with clinical features of SLE having negative test for ANA. These patients appear to represent 1 to 5% of the SLE population. The age of onset and the female predominance are the same for ANA negative SLE as for ANA positive SLE. There are several possible explanations for negative ANA but there is no definitive explanation at this time.

Conclusions: My patient may be a rare case of ANA negative lupus nephritis and this suggests that ANA may not be required in the diagnosis of lupus nephritis.

PUB016

Acute Kidney Injury and Severe Hypokalemia in McKittrick-Wheelock Syndrome: Report of Two Cases

Claudio Angelini, Elisa Merizzoli, Paola Arosio, Manuel Alfredo Podesta, David Cucchiari, Salvatore Badalamenti. Nephrology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy.

Background: McKittrick-Wheelock Syndrome (MWS) is a rare disorder characterized by the pentad: (1)secretory diarrhea induced by a colorectal villous adenoma, (2)pre-renal acute kidney injury (AKI), (3)metabolic acidosis, (4)hypokalemia and (5)hyposthenuria.

Methods: Retrospective analysis of biochemical parameters from two patients admitted for AKI who were previously diagnosed with colorectal adenomas.

Results: Laboratory results were consistent with AKI, associated to dehydration, metabolic acidosis and hyposthenuria in patients who had a previously normal renal function.

These parameters were rapidly corrected by intravenous infusion of saline. Both cases also showed severe hypokalemia, which was treated with intravenous KCl supplementation (80-90 meq/day). All the attempts to wean the patients off this therapy resulted in hypokalemia relapse. Extra-renal potassium loss was confirmed by low urinary potassium levels: this finding, along with medical history and biochemical tests, led to MWS diagnosis.

Conclusions: MWS clinical picture ensues from the secretory diarrhea induced by colorectal villous adenomas. The adenomatous cells undergo a switch from an absorptive to a secretory phenotype, leading to ions and water loss. Non-anion gap metabolic acidosis results from the equal secretion of sodium, chloride and bicarbonate. When AKI develops, retention of organic acids can increase the anion gap. Patients can remain stable for years, until tumor secretion exceeds renal compensation, determining symptoms onset. MWS severity is proportional to the size and distal localization of adenomas, which prevents the reabsorption of secreted fluids. Although hypokalemia correction can only be achieved by surgical resection, prompt rehydration is usually enough to recover from AKI. Nevertheless, owing to MWS rarity, the diagnosis is often delayed, thus increasing the risk of complications.

PUB017

Effect Of Dialysate Flow Direction on Solute Clearances during Continuous Renal Replacement Therapy

Jeong Chul Kim, Flavio Basso, Mauro Neri, Alessandra Brendolan, Massimo de Cal, Claudio Ronco. ‘Dept of Nephrology, St. Bortolo Hosp, Vicenza, Veneto, Italy; ’IRRIV (International Renal Research Institute), Vicenza, Veneto, Italy.

Background: Continuous renal replacement therapy (CRRT) is commonly used in critically ill patients with acute kidney injury (AKI). During CRRT, dialysate can be used to increase solute removal by diffusion. The connection of the dialysate fluid to the filter is usually supplied such that dialysate fluid (Qd) flows in the opposite direction (counter-current) to blood to guarantee the maximum solute clearance by diffusion. However, there is no evidence about the superiority of counter-current on co-current configuration in CRRT. We performed a clinical study to investigate the effect of the direction of Qd on urea and creatinine removal.

Methods: We conducted a prospective study on adult patients admitted in ICU requiring CRRT. At this point ultrafiltration rate was set as zero and Qd was set as 2000 ml/h. Details of blood sampling procedure was represented in fig 1.

The CVVHDF were randomly initiated with co- or counter-current configuration for the first 50 minutes until it was switched to CVVHD. Urea (UCl) and creatinine (CrCl) clearance were calculated to each flow configuration.

Results: Median value of UCl, CrCl and E/P ratio in co-current vs counter-current configuration were: 27.4 vs 33.3 ml/min, 26.7 vs 33.3 ml/min and 0.82 vs 1.0 respectively (p= 0.001).

Conclusions: Counter-current dialysate flow configuration during CRRT provides a higher solute clearance. However, advantages of each configuration should be balanced against the overall performance of the treatment and its simplicity in terms of treatment delivery and circuit handling procedures.
PUB018
Modelling Acute Kidney Injury (AKI) Biomarkers
John W. Pickering,1 Zoltan H. Endre,1,2 1Christchurch Kidney Research Group, Dept of Medicine, Univ of Otago, Christchurch, New Zealand; 2Dept of Nephrology, Prince of Wales Clinical School, Univ of New South Wales, Sydney, Australia.

Background: Many factors may modify the temporal profile of urinary AKI biomarkers, including type of biomarker and underlying CKD. We modelled these physiological differences to explore the effect of increased (hyperfiltration) or reduced GFR (CKD) on the biomarker time-course profiles.

Methods: Single nephron models of the time-courses of pre-formed (eg GGT) or induced (eg NGAL) in tubular epithelial cells, or filtered and normally reabsorbed (eg Cystatin C) biomarkers were modelled based on known physiology. Excretion rates were combined with unique group of single nephron urine flow rates to compute urinary concentrations under scenarios of hyperfiltration, normofiltration, and reduced GFR. Whole kidney scenarios were then constructed for kidneys with normal or reduced nephron number.

Results: Preformed biomarker concentrations peaked earliest after insult with total exclusion limited by pre-injury mass of biomarker, which in turn depended on the number of available nephrons and the rate of biomarker regeneration. Induced biomarkers peaked later and were influenced by nephron number but not limited by this. Filtered biomarker profiles varied with nephron number and GFR with extended time courses compared to other biomarkers.

Conclusions: Preformed biomarkers concentrations can directly quantify tubular injury, but must be measured very soon after renal insult. Induced biomarkers provide a longer window of assessment. Filtered biomarkers have the longest window of opportunity, and measure injury directly and indirectly measure reduced GFR.

Funding: Government Support - Non-U.S.

PUB019
Epidemiology of Acute Kidney Injury in Indian Intensive Care Unit – Single Centre Study
Piyush Mathur,1 Rajasekara Chakravarthi Madarasu,1 Rusheendra Kambhampati,1 Vikranth Reddy,1 Santosh Hedau.1 1Nephrology, Care Hospital, Banjara Hills, Hyderabad, AP, India; 2Nephrology, Care Hospital, Banjara Hills, Hyderabad, AP, India; 3Nephrology, Care Hospital, Banjara Hills, Hyderabad, AP, India; 4Nephrology, Care Hospital, Banjara Hills, Hyderabad, AP, India.

Background: The incidence of acute kidney injury in intensive care units has increased in past few years but exact incidence is not known in because of many confounding factors.

Methods: Single centre study conducted at tertiary care centre from March 2010 to May 2013. Patients admitted who developed AKI and were included in study after taking consent. Demographic data was collected and patients younger than 18 years, patients with end stage kidney disease on maintenance hemodialysis, renal transplant recipients were excluded from study. Risk factors for AKI and APACHE 2 score was calculated at enrolment.

Results: 350 patients were screened during study period for AKI in ICU’s and 300 were included in study as they met AKIN criteria for AKI. 261 patients completed the follow up period of study. Out of these 261 patients who had AKI, 80 required renal replacement therapy. Of the 80 patients who required RRT, 40 were managed on hemodialysis, 37 on SLED and 3 were on CVVHDF. Major risk factors for AKI were old age and diabetes. APACHE 3 score was higher in those who had dialysis requiring AKI as compared to those who had AKI but not dialysis requiring. Multiple factors were responsible for AKI but most common etiology for AKI in Indian ICU setting was sepsis with septic shock. Others being drugs, cardiac surgery, contrast agents. The mortality of septic AKI and AKI due to other causes like cardiogenic, drug induced was significantly different.

Conclusions: Indian ICUs has high incidence of AKI which is mostly multifactorial. Sepsis is most frequent etiology for AKI in a tertiary care ICU. Higher APACHE 3 score at admission to ICU is associated with higher incidence of dialysis requiring AKI.

PUB020
Predictors of Contrast Induced Nephropathy after Coronary Angiogram in Nepalese Population
Sanjib Kumar Sharma,1 Dept of Cardiology, College of Medical Sciences, Bharatpur.

Background: The implications of radio-contrast induced nephropathy (CIN) are many factors may modify the temporal profile of urinary AKI biomarkers, including type of biomarker and underlying CKD. We modelled these physiological differences to explore the effect of increased (hyperfiltration) or reduced GFR (CKD) on the biomarker time-course profiles.

Results: Among the 330 patients studied, diabetes mellitus was present in 84 (28.81%), anemia in 120 (36.36%), e-GFR <60ml/min in 33 (10%), hypertension in 162 (49.09%), and baseline eGFR was <60ml/min in 18 (5.45%) patients. Twenty seven (8.18%) patients experienced CIN. The incidence of CIN in patients with baseline creatinine clearance < 60 ml/min was 45.45%. CIN developed in 10% of anemic and 12.5% diabetic patients.

The amount of the contrast agent administered was similar for CIN and non-CIN patients (138.20±91.34ml vs. 175.56±118.86 ml; p=0.254). No correlation was found between the amount of contrast agent administered and the change of serum creatinine concentration. Multivariate logistic regression analysis found that baseline e-GFR and baseline hemoglobin were independent predictors for CIN.

Conclusions: In this first study of CIN in Nepal, the incidence of CIN was 8.18%. Patients with preexisting kidney disease and anemia were at high risk of CIN.

PUB021
A Case of Shunt Nephritis: Early Diagnosis and Management with a Complete Resolution of Acute Kidney Injury
Ibrahim Quashit,1 Pratik Shah,1 1St. Joseph’s Hospital & Medical Center; 2St. Joseph’s Hospital & Medical Center.

Background: Shunt nephritis is an immune-complex mediated glomerulonephritis associated with chronically infected ventriculotraial shunts inserted for treatment of hydrocephalus. Renal outcome is good with early diagnosis and treatment. Delay in diagnosis can lead to irreversible ESRD.

Methods: 31-year-old male presented with two day history of worsening of his chronic headaches, blurry vision and fever.His past medical history was significant for his ventriculoperoportal shunt at age 16 weeks secondary to congenital hydrocephalus. His last revision was done 9 months ago when his ventriculoperoportal shunt was changed to ventriculotraial shunt. On physical examination only remarkable finding was temperature of 38.6 C. Labs showed hemoglobin of 10 gm/dl and serum creatinine of 2.2 mg/dl. Urine dipstick was positive for hematuria and proteinuria. Urine microscopy showed RBC casts. 24 hour urine protein was 590 mg/24hr. Cerebrospinal fluid (CSF) analysis revealed 172 nucleated cells with predominantly PMN. CSF culture and blood culture were positive for Propionibacterium acnes. Complement levels were low with C3 of 73 mg/dl and C4 of 12 mg/dl. Patient was treated with intravenous vancomycin and infected shunt was removed. Temporary external ventricular drain (EVD) was placed. Once infection cleared, a new shunt was placed and EVD was removed. At the time of discharge his serum creatinine was 4.4 mg/dl which normalized at 0.8 mg/dl two months as outpatient follow up.

Conclusions: Shunt nephritis was first described by Black et al in 1965. The overall incidence of ventricular shunt infection varies between 0.7 to 2.2 %. Patients with shunt infection typically present with fever, anemia, and cerebral manifestations i.e. headaches, blurry vision, and seizures. Renal manifestations include hematuria, proteinuria, renal insufficiency, and hypertension. Predominant finding on renal biopsy is membranoproliferative glomerulonephritis (MPGN). Decreased serum complement levels, presence of cryoglobulins or autoantibodies support the diagnosis of shunt nephritis. Treatment of shunt nephritis includes prompt removal of infected shunt and intravenous administration of antibiotics.

PUB022
Protective Effect of N-Acetylcysteine on Contrast Induced Nephropathy in Patients with Stage 2-4 Chronic Kidney Disease
Irem Ari,1 Mehmet T. Sezer,2 Salih Inal,3 Veysel Kidir,1 Altai Altunat,1 1Internal Medicine, Suleyman Demirel Univ School of Medicine, Isparta, Turkey; 2Nephrology, Suleyman Demirel Univ School of Medicine, Isparta, Turkey.

Background: There is a considerable interest in strategies to prevent contrast induced nephropathy (CIN) because of the increasing prevalence of renal insufficiency and the increasing use of imaging studies using contrast media (CM). The efficacy of N-acetylcysteine (NAC) for preventing CIN is uncertain. We aimed to investigate whether NAC might have a preventive role against the development of CIN in chronic kidney disease (CKD) patients.

Methods: The study included 60 stage 2-4 CKD patients undergoing investigations with CM. Patients were randomized into two groups, 2x1200 mg/day iv NAC and 1500 ml/day iv saline infusion were administered for three days starting one day before the procedure in the study group (n=30). Saline infusion was only given to the control group without altering other treatments of patients. Before the CM injection and two days after the procedure serum Cr, daily protein excretion, KIM-1, NGAL and MCP-1 levels were measured and Cr clearances were calculated.

Results: Baseline clinical and laboratory findings were similar in two groups. Although serum Cr levels were not significantly different between the two assessments in both groups (KIM-1 and MCP-1 levels were 138.20±183.41 vs. 388.57 ± 353.59 ; p=0.018 and 185.05 ± 114.66 vs 295.13 ± 274.49; p=0.026, respectively). In the study group, there was only a slight but not significant increase in MCP-1 and KIM-1 levels.

Conclusions: In conclusion, we assume that in CKD patients who are undergoing investigations with contrast medium administration, the use of NAC + iv saline infusion significantly reduces the risk of developing CIN. Secondly, KIM-1 and MCP-1 seem to be good surrogate markers for predicting renal tubular injury.
A Strange Case of Hyperphosphatemia during Acute Kidney Injury

Davide Ricci, Raffaella Rizzo, Elena Mancini, Antonio Santoro. Nephrology Dialysis Hypertension, Policlinico S.Orsola-Malpighi, Bologna, Italy, Italy.

Background: Hyperphosphatemia (HPb) frequently accompanies acute kidney injury (AKI), due to the reduced urinary excretion. A severe HPb is rare, but may appear during cytolitic syndromes, often resulting in overt AKI. An inaccurate definition of the cause of HPb may lead to a wrong diagnosis of AKI.

Methods: A 77-yr F patient was admitted in the Cardiology Unit because of NSTE-ACS. Renal function was normal (creatinine 0.85 mg/dl). The patient had a history of chronic obstructive pulmonary disease (COPD) and diverticulosis. After near 1 week, the patient developed copious diarrhoea, hypotension, anemia, mild leucocytosis, increased CRP and PCT levels (181 U/L, myoglobin 1384 ng/mL, LDH 318 U/L). An ultrasound scan showed a solid mass (8 cm) in the left kidney. A thorax scan excluded pulmonary infections. The patient appeared dehydrated.

Results: AKI secondary to a cytolytic syndrome and sepsis due to diverticulitis was supposed. In spite of the therapeutic measures, renal function further worsened. The patient was moved to our nephrological department where she was treated with hemodialfiltration. An accurate examination of the clinical history highlighted the administration of 2 enemas with high phosphate content (22 g/100 mL of sodium phosphate). Despite this therapeutic approach, the patient was in general conditions worsened rapidly and she died 24 hours after, because of acute abdomen with septic shock (diverticulitis with intestinal perforation was the hypothesis). Autopsy was declined by the family.

Conclusions: Hyperphosphatemia (HPb) can be a symptom of severe cytolysis. A careful clinical evaluation should be always performed in case of AKI with HPb in order to avoid a wrong diagnosis of AKI.

---

PUB026

The Role of p66shc in Renal Toxicity of Oleic Acid

Jstvan Arany,1 Dustin Reed,1 Luis A. Juncos,2,3 Mehul P. Dixit.1 1Pediatrics, Div of Pediatric Nephrology, Univ of Mississippi Medical Center, Jackson, MS; 2Medicine, Univ of Mississippi Medical Center, Jackson, MS; 3Physiology and Biophysics, Univ of Mississippi Medical Center, Jackson, MS.

Background: Adult and childhood obesity is a growing problem: it is an independent risk factor for development of chronic kidney disease (CKD) and progression to end-stage kidney disease (ESRD). Pathologic consequences of obesity include non-esterified fatty acids (NEFAs)-induced oxidative stress and consequent injury of the kidney. Since the serine36 phosphorylated p66shc is a novel mediator of oxidative stress-dependent kidney injury we studied its role in oleic acid (OA)-induced oxidative stress and consequent injury in cultured renal proximal tubule cells (RPTCs).

Methods: Impact of OA or BSA-bound OA (OA-BSA) on production of reactive oxygen species (ROS), mitochondrial depolarization and cell injury (LDH release) was determined in RPTCs that harbor wild type (wt), knockdown (kd), Ser36-phosphorylation (S36A) or cytochrome c binding-deficient (W134F) p66shc.

Results: OA increased ROS production via the mitochondria –and in less extent via NADPH oxidase- resulting in ROS-dependent mitochondrial depolarization. Further studies demonstrated that mitochondrial depolarization is responsible for injury of cultured cells. Knockdown of p66shc, mutation of its Ser36 or cytochrome c binding sites (S16A or W134F, respectively) attenuated adverse effects of OA. Interestingly, OA also stimulated the promoter of p66shc.

Conclusions: Our results revealed that OA increased expression, Ser36 phosphorylation and mitochondrial cytochrome c binding of p66shc that resulted in mitochondrial depolarization and consequent injury of RPTCs. Hence, these data may offer a novel mechanism by which obesity could lead to development of CKD and ultimately ESRD. Thus, manipulating this pathway may help to prevent obesity-associated renal lipotoxicity.

Funding: Other U.S. Government Support

---

PUB027

Hirsutella Sinensis Antagonize Aristolochic Acid-Induced Epithelial-Myoﬁbroblast Transition through Inhibition of Snail

Xiao-yu Xu, Hong-liang Rui, Yan-yang Wang, Hong Cheng, Yi-Pu Chen. Div of Nephrology, Beijing Anzhen Hospital, Capital Medical Univ, Beijing, China.

Background: Cordyceps sinensis extracts were shown to inhibit aristolochic acid (AA)-induced renal fibrosis in rodent model. However, the molecular mechanism underlying this process has remained unclear. Hirsutella sinensis (HS) is the anamorphic mycelial form of cordyceps sinensis. This study is to investigate if HS could inhibit AA-induced renal tubular epithelial-myoﬁbroblast transition (ETM) and the role of transcriptional factor, snail, in this process.

Methods: Cultured Human renal proximal tubular epithelial cells (HKC) were divided into the following four groups: control group, AA group, AA+ HS group and AA+HS+ SB415286 group. The effect of HS on HKC proliferation and cytotoxicity were determined by MTT assay and LDH release assay, respectively. After treatment with AA or/and HS for 12h, the mRNA expression of snail was measured by real-time PCR. After treatment for 36h, the protein expression of snail was measured by Western Blot.

Results: 1. 10umM AA or/and 10mg/L HS do not affect cell proliferation and have no cytotoxicity on HKC. 2. Compared with the control group, AA stimulation up-regulates the expression of AA and TGF-β1 and down-regulates the expression of CK-18. 3. AA stimulation also up-regulates the expression of snail, which is the key molecular involved in ETM. 4. HS could inhibit AA-induced overexpression of AA and TGF-β1 and snail. HS also up-regulates expression of CK-18. 5. GSK-3β could mediate degradation of snail through inhibition of Snail expression, serine36 phosphorylation of snail and cytochrome c binding of p66shc.

Conclusions: HS could inhibit AA-induced renal tubular epithelial-myoﬁbroblast transition and interstitial ﬁbrosis. Such effect may exert through inhibition of Snail.

Funding: Government Support - Non-U.S.
**PUB028**

Oxidized High-Density Lipoprotein Impairs Function of Human Proximal Tubular Cells via CD36

Changlin Mei, Xiang Gao.  
Kainan Institute of PLA,  
Changzheng Hospital, Second Military Medical Univ, Shanghai, China.

**Background:** The participation of tubular lesions in the progression of chronic kidney disease (CKD) is widely recognized, in which inflammation plays an important role. Previous studies reported the presence of oxidatively modified high-density lipoprotein (HDL) in the serum of CKD patients. Unlike native HDL, oxidized HDL is thought to be an adverse factor and may increase the production of inflammatory in chronic diseases, but the effect of oxidized HDL on renal tubular cells remains unclear.

**Methods:** Human proximal tubular cell line (HK-2) was cultured and stimulated with different concentrations of oxidized HDL (0-50 µg/mL) in the absence and presence of CD36 siRNA. Intracellular reactive oxygen species (ROS), levels, proinflammatory factors, apoptosis and migration in HK-2 cells were assayed. The expression of Src, (tyr527 and tyr416), MAPK protein (p38, JNK and ERK) and NF-κB activity were also detected.

**Results:** Oxidized HDL enhanced ROS production and upregulated expression of proinflammatory factors including TNF-α, MCP-1 and RANTES in HK-2 cells dose-dependently. Incubation with oxidized HDL also increased apoptosis of HK-2 cells and reduced the ability of migration in a dose-dependent manner. Src-family kinase 527, MAPK and NF-κB were activated post oxidized HDL stimulation. All oxidized HDL-mediated effects on HK-2 cells could be significantly attenuated by pretreatment with CD36 siRNA transfection.

**Conclusions:** These findings suggest that oxidized HDL enhances proinflammatory properties and impairs HK-2 cells function largely via scavenger receptor CD36, which might be one of the major players responsible for the progression of chronic kidney disease.

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

**PUB029**

Inflammation Contributes to Podocyte Injuries and Exacerbates the Progression of Diabetic Nephropathy via HIPK2 Signal Pathway

Kun Ling Ma,1 Yang Zhang,1 Chang Xian Wang,2 Jing Liu,1 Wu Yu,1 Bi-Cheng Liu,1 1Institute of Nephrology, Southeast Univ School of Medicine, Nanjing, China; 2Infection Management Dept, Southeast Univ School of Medicine, Nanjing, China.

**Background:** Inflammation plays central roles in the progression of diabetic nephropathy. Homeo-domain interacting protein kinase 2 (HIPK2) is a conserved serine/ threonine nuclear kinase. In response to infection, DNA damage, and oxidative stress, HIPK2 is activated and plays a crucial role in renal injuries. This study aimed to investigate whether inflammation exacerbates the progression of diabetic nephropathy (DN) via HIPK2 signal pathway.

**Methods:** Twenty male db/db mice were randomly divided into two groups: Control (distilled water injection) or inflamed group (10% casein injection). Body weight and 24-hour urinary protein were measured every week. The plasma levels of serum amyloid A (SAA) and tumor necrotic factor-a (TNF-α) were checked by enzyme-linked immunosorbent assay. The morphological changes of renal pathology and ultra-microstructures were checked by pathological staining and electron microscope. Immunofluorescent staining and Western blotting were used to check the expression of podocyte specific proteins, inflammatory cytokines, and HIPK2 pathway related protein in kidneys.

**Results:** The 24-hour urinary protein, plasma levels of SAA and TNF-α, as well as the protein expression of inflammatory cytokines in kidneys were significantly increased in inflamed group compared to the control. Moreover, there were more significant mesangial expansion, collagen accumulation, and foot process effacement in inflamed group compared to the control. Further analysis showed that inflammation markedly decreased the expression of Wilms tumor-1, Smad7, and Smad9, which were specific biomarkers of podocyte, suggesting the acceleration of podocyte injury induced by inflammation. Interestingly, inflammation increased the expression of HIPK2 and decreased the expression of IκBα, which was closely associated with accelerated renal injuries.

**Conclusions:** Chronic inflammation contributes to podocyte injuries and exacerbates the progression of DN via the activation of HIPK2 signal pathway.

**PUB030**

CCN3 Inhibits TGFβ1-Induced Non-Canonical Smad Signalling in Human Podocytes

Tanakumar H. Madne,1 Iain Macphee,2 Mysore Keshavmurthy Phansik,1 Mark Edward Dockrell,1 1SWT Institute for Renal Research, London, United Kingdom; 2St. Georges, Univ of London, London, United Kingdom.

**Background:** The pleiotropic growth factor TGFβ1 mediates some of its diverse effects by regulation of multiple signaling cascades as well as the recruitment of other growth factors such as CCN2/CTGF. Recently CCN3 has been identified as putative antagonist to CCN2/CTGF. In our work investigating the mechanism of TGFβ1’s effect on podocytes, we have investigated novel signalling pathways activated by TGFβ1 in human podocytes in culture and their regulation by CCN3.

**Methods:** Experiments were conducted on conditionally immortalised human podocytes incubated with TGFβ1 (1.25 & 2.5 ng/mL). Western blotting analysis was performed to detect different levels of Smad and p38 expression and activation. Cells were co-incubated 1/3 CCN3 (360mg/mL).

**Results:** TGFβ1 induced canonical Smad signaling significantly phosphorylating Smad 2 & 3 at 1h (p<0.05). As we have previously reported p38 MAP kinase was also significantly phosphorylated by TGFβ1. In addition, phosphorylation of Smad1/5/8 was also observed (p<0.05). Following reports of a requirement for CCN2/CTGF for TGFβ1 activation of Smad1, we co-incubated the cells with the putative CCN2/CTGF antagonist CCN3. Incubation with CCN3 had no effect on activation of Smad2, 3 or p38 but significantly reduced Smad1/5/8 activation (p<0.05).

**Conclusions:** To our knowledge this is the first report of the activation of Smad1/5/8 in podocytes by TGFβ1. Our work with CCN3 suggests that endogenous CCN2/CTGF is expressed by podocytes and can modulate the activation of Smad1/5/8. Previous research demonstrated that Smad 1/5/8 activation can regulate collagen IV promoter activity. Hence, we are currently investigating the role of CCN2/CTGF-mediated collagen IV expression in podocytes and propose this as a mechanism for glomerular basement membrane thickening observed in renal disease.

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

**PUB031**

Molecular Mechanisms of TNF-Receptor 1 Mediated Signaling Pathways in Human Peritoneal Mesothelial Cells

Julia Ranzinger,1 Willie Laue,2 Martin G. Zeier,1 Daniela Heid,1 Peter E. Scheurich,3 Martin G. Zeier,1 1Nephrology, Univ of Heidelberg, Heidelberg, Germany; 2Institute of Cell Biology and Immunology, Univ of Stuttgart, Stuttgart, Germany.

**Background:** Cellular apoptosis is involved in several physiological processes such as immunological responses and can be induced by the activation of death receptors including tumor necrosis factor receptor 1 (TNFR1). Human peritoneal mesothelial cells (HPMCs) play a central role in the context of inflammatory responses during peritoneal dialysis (PD) caused peritonitis. Although TNFR1 is expressed on HPMCs, TNF-induced apoptosis is inhibited in these cells. The aim of our present study is to investigate the molecular mechanisms of TNF-signaling in HPMCs.

**Methods:** HPMCs were isolated from omentum of healthy donors and dialysis fluid from patients undergoing PD. Flow cytometry was applied to determine the expression of TNFR1 on HPMCs from healthy donors in absence or presence of TNF and dialysis solution in comparison to the TNFR1 expression on cells from PD-patients. To investigate TNFR1-mediated signaling, HPMCs were either treated with dialysis solution or TNF and expression patterns of proteins involved in the TNFR1-signaling pathway (NFκB, IκBα, Caspase-3, cFLIPL) were assayed by Western Blot and Immunocytochemistry.

**Results:** We show that incubation of HPMCs with dialysis solution leads to a significant up-regulation of TNFR1 on the cell surface. This correlates with elevated TNFR1-numbers on HPMCs from PD-patients. Concerning the molecular mechanisms of TNFR1-signaling, Western Blot experiments and Immunocytochemistry showed that incubation of HPMCs with dialysis solution results in increased levels of IκBα and cFLIPL. Furthermore, dialysis solution caused a reduction of cFLIPL, protein amounts in the cells. In contrast, stimulation of the cells with TNF led to an increase in phosphorylated IκBα and cFLIPL.

**Conclusions:** This study shows that dialysis solution used in PD-treatment significantly up-regulates TNFR1 in HPMCs. Moreover, we demonstrate that the presence of dialysis solution affects TNF signaling at the proapoptotic signaling pathway by enhancement of IκBα and reduction of cFLIPL.

**PUB032**

Evaluation of Serum Aminotransferases in Patients with Predialysis Chronic Kidney Disease

Luis H.B.C. Sette, Edmundo Pessoa Lopes. 1Universidade Federal de Pernambuco.

**Background:** Patients with chronic kidney disease (CKD) on hemodialysis have lower serum levels of aminotransferase than those with normal renal function and such a profile may compromise the diagnosis, clinical management and treatment of patients with CKD and liver disease. However, it is not known the behavior of these enzymes in patients with CKD and its relations with the GFR or the stages of CKD.

**Methods:** From September 2011 to December 2012, was held an observational and cross-sectional study in patients with chronic kidney disease (CKD) attended at the ambulatory of Nephrology at the Hospital of Clinics of the Federal University of Pernambuco (HC-UFPF). Renal function was assessed by estimated GFR using the formula proposed by Cockcroft-Gault. Patients were classified into stages of CKD, according to the definition of the Kidney Disease Outcomes Quality Initiative (K/DOQI).

**Results:** We evaluated 142 patients with CKD, 72 male (52.1%) with a mean age of 64 ± 16 years. The mean GFR was 29.1 ± 13 mL/min/1.73m2. Patients showed the following distribution according to the stages of CKD: 15 (10.5%) patients stage 5; 70 (49.3%) stage 4; 57 (40.2%) stage 3 (38%) and 3 (2.1%) patients stage 2. The mean serum ALT and AST reduces in proportion to the decrease of GFR (p = 0.006 and p = 0.049, respectively).

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

883A
Serum ALT levels were higher in the 57 patients with stages 2 and 3 compared to 85 patients at stages 4 and 5 (p < 0.03).

**Conclusions:** Serum ALT and AST correlated with GFR and the reduction of these enzyme levels were in accordance with the progression of CKD.

**PUB034**

**NGAL and NT-proBNP Levels in Type II Diabetic Patients with Macroproteinuria**

**Hulya Taskapan,1 Mehmet Cagatay Taskapan,2 Özkan Ulutas,1 1 Nephrology, Inonu Univ Medical Faculty, Malatya, Turkey; 2 Biochemistry, Inonu Univ Medical Faculty, Malatya, Turkey.

**Background:** In patients with heart failure plasma N terminal-pro brain natriuretic peptide (NT-proBNP) levels are correlated to urine Neutrophil gelatinase-associated lipocalin (NGAL) levels. We prospectively evaluated the relationship among glomerular filtration rate (eGFР), urine albumin to creatinine ratio, urine and serum NGAL levels and NT-proBNP in 20 type 2 diabetic patients with macroalbuminuria at 4-month intervals.

**Methods:** In 20 diabetic patients with macroproteinuria, serum creatinine, albumine, N terminal-pro brain natriuretic peptide (NT-proBNP), serum and urine NGAL levels, urine microalbumin, urine creatinin were measured at the baseline, at the 4th month and at the 8th month. The baseline results of the patients were compared with those of 20 healthy, age and sex matched controls.

**Results:** Diabetic patients had higher urine and serum NGAL, NT-proBNP levels, and lower eGFR. The eGFРs at the baseline, 4th and 8th month were 29.6±12.0, 27.8±13.7 and 22.9±10.4mL/min/1.73 m², respectively. No significant change in urine NGAL levels was detected (p>0.05), whereas there were significantly increases in NT-proBNP, serum NGAL levels, and urine albumin to creatinine ratio and significantly decrease in eGFР as the study progressed. (p<0.05). The baseline and the 4th month urine albumin to creatinine ratio were positively correlated to NT-proBNP levels measured at the same periods (r=0.451; p=0.046; r=0.489; p=0.029 respectively). In all measurements urine albumin to creatinine ratio were negatively correlated to serum albumin levels measured at the same periods (r=-0.792; p<0.000; r=-0.716; p<0.000; r=-0.531; p=0.016 respectively).

The 4th month microalbumin to urine creatinine ratio was positively correlated with serum NGAL (r=0.478; p=0.033). The 8th month eGFР was negatively associated with urine NGAL (r=-0.471; p=0.039). None of eGFР measurements was correlated with NT-proBNP (p>0.05). Neither serum NGAL nor urinary NGAL levels is associated with NT-proBNP levels (p>0.05).

**Conclusions:** Our findings showed an association between serum NT-proBNP levels and proteinuria in diabetic patients with macroalbuminuria but not with normal NGAL levels.

PUB035

**Iron Management in Non Dialysis CKD Patients: The Italian Multicenter Prospective Study in Renal Clinics**

Roberto Minutolo,1 Francesco Locatelli,2 Roberto Benvegnù,3 Ugo Pentangelo,3 Giuseppe Conte,1 Luca De Nicola.1 1Nephrology, Inonu Univ Medical Faculty, Malatya, Turkey; 2A Manzoni Hospital, Lecco, Italy; 3For the RECORD-IT Study Group.

**Background:** Conventional treatment with epoetin to manage anemia in chronic kidney disease (CKD) is sometimes hard to target hemoglobin level defined by KDIGO guidelines. The aim of this study was to confirm the effectiveness of darbepoetin alpha (DA) on hemoglobin control in patients with CKD with preserved kidney function and compliance to iron therapy was evaluated.

**Methods:** We prospectively evaluated iron management in two visits, performed 6 months apart, in 744 CKD stage 3-5 patients followed in 19 renal clinics from 26 months. Iron deficiency (ID) was defined as TSI<20% and/or ferritin<100 ng/mL. Endpoints were the change of ID prevalence between basal and month-6 visit (primary) and the prevalence of clinical inertia to iron therapy, that is, the lack of iron prescription despite ID (secondary).

**Results:** Age was 69±13 yrs, GFR 28±10 mL/min/1.73 m² and male gender, diabetes and prior CVD accounted for 57%, 30% and 30% respectively. CRP [3.0 mg/L (5.3-8)], TSAT [24.9±9.5] ferritin [102 ng/mL (54-193)] did not change at month 6. Table shows changes between the two visits by iron status at baseline (§P<0.05 vs ID, *P<0.05 vs basal).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal</th>
<th>Month 6</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (&lt;11 g/dL)</td>
<td>16.1</td>
<td>17.2</td>
<td>0.00</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>28.8</td>
<td>27.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Ferritin (mg/L)</td>
<td>201</td>
<td>175</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Epoetin (IU/kg)</td>
<td>13</td>
<td>1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>9.6</td>
<td>9.7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Conclusions:** Therefore, abating clinical inertia for iron therapy likely represents a main area of improvement in the nephrology management of renal anemia.

PUB036

**25(OH)Vitamin D and Calcitriol: Dissimilar Actions on Left Ventricular Hypertrophy**

Bruno C. Silva, Rosa M. A. Moyes, Manuel C. Castro, Rosilene M. Elias. Nephrology Div, Univ of Sao Paulo, Sao Paulo, Brazil.

**Background:** Hypovitaminosis D has been associated to cardiovascular (CV) morbidity and mortality both in general population and in patients with chronic kidney disease. Observational studies have shown that receiving any vitamin D (25(OH)vitamin D or calcitriol) reduced CV risk. Whether the effect of 25(OH)vitamin D (VdD) is independent of calcitriol is still controversial. The aim of this study was to evaluate the role of VdD levels on left ventricular hypertrophy (LVH) in patients on hemodialysis.

**Methods:** We performed a cross-sectional study, including 46 patients who underwent conventional chronic hemodialysis program at a single center facility (University of Sao Paulo). Clinical, laboratory, demographic, and echocardiographic data were collected. LVH was categorized as LVMI >125g/m² or as LVH index (LVH-I) > or < 125g/m². Comarison between these 2 groups was performed using unpaired t tests. Multivariate analysis was also undertaken with LVH as dependent variable.

**Results:** Of 46 patients, 26 were male, mean age of 47±18 years and dialysis vintage of 8.7 years (1 to 30 years). Mean hemoglobin levels were 11.3±1.5 g/dL and VdD levels of 26.1±12.4 ng/mL (82.6% had levels below 30 mg/mL, and 41.6% below 15 ng/mL). Nineteen patients (41.3%) were using calcitriol. In univariate analysis, VdD was the only significant variable associated to LVH, showing that levels were lower in patients with LVHMI >125g/m² (25.2±12.9 vs 26.1±12.4 ng/mL). In both groups, no significant rise was observed (p>0.05). Neither serum 25(OH)vitamin D nor urinary 25(OH)vitamin D deficiency (<15ng/mL) was independently associated to LVH, when adjusting for calcitriol use, hemoglobin levels, and gender (HR 73.06, p=0.006).

**Conclusions:** 25(OH)vitamin D deficiency is associated to reduced LVH, and its action seems to be independent of active vitamin D3 (calcitriol). Our results are supportive of prescribing VdD to patients on hemodialysis, even for those patients already taking calcitriol.

PUB037

**The Efficacy and Usefulness of Darbepoetin Alpha in Patients with Chronic Kidney Disease: An Observational Clinical Trial**

Noriuki Iino, Junichiro J. Kazama, Ichiei Narita. Clinical Nephrology and Rheumatology, Niigata Graduate School of Medical and Dental Sciences, Niigata, Japan.

**Background:** Conventional treatment with epoetin to manage anemia in chronic kidney disease (CKD) is sometimes hard to target hemoglobin level defined by KDIGO guidelines. The aim of this study was to confirm the effectiveness of darbepoetin alpha (DA) on hemoglobin control in patients with CKD with preserved kidney function and compare the result with those patients on the previous epoetin treatment. In the ESA-naive group, mean hemoglobin level rapidly raised to target levels and was maintained during the study period. On the other hand, mean hemoglobin levels slowly increased in previously epoetin-treated patients. After 12 months of the investigation, differences of mean hemoglobin levels were still significant. In the group who had been on darbepoetin, the hemoglobin level finally diminished. However, to maintain same levels of hemoglobin, requirement dose of DA was significantly different between them.

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

884A
Conclusions: Darbepoetin alpha once every 4 weeks successfully maintained stable hemoglobin levels in patients with CKD with preserved renal function, for prolong period.

Funding: Government Support - Non-U.S.

PUB038
Prescribing in Renal Impairment within the Acute Hospital Setting – A Prospective, Observational Study

Michelle M. O’Shaughnessy,1 Niamh Allen,2 Emma Louise Payne,darson,3 Lise Meurant,4 Danv,2 Peter J. Lavin,2 Tamasine C. Grimes,3,4 1Dept of Nephrology, Trinity Health Kidney Center, Tallaght Hospital, Dublin, Ireland; 2Dept of Pharmacy, Tallaght Hospital, Dublin, Ireland; 3Trinity College Univ, Dublin, Ireland.

Background: Patients with renal impairment (RI) are susceptible to adverse drug reactions. We studied the nature and frequency of potentially inappropriate prescribing (PIP) amongst hospitalised patients with RI. We examined trends in, and risk factors for, PIP and measured agreement between renal prescribing guidelines.

Methods: This was a single-centre, prospective, observational study conducted between October 2012 and March 2013. Hospitalized patients with RI were stratified according to estimated GFR and randomly selected for study inclusion. Prescriptions were reviewed at three time-points (pre-admission, admission, discharge) and according to two renal prescribing guidelines, the British National Formulary (BNF) and the Renal Drug Handbook (RDH). Blood transfusions in 58% (37-87%), only 27% (9-53%) received intravenous iron. Notably, 17% of patients Within 12 months prior the survey, 86% (80-94%) received iron treatment. Despite ESA use pharmacists and nurses were not.

Factors for PIP, whereas severity of RI, recognition of RI by treating team, and clinical pharmacy input were not.

Conclusions: PIP is common amongst hospitalized patients with RI, although prevalence rates vary depending upon severity of RI, referenced prescribing guideline, timing of assessment and patient co-morbidity. In particular, the impact of disagreement between renal prescribing guidelines upon clinical outcomes requires further study.

PUB039
Anemia Management Practice in Chronic Kidney Disease in Eastern Europe

Andrzej Wiecek,1 Lyudmila Biriukova,1 Ivan Rychlik,2 Gabriel Miculescu,3 Jacek Lange,4 Daniell Mitchell.5
1Medical Univ Silesia, Katowice, Poland; 2RNMU, Moscow, Russian Federation; 3Fresenius Medical Care, Prague, Czech Republic; 4Medical Univ, Bucharest, Romania; 5Vifor Pharma, Glattbrugg, Switzerland.

Background: Anemia and iron deficiency (ID) are frequent in chronic kidney disease (CKD) and should be managed with an erythropoiesis-stimulating agent (ESA) and iron. This study evaluated current practice in diagnosis and treatment of CKD-associated anemia in Eastern Europe.

Methods: Nephrologists from Bulgaria, Czech Republic, Poland, Romania, Russia, Slovakia, and Slovenia were surveyed (Jan-Feb 2012) for the use of diagnostic tests and therapies in their 5 CKD patients (stage 3 or 4) that were treated for anemia in the prior 6 months. Data shown for all patients and range across countries.

Results: 163 nephrologists reported data of 855 anemic CKD patients (stage 3: 47% [26-59%]; female: 52% [44-57%], mean age: 58y [52-65y]). At anemia diagnosis, 97% (94-100%) were tested for hemoglobin (Hb); 48% (23-71%) for serum ferritin and 46% (26-69%) for transferrin saturation (TSAT). Median 1Hb, ferritin and TSAT were 100g/L (88-110g/L), 84µg/L (12-102µg/L) and 19% (15-24%), respectively. Moderate-to-severe anemia (Hb ≤100g/L) was diagnosed in 67% (42-85%) of patients; 11% (1-36%) presented with Hb ≤80g/L. Insufficient iron for erythropoiesis (TSAT <20%) was seen in 65% (37-84%) and depleted iron stores (ferritin <100µg/L) in 56% (43-100%) of tested patients. Within 12 months prior the survey, 86% (80-94%) received iron treatment. Despite ESA use in 58% (37-87%), only 27% (9-53%) received intravenous iron. Notably, 17% of patients in the Czech Republic and 14% in Russia received intramuscular iron. Blood transfusions were given to 7% (1-11%) of patients.

Conclusions: Current anemia and iron status management in CKD patients varies substantially across Eastern Europe and is often not in line with recommendations. The high proportion of moderate-to-severe anemia and ID suggest insufficient iron status management. Similar findings in Western Europe suggest that improving awareness and implementation of guidelines for management of CKD-related anemia and ID is a pan-European if not a global need.

Funding: Pharmaceutical Company Support - Vifor Pharma sponsored the study, medical writing support has been provided by SPL Regulatory Affairs & Medical Communication and funded by Vifor Pharma

PUB041
Posterior Reversible Encephalopathy Syndrome in Patients with Chronic Kidney Disease


Background: Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiologic entity characterized by neurologic symptoms and typical neuroimaging transient changes. PRES is consequence of an endothelial dysfunction of the cerebrovascular barrier. It is associated with many mediators: rates of increase in blood pressure, all causes of acute kidney injury, and patients with chronic kidney disease (CKD) may have an increased risk for this syndrome.

Methods: We report three cases of PRES in patients with CKD on renal replacement therapy.

Results: The patients were three women, had a mean age of 20 years, two were in peritoneal dialysis and one in hemodialysis. The patient didn’t have an autoimmune disease and weren’t receiving immunosuppression. The presenting symptoms were bilateral, loss of consciousness and seizures. All cases progressed to generalized tonic-clonic seizures and one patient was in status epilepticus at admission. All patients had abrupt increases in blood pressure. Hypertension was consequence of anti-hypertensive therapy withdrawn in hemodialysis patient. Patients on peritoneal dialysis coexisted signs of failure of the technique with significant hypervolemia. Brain magnetic resonance imaging (MRI) was performed in all patients and showed extensive bilateral white-matter abnormalities suggestive of edema, not only in the posterior regions of the cerebral hemispheres, but also in other cerebral areas, in the brain stem, and in the cerebellum. The patients were treated with hemodialysis, antihypertensive and antiepileptic drugs. Resolution of seizures occurred in 3 to 16 hours and complete neurologic symptoms were resolved in average after five days. In two patients the follow-up MRI revealed imagiological significant improvement.

Conclusions: These cases emphasize the role of hypertension and hypervolemia as inducing mechanisms of PRES and stress the importance of considering this syndrome in the early diagnosis and treatment of seizures in CKD patients. This is essential since the early diagnosis and treatment may allow complete resolution of neurologic changes, without persistent cognitive sequelae.

PUB042
Low Formic Acid Maybe Involved with Decreased ATP Production in ESRD Patients

Emiko Miyazawa,1 Hiroyuki Terawaki,2 Sadayoshi Ito,1 Masaaki Nakayama,2 1Dept of Nephrology, Endocrinology, and Vascular Medicine, Tohoku Univ, Sendai, Japan; 2Dept of Nephrology and Hypertension, Fukushima Medical Univ, Fukushima, Japan.

Background: Formic acid (FA) is an essential substance for de novo synthesis of purine nucleotides. FA is combined with folic acid and incorporated into purine synthesis pathway as formyl-tetrahydrofolate. FA is used as a constituent of C2 and C8 of purine nucleotides. We previously reported that endogenous FA exists in human plasma. But only a limited number of reports examined about level of FA in ESRD and its physiological role.

Methods: Patients with ESRD (CKD 5 and CKD 5D, n=111) and predialysis (CKD 3a-4, n=51) were subjected for analysis of plasma FA and tryptophan (precursor of FA). FA and tryptophan were measured by high-performance liquid chromatography (HPLC). Adenosine triphosphate (ATP) levels were measured by luciferase luminescence method in (a) whole blood, (b) mononuclear cell, and (c) neutrophil after incubation for three hours with and without addition of FA, and examined differential rates of increase.

Results: The levels of FA (mean ± SD) were 3.04 ± 1.09 µM in ESRD, 1.57 ± 1.10 µM in predialysis CKD, and 3.71 ± 1.16 µM in control (P<0.05). Rates of ATP change after incubation for 3 hours with the addition of FA were (a) 2.52 times, (b) 0.97 times, (c) 1.16 times the controls. Significant increases were seen in whole blood and neutrophil (P<0.01 and P<0.007 respectively), but ATP was not changed in mononuclear cell by t-test.

Conclusions: Taken together the result that plasma FA was lower in ESRD, and ATP levels were significantly increased when cultured with the addition of FA to isolated neutrophil in healthy subject. It suggests that FA enhances not only purine metabolism but also ATP production. Lower FA maybe involved with the decreased ATP production in ESRD. The clinical relevance of this pathology needs to be addressed.

PUB043
Clinical Utility of Reticulocyte Hemoglobin, a Parameter Obtained on High-End Hematology Analyzers, in the Diagnosis and Assessment of Functional Iron Deficiency in Predialysis Chronic Kidney Disease

Alan F. Almeida,1 P. Gudsoorkar,1 J. Kothari,1 R. Sirsat,1 S. Khodaiji,2 K. Sehgal.2
1Dept of Nephrology, P.D. Hinduja Hospital, Mumbai, India; 2Hematology, P.D.Hinduja Hospital, India.

Background: Functional iron deficiency (FID) can complicate the management of the anemia of CKD. This study was undertaken to assess the utility of reticulocyte hemoglobin (Ret-Hb) as a marker for the assessment of FID.

Methods: CKD predialysis patients (Stage 3-5) with hemoglobin <11g%, transferrin saturation ≥20% and Serum Ferritin <100mg/ml were included. They received intravenously 500 mg of ferrous carboxymaltose. soluble transferrin receptor assay (sTfr), Ret-Hb (Sysmex XE-2100), Ultra sensitive CRP, serum folate vitamin B12 measured before and Hb, Ret-Hb and sTfr was checked 1 month after IV iron therapy.

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

Underline represents presenting author.
Results: 180 patients with CKD (stage 3-5) were screened. 47 enrolled in the study (19[40%] males, 28[60%] females) had a mean age of 46.6 years (SD 13.7 yrs). The most common renal disease was CT (36%), followed by GGN (33%), and then ID (16%). At follow-up, median (IQR) eGFR was 45(40-50) at stage 4(45%), followed by stage 5(38%). 4 weeks following iron infusion, a statistically significant increment in Hb (p<0.001), Ret-He increased from 23.58 (pre-infusion) to 24.55 (post-infusion; p<0.001). tSta assay showed a significant decrease with iron treatment (p<0.001). Further analysis of patients with definite ID (confirmed by generating Thomas plot) showed a significant improvement in Hemoglobin and Ret-He.

Conclusions: Ret-He is a useful test to assess the status of hemoglobinization of RBC. A combination of Ret-He, Sr ferritin and sTfr assay along with the Thomas plot can help to optimize the patients as FID. Alter categorization, the patients can be subjected to intervention in the form of oral iron/ IV iron / Erythropoetin alone / Erythropoetin plus IV iron. The Thomas plot will help in the diagnosis and also the follow up of patients of anemia of renal disease. Whether Ret-He alone or in combination with other parameters, like sTfr and Sr ferritin, will require further studies with larger sample sizes.

Funding: Private Foundation Support

PUB044
The Activation of Mineralocorticoid Receptor in Adipose Tissues in CKD Rat Impaired Glucose Metabolism through Tissue ADMA Increase Kozi Kosova, Shu Wakino, Ayumi Yoshihiji, Hitoshi Minakuchi, Kazuhiro Hasegawa, Naoki Washida, Koichi Hayashi, Hiroshi Itoh. Internal Medicine, Keio Univ School of Medicine, Tokyo, Japan.

Background: Recent studies revealed the influence of mineralocorticoid receptor (MR) activation by aldosterone (Aldo) and asymmetric dimethylarginine (ADMA) on the glucose metabolism. We examined whether the activation of MR and ADMA affected insulin sensitivity (insulin resistance, IR) in kidney of body resistant rats.

Methods: We rendered SD rats renal insufficiency with 5/6th nephrectomy (Nx group) and were treated with MR blocker spironolactone (Spi group). The results of oral glucose tolerance test (OGTT) and intraperitoneal insulin tolerance test (IP-ITT) were compared among each group. ADMA levels were analyzed among insulin stimulation, and fibrils were differentiated with/without the addition of Spi.

Results: In OGTT, rats in Nx showed impaired glucose tolerance. In ITT, the decline in blood glucose was blunted. These changes were partially reversed in Spi. The phosphorylation of Akt after insulin stimulation was attenuated in adipose tissue, which were restored in Spi. These changes were not observed in muscle and liver tissue. MR expression in the nuclear fraction was increased in the adipose tissues in Nx. The expression of SGK1 (Serum/glucocorticoid regulated kinase 1), MR target molecule was upregulated in Nx. These changes were not observed in muscle and liver tissue. MR expression in the nuclear fraction was increased in the adipose tissues in Nx.

Conclusions: In the activation of Aldo/MR pathway in the adipose tissue affected at least in part the insulin resistant state. The activation of adipose tissue MR downregulated DDAH and increased the levels of ADMA, which blocked the insulin signaling.

PUB045
Inflammatory Cytokine TNFα/IL-6 Related to Muscle Wasting and Up-Regulated Expression of Myostatin and Atrogin-1 Huiling Wang. Nephrology Div, Jinmin Hospital, Shanghai, China.

Background: Although plenty of research confirmed increased systemic inflammation related to malnutrition in advanced chronic kidney disease (CKD), few clinic research revealed the mechanism of inflammatory cytokines impacted muscle wasting in patients with CKD. This study investigates the serum cytokines level and muscle wasting of patients with underlying maintenance hemodialysis (HD) and the expression of genes involved in the regulation of muscle mass and that for the inflammatory cytokine TNFα/IL-6 in muscle biopsy.

Methods: HD patients were selected according to the enrolled standard as HD group, 30 healthy adults with gender and age matched as control(Ctl). We collected the biochemical and anthropometry data, measured inflammatory cytokine such as C-reactive protein (CRP), interleukin-6(IL-6) and tumor necrosis factor alpha(TNF alpha) by ELISA with their serum samples. Then we got muscle sample from 8 HD patients and 10 Ctl patients, observed the muscle histology by light scope after HE staining, and analyzed the transcriptional levels of myostatin and Atrogin-1, TNFα/IL-6 by real-time PCR.

Results: In the 2 groups, mRNA of myostatin in muscle biopsy increased 2.43 fold respectively; and the TNFα, IL-6 mRNA increased 8.37 fold and 3.36 fold respectively measured by RT-PCR.

Conclusions: CKD patients undergoing hemodialysis present elevated inflammatory cytokines level and obviously muscle wasting. Up-regulation of TNFα/IL-6 expression stimulating the transcription of myostatin and Atrogin-1, might be an important mechanism of muscle wasting in CKD.

Funding: Government Support - Non-U.S.

PUB046
Assessment of Coronary Artery Calcification in Patients with Coronary Artery Disease with and without Chronic Kidney Disease Anil Kumar Yadav, Abhishek Kumar, Sunil Agarwal, Alpana Raizada, Shuchi Bhatt, Basu Dev Banerjee, Om Parkash Kalra. Univ College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India.

Background: Cardiovascular disease (CVD) is the main cause of morbidity and mortality in patients with chronic kidney disease (CKD). Vascular calcification, such as coronary artery calcification (CAC) is considered to be the causal link between them; however the role of Multidetector Computed Tomography (MDCT) for assessment of CAC is less well studied. In this study, we assessed CAC in patients of CAD with and without CKD using MDCT.

Methods: We conducted a cross sectional study, comprising of 75 patients, 25 in each of the 3 groups: Group I- CAD without CKD, Group II- CAD with CKD stage 3/4 and Group III- CAD with CKD stage 5 on maintenance hemodialysis (MHD) ≥3 months. Patients with diabetes mellitus were excluded. Assessment of CAC was done using MDCT by assigning a scoring system by Agatston as a CAC score. In addition, CAC score was correlated with calcium phosphorus product, intact parathyroid (iPTH) level, duration of CKD and duration of MHD.

Results: The mean CAC score was 75.05±193.35 (median 0), 163.62±399.17 (median 1) and 142.48±701.12 (median 0) in patients of Group I, II and III respectively. The CAC score was higher in patients with CKD; however, the difference was not significant (p=0.792). We found a positive correlation between CAC and duration of CKD in group II (r=0.554, p=0.004). Patients having CKD for ≥12 months duration had mean CAC score 24.36±6.17 and those having CKD for <12 months duration had mean CAC score 410.82±602.19. We also found a positive correlation of CAC with duration of dialysis (r=0.605, p<0.001). Patients who were on MHD for ≥12 months had mean CAC score 3.36±7.70 and those on MHD <12 months had mean CAC score 390.78±1168.99; however, in our study, there was no correlation between CAC and calcium phosphorus product and iPTH levels.

Conclusions: The coronary artery calcification was found to have a positive correlation with the duration of CKD and duration of maintenance hemodialysis. Further no correlation was found between CAC score and calcium phosphorus product and iPTH levels.

Funding: Government Support - Non-U.S.

PUB047
Does Impaired Renal Function Interfere with the Development of Coronary Collateral Circulation in Patients with Acute Myocardial Infarction? Sang Heon Suh, Ha Yeon Kim, Yong Un Kang, Chang Seong Kim, Joon Seok Choi, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim. Depts of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea.

Background: It has been suggested that low estimated glomerular filtration rate (eGFR) was associated with poor collateral flows in patients with acute myocardial infarction (AMI). We investigated the association of impaired renal function with coronary collateral development. The association of coronary collateral circulation and impaired renal function with clinical outcomes of AMI was also examined.

Methods: We retrospectively analyzed 1,760 patients diagnosed with AMI between November, 2005 and March, 2009. eGFR < 60 mL/min/1.73m² was defined as impaired renal function. According to Renoptrop classification, collaterals were considered present with scores ≥1 and were considered adequate with scores ≥ 2.

Results: Univariate analysis revealed eGFR was lower in patients with visible collateral circulation, while other high risk features of coronary artery disease (CAD), such as elevated hsCRP, N-terminal pro-brain natriuretic peptide, low thrombolysis in myocardial infarction (TIMI) grade before revascularization and low ejection fraction (EF) were also associated with the development of visible collateral flow. Multivariate logistic regression analysis, however showed there is no significant association between impaired renal function and coronary collateral development, although other factors such as low TIMI grade before revascularization and low EF exerted significant impact on the development of coronary collateral vessels even after the adjustment of confounders. Cox proportional regression analysis for 24-month survival demonstrated impaired renal function, but not the development of any visible collateral, was one of the independent risk factors for all-cause mortality.

Conclusions: It is supposed the development of coronary collateral circulation is independent of renal function. Coronary collateral circulation might be mere a reflection of the severity of CAD rather than a guardian of myocardium against AMI.
PUB048

Weekend Weight Gain in Late Stage Chronic Kidney Disease
Steven Fishbane, Shahlla Chidella, Candice Halinski, Sofia Agoritsas. Div of Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY.

Results: Results: FGF-23 was significantly higher in the CKD-D group compared to control (0.72 ± 6.57 pg/ml vs 8.58 ± 5.02 pg/ml, p < 0.0001 (Mann-Whitney test)). The CKD group had significantly increased FGF-23, at 17.1 ± 6.36 pg/ml, compared to control (8 ± 0.6 pg/ml, p < 0.0001). Between the CKD groups there was a significant difference (p < 0.0001). Both CKD groups, had significantly higher FGF23 level than the control (p < 0.0001).

Conclusions: Patients with a CKD express increased levels of plasma FGF-23 compared to healthy control; 2. FGF-23 can be used as a biomarker for early CKD and high incidence of pulmonary hypertension.

PUB051

Barriers to Angiotensin Inhibitor Use in Advanced Chronic Kidney Disease
Shayan Shirazian, Candace D. Grant, Joseph Mattana. Medicine, Winthrop Univ Hospital, Mineola, NY.

Background: Angiotensin inhibition with an ACEi or ARB is recommended for the treatment of hypertension (HTN) in patients with chronic kidney disease (CKD) and proteinuria regardless of GFR or presence of diabetes (DM). In patients with advanced CKD, angiotensin inhibitors (AIs) may be more conservatively utilized due to known adverse effects. The objective of this study was to determine the frequency with which AIs are used in patients with HTN, proteinuria and stage 4 or 5 CKD and to identify reasons why they are not utilized.

Methods: In this cross-sectional study, electronic charts from patients with stage 4 or 5 HTN and HTN seen at an outpatient nephrology practice were reviewed. Eligible patients had moderately or severely increased albuminuria or urine protein to creatinine ratio greater than 150 mg/g at least once during the year prior to study. The frequency of AI use was determined and documented reasons for not using these medications were collected. Groups receiving and not receiving an AI were compared using chi-squared tests for categorical variables and unpaired t-tests for continuous variables.

Results: Two-hundred and four charts were reviewed and 89 patients with HTN, stage 4 or 5 CKD and proteinuria were identified. Fifty-three percent had DM, 57% were male, 75.3% were white, the average age was 70 and the average estimated GFR was 20 mL/min/1.73m2. Of these patients, 46 (52%) were not taking an AI. Documented reasons for not being on an AI included: hyperkalemia (15/46), AKI (9/46), cough or allergies/anaaphylaxis (4/46) and no documented reason (18/46). There were no significant differences between the groups on and off an AI with regards to DM status, gender, ethnicity, age, or average estimated GFR.

Conclusions: In this study the frequency of AI use among patients with stage 4 or 5 CKD and proteinuria was low, with hyperkalemia and AKI being the most commonly documented reasons for non-use and for a substantial number no reason is given. These findings suggest that there may be substantial opportunities to increase AI use, and future efforts should focus on strategies for increasing tolerance to AI therapy in patients with advanced CKD rather than simply recommending their use.

PUB049

Test Battery to Assess Physical and Cognitive Function in Stage 3-4 Chronic Kidney Disease
Kristen L. Jablonski, Jamie Justice, Douglas R. Coons. 1Faculty of Medicine, Bar Ilan Univ Galilee, Israel; 2Diabetic Nephropathy Lab, Poriya Medical Center, Israel; 3Dept of Integrative Physiology, Univ of Colorado Denver, Aurora, CO.

Background: Background: Physical and cognitive function is impaired in non-dialysis dependent chronic kidney disease (CKD), but has not been well characterized using a battery of tests evaluating multiple domains in a given cohort. Furthermore, there is limited published data regarding the utility of these tests in patients with CKD not requiring dialysis, despite wide validation in the general gerontology literature.

Methods: Methods: We compared 10 patients with stage 3-4 CKD (estimated glomerular filtration rate [eGFR] 29-4 mL/min/1.73 m2) matched for age (59±3 years) and gender (8M/2F) to 10 healthy controls (eGFR 89±3 mL/min/1.73 m2).

Results: Results: Patients performed worse than controls on the 400 m walk (endurance: 196.5± vs. 308.5±25 seconds; p<0.001), timed up and go (TUG) (mobility: 5.6±0.3 vs. 9.3±0.6 seconds; p<0.001), rapid step test (balance: 41.2±1.3 vs. 70.1±6.2 seconds; p<0.001), hand grip strength (strength: 43.0±22 vs. 20±5±3.2 kg; p<0.005), grooved pegboard (dexterity: 67.3±5.1 vs. 125.9±24.3 seconds; p<0.05), and trailmaking test part A and B (cognitive function; A: 29.9±3.5 vs. 52.8±9.6 seconds; B: 64.4±8.2 vs. 132.3±20.7; both p<0.05).

Conclusions: Conclusions: These results confirm physical and cognitive function impairments across multiple domains in patients with stage 3-4 CKD and establish the need for intervention strategies.

Funding: Funding: Other NIH Support - NIA R21 HL107105

PUB050

Fibroblast Growth Factor 23 and Pulmonary Hypertension in Patients with Chronic Kidney Disease and Hemodialysis
Farid M. Nakhol, Nadia Thawli, Ana Roth, 1Farber Evgeny, 2Aivva Peleg. 1Nephrology, Fornia Medical Center, Israel; 2Diabetic Nephropathy Lab, Fornia Medical Center, Israel.

Background: Background: The pathogenesis of Pulmonary Hypertension in advanced chronic kidney disease and Hemodialysis is hypothesized to be explained by different mechanisms. AV fistula, parathyroid hormone and hyperphosphatemia. A new player, the Fibroblast growth factor 23 (FGF 23) regulates phosphorus metabolism and is a strong predictor of mortality in dialysis patients. FGF 23 is thought to be an early biomarker of disordered phosphorus metabolism in the early stages of chronic kidney disease (CKD), and can cause pulmonary hypertension probably via vascular calcification. Our group had described high incidence pulmonary hypertension and increased mortality in HD patients.

Methods: Methods: Forty one CKD patients on hemodialysis treatment (CKD-D group) and 44 patients with stage 3-4 CKD not on dialysis therapy and healthy group (21), were measured weights weekly for 2 years. The CKD-D group, FGF-23, compared to healthy control, by using ELISA (Millipore, St. Charles, MI, USA ), and arterial pulmonary pressure (PAP) by transthoracic echocardiography.

Results: Results: Serum 25-hydroxy vitamin D levels (r=-0.31, p<0.01) and serum bicarbonate (r=-0.242, p<0.01) were negatively correlated with UPCR, both for the population as a whole (r=-0.366, p=0.01) as well as for patients with UPCR greater than or equal to 0.5 (r=-0.289, p<0.01), suggesting that the relationship with albumin is not restricted to only those patients with significant proteinuria.

Conclusions: Conclusions: These findings suggest that lower vitamin D levels, reduced serum bicarbonate, lower serum albumin levels, elevated phosphorus levels and elevated parathyroid hormone levels may be associated with higher urine protein excretion in patients with CKD-4 and 5. It is plausible that treating these abnormalities in the advanced CKD population might have additive favorable effects on urine protein excretion, though a cause and effect relationship is not clear. Future interventions, possibly through dedicated CKD clinics, should focus on intensive combined therapies to reduce proteinuria in patients with advanced CKD.

PUB052

Variables Associated with Increased Proteinuria in Patients with Advanced Chronic Kidney Disease
Shayan Shirazian, Candace D. Grant, Joseph Mattana. Medicine, Winthrop Univ Hospital, Mineola, NY.

Background: Reducing proteinuria is an important aim of therapies to slow the progression of chronic kidney disease (CKD) and typically entails aggressive use of ACEI/ ARB therapy and blood pressure reduction. With advanced CKD however, markedly altered mineral, acid-base and hormone metabolism among other abnormalities might also exert adverse effects on proteinuria and contribute to CKD progression. Knowledge of such associations might help improve antiproteinuretic strategies in this population.

Methods: We carried out a cross-sectional study of 187 adult patients with CKD-4 and 5 in an outpatient nephrology practice utilizing an electronic health record and examined the relationship between urine protein excretion and several laboratory variables which are commonly affected by advanced CKD.

Results: Results: Urine protein-to-creatinine ratio (UPCR) was positively correlated with serum phosphorus (r=0.218, p<0.01) and serum intact parathyroid hormone levels (r=0.181, p<0.01). A negative correlation was found for UPCR and serum bicarbonate (r=-0.242, p<0.01) and serum 25-hydroxy vitamin D levels (r=-0.283, p<0.01). Serum albumin levels were negatively correlated with UPCR both for the population as a whole (r=-0.366, p<0.01) as well as for patients with UPCR greater than or equal to 0.5 (r=-0.289, p<0.01), suggesting that the relationship with albumin is not restricted to only those patients with significant proteinuria.

Conclusions: Conclusions: These findings suggest that lower vitamin D levels, reduced serum bicarbonate, lower serum albumin levels, elevated phosphorus levels and elevated parathyroid hormone levels may be associated with higher urine protein excretion in patients with CKD-4 and 5. It is plausible that treating these abnormalities in the advanced CKD population might have additive favorable effects on urine protein excretion, though a cause and effect relationship is not clear. Future interventions, possibly through dedicated CKD clinics, should focus on intensive combined therapies to reduce proteinuria in patients with advanced CKD.
PUB053

Epoxycosatrienoic Acid Prevents Renal Fibrosis and Inflammation via Peroxisome Proliferators-Activated Receptor Activation in Obstructive Nephropathy
Jinu Kim, Babu J. Padanilam.1 Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE;2 Medicine, Div of Nephrology, Univ of Nebraska Medical Center, Omaha, NE.

Background: Epoxycosatrienoic acids (EETs), lipid metabolites produced from arachidonic acid, have anti-inflammatory and profibrotic functions in the cardiovascular system. Soluble epoxide hydrolase (sEH) converts EETs to inactive dihydroxyeicosatrienoic acids. Based on previous studies, we hypothesized that genetic or pharmacological inhibition of sEH would attenuate tubulointerstitial fibrosis and inflammation induced by unilateral ureteral obstruction (UUO) in mouse kidneys.

Methods: UUO was performed by ligation of the left ureter near the kidney pelvis in sEH-knockout (sEH-KO) and wild-type (WT) mice. In WT mice, sEH inhibitor was used to decrease leukocyte influx and proinflammatory protein expression during UUO. Consistently, chronic sEH inhibition or 11,12/14,15-EET treatment enhanced PPAR activity.

Results: These data demonstrate that EETs anti-inflammatory and fibroprotective effects are mediated via PPAR activation. Our data suggest the potential use of sEH inhibitors or EETs in treating fibrotic diseases.

PUB054

Soap Bar Placebo for the Treatment of Nocturnal Leg Cramps in a Chronic Kidney Disease Clinic
Martin Sedlacek. Dartmouth Hitchcock Medical Center, Lebanon, NH.

Background: Nocturnal leg cramps are a frequent complaint in the chronic kidney disease (CKD) population that we screen for in our specialized CKD clinic. Putting a soap bar under the bed cover is a popular remedy which most likely acts as a placebo. In the absence of a specific treatment for leg cramps we suggest that our patients try the soap bar placebo. As there is no generally accepted objective assessment of leg cramps we record the assessment that patients make of their symptoms.

Methods: The electronic medical records of the most recent 100 consecutive patients with chronic kidney disease seen in our CKD clinic by one physician were analyzed.

Results: Of 100 patients there were 47 women and 53 men with a mean age of 71 years and an age range of 31 years to 93 years. 15% were in stage 3 CKD, 56% in stage 4 CKD and 29% in stage 5 CKD. 44% had diabetes mellitus. 58 patients had leg cramps (58%) and 30 of these tried out the soap bar and 7 were interested but had not tried yet. Of the remaining 21 patients some were content to use other remedies (tonic water, ice, magnesium, vitamin E, oxycodone, and saltine crackers) and some had only mild symptoms or had other reasons not to try the soap bar. There was a statistical tendency for muscle cramps to be more frequent in women and patients with diabetes mellitus and electrolyte abnormalities. Of the 30 patients who tried the soap bar 18 (60%) reported improvement of the leg cramps. The response was variable, ranging from mild to dramatic.

Conclusions: The pathogenesis of nocturnal leg cramps is unknown and likely involves muscle, peripheral and central nervous system. We found that besides correction of electrolyte abnormalities and changing possible offending medications, soap bar placebo was an effective treatment for leg cramps in most patients who tried it. Interestingly, there was improvement of symptoms even though the placebo was suggested to patients openly as a placebo.

PUB055

Myoclonus in Renal Failure: Two Cases of Gabapentin Toxicity
Lili Chan, Milisha Shah, M. Bridge, Kenneth Kaufman, Amay Parikh.1 UMDNJ-Robert Wood Johnson Medical School; 2Robert Wood Johnson Univ Hospital.

Background: Antiepileptic drugs (AEDs) are used in the treatment of epilepsy, pain, and other neurological diseases may impact the child's toxicity and addiction associated with AEDs. Gabapentin is an AED that is cleared solely by renal excretion and dosing requires consideration of the patient's renal function. We report 2 cases of myoclonic activity associated with gabapentin toxicity in the setting of renal disease and address treatment of the diaheral.

Methods: Case 1: 78-year-old woman with congestive heart failure, history of thromboembolism, hypertension, diabetes mellitus, asthma and diabetic peripheral neuropathy presented with tremors involving her upper extremities for 3 days prior to admission. Evaluation revealed acute kidney injury (AKI) secondary to increased furosemide and lisinopril with hyperkalemia and azotemia. The patient was noted to have severe myoclonus. Prior to admission, the patient was being treated with gabapentin 900 mg total daily dose. The patient did not have any history of renal disease, but presented with increased glomerular filtration rate of 13 mL/min/1.73 m². With discontinuation of gabapentin and initiation of hemodialysis, marked improvement in her myoclonus occurred. Case 2: 55-year-old man with end-stage renal disease on peritoneal dialysis (PD), diabetes mellitus, hypertension, neuropathic pain, and peripheral vascular disease with toe gangrene.

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

Underline represents presenting author.

PUB056

Lithium Reduced Chronic Tubulointerstitial Nephropathy; Rate of Progression and Prognostic Markers towards ESRD in the North-Eastern Part of The Netherlands: The Case for Early Referral
Amika M.A. Berends,1 Frank G.H. van der Kleij,2 Riko Nap,3 Casper F.M. Franssen,2 Judith I. Dusselaar.1-2 1Dept of Internal Medicine, Div of Nephrology, Scheper Hospital Enmen; 2Univ Medical Center Groningen, Netherlands.

Background: Lithium, the treatment of choice for bipolar disorder, is known for its renal toxicity. Current guidelines advise a nephrologic consult when kidney function becomes moderately impaired (CKD stage 3A, GFR 45–59 mL/min/1.73m²) . The purpose of this study was to examine the course of renal function, and the effects of nephrologic interventions on renal function of patients on lithium.

Methods: In this, partially, retrospective study, we included all patients using lithium that were referred to our hospital for renal function decline from 1995 up until now. Subjects are prospectively followed. CKD was defined as eGFR <60 mL/min/1.73m².

Results: Data on thirteen patients (50.8% male) was available up until now. All referrals were between 35 and 51 years (range 44-71), mean duration of treatment 18±10 years, and mean follow up time 35 months (range 8-132). eGFR was inversely related to duration of lithium use at referral (r = -0.57 95%C.I. [-0.85,-0.25]), and to last follow up (r = -0.73 95%CI [-0.95,-0.54]). CKD-stage, after correction for age, gender and hypertension, was strongly associated with cumulative lithium exposure (p=0.0037). In 8 patients, lithium therapy was ceased (mean eGFR at cessation: 26±15); renal function improved in none, and four progressed to ESRD.

Conclusions: Lithium induced nephroathy proves to be irreversible, despite cessation of lithium even at CKD stage 3A. Our data might entail an underestimation of known incidence rates of lithium induced chronic tubulointerstitial nephritis and its progression towards ESRD. Future studies are therefore indicated to evaluate the effects on renal function when the CKD-stage threshold for nephrologic evaluation is lowered. And, because preserving mental wellbeing is a factor to keep in mind when caring for these patients, those studies should include continuation of lithium as well, since no acceptable alternative to lithium is available as yet.

Funding: Government Support - Non-U.S.

PUB057

Estimating Glomerular Filtration Rate in Chinese Patients with Type 2 Diabetes: A Of Creatinine-Based Equations
Jin-Xia Chen, Chenggang Shi,1 Jianhua Huang,2 Xilian Qiu,2 Cailian Cheng,1 Xun Liu.1 Diabetes: A of Creatinine-Base Equations

Methods: The electronic medical records of the most recent 100 consecutive patients with type 2 diabetes mellitus and renal disease were included. Glomerular filtration rate (GFR) was estimated by Cockcroft-Gault equation (CG), Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), Chinese equation, previously Japanes equation (Japan-1), new Japanese equairion(Japan-2), Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), Chinese equation, previously Japanes equation (Japan-2), new Japanese equation(Japan-2) by using the eGFR (mg/dl) by the following formulas:

1. CG equation(CKD-EPI): eGFR=186 x (serum creatinine in mg/dl) ^ -1.154 x (age in years) ^ 0.200 x (0.742 if female) (0.736 if >70 years old).
2. Chinese equation: eGFR=186 x (serum creatinine in mg/dl) ^ -1.154 x (age in years) ^ 0.200 x (0.742 if female) (0.736 if >70 years old).
3. Japanes equation (Japan-1): eGFR=194 x (serum creatinine in mg/dl) ^ -1.094 x (age in years) ^ 0.283 x (0.739 if female) (0.739 if >70 years old).
4. Japanes equation (Japan-2): eGFR=194 x (serum creatinine in mg/dl) ^ -1.094 x (age in years) ^ 0.283 x (0.739 if female) (0.739 if >70 years old).

Results: None of the equations had accuracy up to the 70% level with a deviation less than 30% from sGFR. The agreement limits of all the equations exceeded the prior acceptance tolerance de

Funding: Government Support - Non-U.S.

888A
CKD. 2) low levels are associated with elevated levels of iPTH and may explain the kidney function (NL) and CKD subjects, and explored its relationship to kidney function. We examined 25(OH)D3 levels in a large sample of people with normal serum calcium (Ca), phosphorus (P), or intact parathyroid hormone (iPTH) for level of between the level of 25(OH)D3 and number of servings of dairy products (r=0.14), serum and iPTH levels in CKD were different from NL (Table). A positive correlation was present Gaber, Wadi N. Suki.

Correlation of 25(OH)D3 Levels with Diet, Serum Calcium, Phosphorus, and Parathyroid Hormone in Normals and in People with Chronic Kidney Disease Stages I–IV from NHANES 2003–2006

Background: Little is known about the prevalence of low vitamin D [25(OH)D3] levels in stages of chronic kidney disease (CKD) or the correlation of 25(OH)D3 with diet, serum calcium (Ca), phosphorus (P), or intact parathyroid hormone (iPTH) for level of kidney function. We examined 25(OH)D3 levels in a large sample of people with normal kidney function (NL) and CKD subjects, and explored its relationship to kidney function, diet, serum Ca, P, and iPTH.

Methods: Subjects were from NHANES 2003-2006. Renal function was estimated using the CKD-Epi equation. Intake of dairy products was collected. The mean age was 36.2±13.4 years; 86.7% were female. The mean observation period was 9.8±7.6 years. Urinary protein was 4.0±4.1 g/gCr and eGFR was 79±33 ml/min/1.73m² at biopsy. ISN/RPS class was as follows; II 12.7%, III 14.6%, IV 41.8%, V 14.6%, III/IV 15.4%. During observation periods, 18 patients died; infection (n=5), uncontrolled lupus (n=3; CNS lupus, pulmonary hemorrhage and renal failure), malignancies (n=2), cardiovascular death (n=2), gastrointestinal death (n=3), others (n=1; cardiac, stroke, breast and colorectal cancer). Mean age at biopsy was 36.2±13.4 years and 86.7% were female. The mean observation period was 9.8±7.6 years. Urinary protein was 4.0±4.1 g/gCr and eGFR was 79±33 ml/min/1.73m² at biopsy. ISN/RPS class was as follows; II 12.7%, III 14.6%, IV 41.8%, V 14.6%, III/IV 15.4%. During observation periods, 18 patients died; infection (n=5), uncontrolled lupus (n=3; CNS lupus, pulmonary hemorrhage and renal failure), malignancies (n=2), cardiovascular death (n=2), gastrointestinal death (n=3), others (n=1; cardiac, stroke, breast and colorectal cancer).

Conclusions: Only 45% of NL (26.9% US adults) had a 25(OH)D3 level ≥30 ng/ml. 25(OH)D3 and iPTH levels in CKD were different from NL (Table). A positive correlation was present between the level of 25(OH)D3 and number of servings of dairy products (r=0.14), serum Ca (r=0.12) and P (r=0.03). Correlation with iPTH was negative (r=0.25); all p<0.001.

25(OH)D3, ng/mL, mean±SE

<table>
<thead>
<tr>
<th>Variable</th>
<th>NL</th>
<th>K/D1</th>
<th>K/D2</th>
<th>K/D3a</th>
<th>K/D3b</th>
<th>K/D3b</th>
<th>K/D3</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D3, ng/mL, mean±SE</td>
<td>23.5±6.0</td>
<td>23.1±6.9</td>
<td>20.2±6.5</td>
<td>21.5±6.4</td>
<td>24.2±6.0</td>
<td>20.7±5.0</td>
<td>24.2±6.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median, range</td>
<td>23.2–28.6</td>
<td>20.4–46.8</td>
<td>19.7–75.3</td>
<td>23.3–72</td>
<td>24.3–65</td>
<td>20.5–51</td>
<td>24.2–60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iPTH, ng/mL, mean±SE</td>
<td>13.6±6.4</td>
<td>14.5±1.6</td>
<td>17.6±1.6</td>
<td>17.6±0.9</td>
<td>20.4±2.1</td>
<td>16.9±1.7</td>
<td>20.5±1.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median, range</td>
<td>18.6–31.5</td>
<td>16.0–12.156</td>
<td>22.1–12.316</td>
<td>21.0–6.306</td>
<td>20.2–6.29</td>
<td>16.1–10.491</td>
<td>20.5–10.93</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions: We conclude that 1) low 25(OH)D3 levels are prevalent in NL and CKD, 2) low levels are associated with elevated levels of iPTH and may explain the hypophosphatemia observed in NL, and 3) dietary intake of dairy products contributes significantly to serum 25(OH)D3.

Prevalence of Cardiovascular Risk Factors and Kidney Function Progression among a Developing World Chronic Kidney Disease Sample

Background: CKD patients had high cardiovascular (CV) mortality and morbidity. Identifying the specific population CV risk factors is detrimental in implementing a successful preventive medical plan. The eGFR drop 3-5 ml/min annually in CKD patients.

Reduction of kidney function increases the CV burden. The aims of this study were to identify the CV risk factors profile among CKD outpatient population, and to determine the progression of kidney function and its related factors.

Methods: This is a retrospective analysis of adult CKD patient followed in our nephrology department, from Oct 2003, for 8.5 years. Patients with lupus, transplant recipients, and pregnant patients were excluded. Demographic variables and CV risk factors were collected from electronic charts. Calculated eGFR by CKD EPI was used as an estimate for kidney function on the first and last OPD visit. SPSS 18 was used for analysis.

Results: Total patients were 245. Mean follow up was 23.6 months (SE 1.6), mean age 58.7 years (SE 0.9), mean BMI 30.5 kg/m² (SE 0.5). Male 61% of the total population. Mean eGFR was 45.4 ml/min (SE 1.4), and 51% of the populations were having CKD stage III. The average number of CV risk factors was 4 and 95% of the population was having two or more CV risk factors. Hypertension was the most common CV risk factor present among 91% of the population. DM was present among 60%. Hypertension was more prevalent with advanced CKD stage. Uric acid levels increases significantly with the stage of CKD. The eGFR over 2 years of management was stable for the total population. Improvement in eGFR was noticed in 2ml/min among CKD stage III and IV and eGFR decreased 4ml/min in non-Hypertensive patients. Certain factors were related to final eGFR.

Conclusions: High Cardiovascular risk was found in CKD patients. HTN was the most common CV risk factors present in our CKD population. For the total population eGFR did not decline over two years of treatment; moreover it improved in non-HTN patients and patients with CKD stages III and IV.

Long-Term Mortality and Its Risk Factors in Patients with Lupus Nephritis: A Cohort of 158 Patients at a Single Center in Japan

Background: Lupus nephritis (LN) is a major cause of morbidity and mortality in SLE patients. Although the mortality of LN patients has been reported from various countries, little is known about mortality and its risk factors in Japan.

Methods: One hundred fifty-eight LN patients who received renal biopsy at our hospital from 1975 to 2012 were retrospectively analyzed.

Results: The mean age was 36.2±13.4 years; 86.7% were female. The mean observation period was 9.8±7.6 years. Urinary protein was 4.0±4.1 g/gCr and eGFR was 79±33 ml/min/1.73m² at biopsy. ISN/RPS class was as follows; II 12.7%, III 14.6%, IV 41.8%, V 14.6%, III/IV 15.4%. During observation periods, 18 patients died; infection (n=5), uncontrolled lupus (n=3; CNS lupus, pulmonary hemorrhage and renal failure), malignancies (n=2), cardiovascular death (n=2), gastrointestinal death (n=3), others (n=1; cardiac, stroke, breast and colorectal cancer).

Conclusions: Long-term survival rate of our facility is comparable to those of previous reports. From our cohort, older age, complication with CNS lupus and progression of kidney dysfunction were independent risk factors for death as follows; older age [per 1-year increase; Hazard Ratio (HR) 1.09], complication with CNS lupus [HR 14.1] and progression of kidney dysfunction [HR 5.49].

Epidemiology of Nephropathies in Irregular Immigrants in Northern Italy

Background: There are about 544,000 irregular immigrants in Italy (out of 60 millions inhabitants). Nephropathies epidemiology in the birth areas of these people is unknown.

Aim of this study was to evaluate the prevalence of renal disease among irregular immigrants in Turin.

Methods: The survey was conducted in the health reception center for immigrants from January to December 2012. It was based on: 1) anamnestic evaluation through a questionnaire in 7 languages; 2) serum creatinine (Scr); 3) glomerular filtration rate (GFR-EPI); 4) urine examination; 5) blood pressure.

Results: Data for 494 people (men = 270, women = 224) were examined. 50 subjects reported hematuria, 90 dysuria, 21 infectious diseases, 67 previous malaria. 23 patients were diabetic (4.6%); in 1 case diabetes was a new diagnosis. Familiarity for kidney disease was found in 4 patients (2 stones, 2 polyuric
Euthyroid hyperthyroidism, hypertension in 29 (5.8%). 63 patients (12.7%) had microhematuria, 67 (13.5%) proteinuria, 15 (3%) both hematuria and proteinuria. Mean SCr was 0.79±0.25 mg/dl, eGFR (S i) was 109±37.3 ml/min/1.73m². 13 patients had SCr >1.3 mg/dl (of these also had urinary abnormalities and/or hypertension). We also found: 1 renal glycosuria, 1 schistosomiasis (Schistosoma mansoni), 4 renal stones. 99 patients (20%) were recalled: 69 came. Eventually, 10 patients (2%) were sent to the GP to monitor blood pressure or diabetes. 41 (8.2%) were integrated in a nephrologist follow-up: of these only 8 turned up to the second visit.

Conclusions: This survey on irregular immigrants in Northern Italy identified 10 patients (2%) to be monitored by the GP because of hypertension or diabetes and 41 (8.2%) to follow the renal protocol for possible ongoing nephropathies or for polyclavistic disease or stones. Moreover, 1 schistosomiasis, 1 new diabetes and 1 renal glycosuria were detected. The studied people are young: Italian people in the same age range have a lower frequency of nephropathy. Poor patients compliance prevented a correct survey and diagnosis. This represents a main issue for the outcome and for the consequent wasted resources.

PUB064
Chronic Kidney Disease and Risk of Cardiovascular Events and Death among Asian Adults
Cynthia Chi Wai Lim, Boon Wye Teo, Wan Ting Tay, Carol Y. Cheung, Su-chi Lim, Khuan Yew Chow, Jeannette Lee, E. Shyong Tai, Tien Yin Wong, Charunruen Sabanayagam. 1Dept of Renal Medicine, Singapore General Hospital; 2Dept of Medicine, National Univ of Singapore; 3Singapore Eye Research Institute, Singapore; 4Diabetes Center, Khoo Teck Puat Hospital; 5National Registry of Diseases Office, Singapore; 6School of Public Health, Yong Loo Lin School of Medicine, National Univ of Singapore; 7Dept of Ophthalmology, National Univ of Singapore.

Background: To examine the association between chronic kidney disease (CKD) and adverse outcomes in a multi-ethnic Asian population using data from two independent studies in Singapore.

Methods: A prospective cohort study of 7098 individuals who participated in two population-based studies conducted from 2004-2007: the Singapore Malay Eye Study (n=3148 Malay adults aged 40-80 years) and the Singapore Prospective Study Programme (n=3950 Chinese, Malay and Indian adults aged ≥40 years) was conducted. CKD was assessed from estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (ACR). eGFR was categorized into <60, 60-59.9, <45 ml/min/1.73 m² and ACR into <30, 30-299, ≥300 mg/g. Outcomes were (1) incident cardiovascular disease (CVD) and CVD mortality, and (2) all-cause mortality identified by linkage with national disease/death registries.

Results: Over a median follow-up of 4.3 years, 4.6% developed CVD outcome and 6.1% died. Lower eGFR and higher ACR were associated with both outcomes in a dose-dependent manner. Compared to eGFR ≥60, the adjusted HR (95% CI) of incident CVD/CVD mortality and all-cause mortality was 1.57 (1.08-2.77) and 1.99 (1.51-2.61) for eGFR <30, 30-299, ≥300 mg/g. Outcomes were (1) incident cardiovascular disease (CVD) and CVD mortality, and (2) all-cause mortality identified by linkage with national disease/death registries.

Conclusions: These findings indicated the presence of mild executive dysfunction, particularly for behavioral initiation, self-monitoring, and working memory. It will be important for nephrologists to be aware of the executive capabilities of their patients, especially with respect to how these capabilities affect adherence to medical care and ongoing medical management.

Funding: Other U.S. Government Support

PUB065
Cardiovascular Risk Factor Profile, Hypertension Control, and Progression of Kidney Function among Diabetic and Non-Diabetic in a Developing World Sample
Jafar Al-Said, Teerath Kumar, Soni Murdeshwar. 1Dept of Renal Medicine, 2Children's Hospital of Philadelphia, 3Univ of North Carolina School of Medicine, Chapel Hill, NC; 4Children's Hospital of Philadelphia, Philadelphia, PA.

Background: Cognitive deficits in individuals with mild to severe CKD are well documented; however, few studies have examined executive function in children and young adults with CKD. Such measurement approaches may provide a cost effective strategy for nephrologists working with this population and provide useful clinical information with respect to health care management for individuals with CKD.

Methods: Cross sectional observational study of 42 children and young adults with CKD (eGFR below 90 ml/min/1.73m²), ages 8 to 25 years. The primary instrument was the Behavior Rating Inventory for Executive Functioning (BRIEF) completed by either the parent, for subjects (ages 8 to 18), or the adolescent/young adult (ages 19 to 25). Scores across the two versions of the BRIEF were combined for comparison purposes. Initial data analyses included descriptive findings of the CKD sample, with elevated ratings of at least one standard deviation above the normative mean reflecting risk for impairment.

Results: Mean(SD) age and eGFR were 15(3) yrs and 42(23) ml/min/1.73m². The sample was 64% male and 67% Caucasian. 29% had transplant and 5% were on dialysis after a failed transplant. Results showed that none of the Behavior Regulation scales were significantly elevated when compared to normative expectations, with the Behavioral Regulation Index (BRI) falling within the average range (BRI T-Score = 54.39). The Metacognitive Index (MI) and Global Executive Composite (GEC) were also within average range (MI T-Score = 59.64, GEC T-Score = 59.64), although weaknesses were noted for Working Memory, Initiate, and Monitoring scales with associated effect sizes greater than 0.5 SD.

Conclusions: These findings indicated the presence of mild executive dysfunction, particularly for behavioral initiation, self-monitoring, and working memory. It will be important for nephrologists to be aware of the executive capabilities of their patients, especially with respect to how these capabilities affect adherence to medical care and ongoing medical management.

Funding: Other U.S. Government Support

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

890A
Incidence of Proteinuria Is a Simple Sign of Poor Outcome in Cancer Patients Receiving Gemcitabine

Masaki Hara,1 Minoru Ando,1 Ken Tsuchiya,2 Kosaku Nitta.2
1Renal Div, Dept of Medicine, Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Tokyo, Japan; 2Dept IV of Internal Medicine, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan.

Background: Gemcitabine (Gem) is a widely used as an anti-cancer drug. Gem administration induces glomerular thrombotic microangiopathy, resulting in the emergence of proteinuria and/or kidney dysfunction. This study attempted to ascertain both incidence of proteinuria and an association between incident proteinuria and mortality in Gem recipients.

Methods: A prospective cohort study was conducted in 60 non-proteinuric patients with pancreatic or biliary cancer (mean age, 67 years), who received the first single therapy of Gem and who lived over 6 months following the administration. Incident proteinuria was defined as dipstick test ≥1+ persistent in at least two consecutive examinations within 6 months. Cumulative mortality was analyzed by the Kaplan-Meier method, stratified by presence and absence of incident proteinuria. Multivariable proportional hazards regression analysis was used to calculate hazard ratio (HR) with its 95% confidence interval (CI) for all-cause mortality, adjusted for age, gender, disease severity, and estimated glomerular filtration rate (eGFR).

Results: Incidence of proteinuria was 23.3% in the first 6 months, and mortality rate was 45.0% in the follow-up period (median, 251; range, 20 – 550 days). Cumulative mortality was significantly greater in patients who developed proteinuria (64.2%) than those who did not (38.2%) at the time of 450 days following the Gem administration. The HR (95% CI) of proteinuria incidence was 3.36 (1.44 – 7.49; P = 0.0060), as compared with the absence of incident proteinuria.

Conclusions: Incidence of proteinuria may be a harbinger of near-term death in Gem recipients.

Sex and Racial Differences in End-Stage Renal Disease Risk in Diabetes

Margaret K. Yu,1 Xiaoao Ding,1 Bessie A. Young.1,2 1Univ of Washington; 2VA Puget Sound Health Care System.

Background: Chronic kidney disease (CKD) is more common in women than in men, however few studies have examined the relationship between sex and risk of end-stage renal disease (ESRD). Furthermore, although racial/ethnic minority women have a high burden of CKD risk factors, there is little information regarding ESRD risk by sex and race. The objective of this study is to assess sex and racial differences in 10-year incident ESRD risk in a primary care diabetic population.

Methods: The Pathways Study is a prospective, observational cohort of ambulatory, diabetic patients from a large managed care population in Seattle, WA. Self-reported race/ethnicity was used to categorize subjects as non-Hispanic white, non-Hispanic black, Asian, or other. Subjects were followed for 10 years for incident ESRD. Cox proportional hazards regression was used to estimate the risk of incident ESRD by sex and race/ethnicity, after adjustment for age, marital status, education, smoking, diabetes duration, hemoglobin A1C, baseline estimated glomerular filtration rate (eGFR), microalbuminuria, body mass index (BMI), and depression, taking into account mortality as a competing risk.

Results: Of the 3,877 total subjects, 1864 (48.1%) were women. Racial composition did not vary by sex (79.4% non-Hispanic white, 8.4% non-Hispanic black, 8.0% Asian, and 4.2% other races). Women were less likely to be married or have a high school education and had higher BMI and baseline eGFR compared to men. 78 subjects developed ESRD over 10 years. Amongst men, non-Hispanic blacks had the highest incidence of ESRD (6.55 per 1000 person-years vs 3.45 in Asians, 3.37 in other races, and 2.62 in non-Hispanic whites).

Conclusions: Prevalence of Heart Failure in a Cohort of Patients with Chronic Kidney Disease: Results from the German Chronic Kidney Disease Study

Anna Kottgen,1 Hanna Beck,2 Stephanie Titze,3 Silvia Huebner,4 Martin Busch,5 Florian Kronenberg,6 Vera Krane,7 Kai-Uwe Eckardt.2 1Univ of Freiburg, Germany; 2Univ of Erlangen-Nürnberg, Germany; 3Univ of Jena, Germany; 4Univ of Innsbruck, Austria; 5Univ of Würzburg, Germany.

Background: Reduced kidney function is a risk factor for the development and progression of heart failure, but there is limited data on the prevalence of heart failure from large cohorts of patients with chronic kidney disease (CKD) of moderate severity. In this initial analysis, we examined the prevalence and correlates of self-reported heart failure in the German Chronic Kidney Disease (GCKD) Study.

Methods: The GCKD Study is a prospective observational cohort. Between 2009 and 2012, 5217 CKD patients aged 18 to 74 years with an eGFR of 30 to <60 ml/min/1.73m2 or eGFR ≥60 and overt proteinuria during screening were enrolled. As part of a detailed standardized interview including cardiovascular disease history, patients were asked if they were suffering from heart failure. Patients not meeting inclusion criteria or with missing information were excluded from analysis. GFR was estimated from serum creatinine by the 4-variable MDRD Study equation. Factors associated with heart failure were identified using logistic regression.

Results: The overall prevalence of self-reported heart failure was 18% (18% among men and 17% among women). Heart failure prevalence was considerably higher in patients with coronary heart disease (43% vs. 11% without) and those with diabetes (26% vs. 13% without). Overall, heart failure prevalence increased with lower eGFR from 5% among patients with eGFR of <30 ml/min/1.73m2, 13% for eGFR 30-60, 17% for eGFR 60-89, 20% for eGFR 30-44, to 21% for eGFR <30 ml/min/1.73m2. The strongest associations of prevalent heart failure were observed with older age, presence of coronary heart disease, valvular heart disease, higher BMI, hypertension and diabetes.

Conclusions: Heart failure is common among patients with CKD, and constitutes a large burden of disease. Alternative definitions of heart failure using information from signs and symptoms of heart failure as well as from biomarkers will be evaluated.
PUB072
Improved In-Hospital Morbidity and Mortality for Patients Treated by Hemodialysis Undergoing Orthopedic Procedures. David Bennett, Ting-jung Pan, Steven K. Magid, Stephen Lyman, Mayu Sasaki, Jeffrey L. Silberzweig. New York-Presbyterian Hospital-Weill Cornell Medical College; The Rogosin Institute; Hospital for Special Surgery.

Background: In the in-hospital post-operative medical course for patients with Chronic Kidney Disease (CKD) treated by hemodialysis (HD) undergoing orthopedic procedures, there has been no formal study to report. Our mortality results do not significantly differ from the in-hospital mortality (up to 28.5%), but do not clearly identify the deceased patient population or focus on the in-hospital period.

Methods: We identified patients at a single institution between 2005-2008 and reviewed their charts for age, sex, comorbidities, complications, mortality, length of stay (LOS), cause of death, and discharge disposition. We compared our patients to the New York State (NYS) administrative database for mortality and LOS. Our study was performed using two sample-t-test for continuous variables and Fisher’s exact tests for categorical data.

Results: 35 patients underwent 58 orthopedic procedures, most on the hip (46.6%) or knee (19.0%). Patients were previously treated with HD for an average of 6.8 +/- 9.6 years. The most common causes of CKD were diabetic nephropathy (20.7%), hypertensive nephropathy (15.5%), and collagen vascular disease (13.8%). They were 17 post-operative complications in 14 patients (24.1%) and 1 in-hospital death occurred (1.7%). The average LOS was 9.1 +/- 5.0 days. Most patients were discharged to rehab (44.8%), but many went home (31.0%). The mean LOS was 2.2 days less than the NYS hospital average (95% CI: 0.8, 3.6, p-value=0.003) but the difference in mortality was not statistically significant (p-value>0.05).

Conclusions: The in-hospital post-operative medical course for patients with CKD treated by HD undergoing orthopedic procedures has not been well reported. By studying patients at a single institution, we have better defined the patient population and their post-operative course. Our results do not corroborate the high morbidity/mortality rate previously reported. Our mortality results do not significantly differ from other NYS hospitals.

PUB073
Albuminuria Is Associated with Diabetic Retinopathy in Ethnic Minorities. Amit J. Joshi, Albert M. Osei, Imran Tahir, Bhavi Paresh Pandya, Penny D. Hart. Section of Nephrology, Stroger Hospital of Cook County, Chicago, IL; Dept of Medicine, Stroger Hospital of Cook County, Chicago, IL; Staten Island University Hospital, Staten Island, NY.

Background: Diabetic nephropathy remains the most frequent cause of end-stage kidney disease (ESKD) in the United States. The association between the presence of diabetic retinopathy and diabetic nephropathy is well described; however, there are no data on whether presence of diabetic retinopathy is associated with progressive renal disease (defined as degree of albuminuria ± change in serum creatinine). We examined and herein describe the clinical characteristics of such patients at a large inner city hospital.

Methods: We retrospectively examined medical records of adult patients (≥18 years) with diabetes seen in the Ophthalmology clinic of our institution from Jan. and Feb. 2012. Data on baseline demographics, duration of diabetes, type of retinopathy, renal function, degree of albuminuria, use of renin-angiotensin-aldosterone system (RAAS) blockers, and other clinical parameters was collected.

Results: 245 patients had adequate data for clinical analysis. Mean age was 59.9 ± 15.1 years and women accounted for 47% of the study cohort. Hispanics constituted 41%, African Americans 38%, Caucasians 9%, and other races 12%. 144(59%) patients had proliferative retinopathy, 73(30%) had nonproliferative retinopathy, 16(7%) patients had both proliferative and nonproliferative retinopathy, and 12(4%) patients had no retinopathy. Longer duration of diabetes was associated with increased severity of retinopathy (P = 0.0018). No difference was noted with respect to retinopathy severity and cerebrovascular disease, coronary artery disease or statin use. Degree of albuminuria influenced the severity of diabetic retinopathy; proteinuria (≥ 300 mg/d) had a significant impact on initial creatinine or interval change in creatinine (P-value was insignificant). No other diagnostic difference was noted in terms of glycated hemoglobin level, age, initial creatinine, duration of diabetes, or use of RAAS blockers.

Conclusions: Albuminuria and longer duration of diabetes are associated with increased severity of retinopathy in ethnic minority patients.

PUB074
Risk Factors Associated with End-Stage Renal Disease and Fatality in Patients with Chronic Kidney Disease. Ya-Wen Chuang, Cheng-Hsiu Chen, Fung-chang Sung. Div of Nephrology, Dept of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; Dept of Public Health, China Medical Univ, Taichung, Taiwan; Taichung Tzu Chi General Hospital, Taichung.

Background: With the highest prevalence of end-stage renal disease (ESRD) worldwide, there is no study for patients in Taiwan on the prognosis of chronic kidney disease (CKD) by stage. This study evaluated the risk of ESRD and fatality for patients with stage 3, 4, and 5 of CKD.

Methods: We identified 4702 patients with CKD of stages 3-5 from nephrology clinics at the Taichung Veteran General Hospital from December 2001 to December 2011. Patient prognostic data were extracted from the baseline to July 31, 2012, ESRD diagnosed, death or loss to follow-up. We used Cox models to identify risk factors associated with ESRD and deaths by CKD stage and age, and Kaplan-Meier method to measure the cumulative events of ESRD and death.

Results: Patients with CKD consisted of 64% of males, with 60% of patients aged ≥65 years and 39% having diabetes. The incidence of ESRD in CKD patients of stages 3, 4, 5 were 1.95%, 10.60%, 46.7%, with the fatalities of 4.56%, 6.23%, 4.69%, respectively. The elderly were at a lower risk for ESRD, but at an elevated risk for death. Diabetic patients were at higher risk than non-diabetic patients for ESRD and death.

Conclusions: The risk of ESRD for patients with CKD increases rapidly with the advance of stage; but the differences in fatality are not so acute among the 3 stages of patients. The elderly CKD patients are less prone to ESRD, but at an elevated risk of death.

PUB075
The Asymptomatic Ankle-Brachial Index Abnormality Can Predict Poor Prognosis of Arteriosclerosis-Based Chronic Kidney Disease Patients. Yui Kamijoe, Koji Hashimoto, Makoto Harada, Taro Kanno, Makoto Higuchi. Dept of Nephrology, Shinshu Univ School of Medicine, Matsumoto, Japan.

Background: World Health Statistics 2013 indicated that average life of Japanese is the longest. Furthermore, Ministry of Health, Labour and Welfare reported that average life of Nagano prefecture’s people is the longest in Japan; therefore characteristics of chronic kidney disease (CKD) in Nagano might differ, greatly be affected by arteriosclerotic lesions by ageing.

Methods: To reveal the arteriosclerotic effects, we investigated the ankle-brachial index (ABI) of CKD patients in Nagano (n=144, mean age 70) and followed up prospectively (2.3 years). We analyzed hazard ratio (HR) of ABI abnormality (ABI<1.0 or ABI≥1.3) influencing incidence of cardiovascular diseases (CVD) and worsening of kidney function, mortality, CVD-free survival, and all-event-free survival, using multivariate Cox regression analyses. We also analyzed ABI-abnormality-related factors using multivariate logistic regression analyses.

Results: The mean eGFR and proteinuria were 41 ml/min/1.73m² and 0.5 g/gCr, respectively. Twenty six percent patients had well controlled diabetes mellitus (DM, mean HbA1c 6.1%), indicating a little contribution of DM nephropathy. We detected ABI abnormality in high rate (24%), and most patients were asymptomatic. Multivariate analyses demonstrated that ABI abnormality was the strongest risk factor of incidence of CVD (adjusted HR 5.3, 95%CI 1.8-16.2), CVD-free survival (adj-HR 4.4, 95%CI 1.7-11.5), and all-event-free survival (adj-HR 3.1, 95%CI 1.3-7.0). The strongest risk factor of worsening of kidney function and that of mortality were ABI reduction and age, respectively. ABI abnormality was greatly related to the GFR reduction (Odds ratio 1.84, 95%CI 1.2-2.8), while it was not related to presence of DM.

Conclusions: This study suggests that asymptomatic ABI abnormality is highly detected in arteriosclerosis-based CKD patients, and strongly relates to lethal events and survival rate. GFR reduction is a very important independent risk factor of ABI abnormality; therefore we should conduct ABI measurement for all CKD patients regardless of presence of DM.

PUB076

Background: Renin-angiotensin-aldosterone system (RAAS) inhibition has been used to slow chronic kidney disease (CKD) progression in diabetic (DN) and non-diabetic proteinuric nephropathies. However, in advanced CKD, their withdrawal can delay the onset of renal replacement therapy (RRT).

The aim was to evaluate the effect of discontinuation of RAAS inhibitors in patients with CKD stage 4-5 and to assess K levels.

Methods: Observational prospective study made in patients who were being treated with angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) and whose estimated glomerular filtration rate (GFRe) was lower than 25 ml/min. We recorded creatinine and K in serum, GFR (MDRD-4IDMS) and mean arterial blood pressure (MAP) every 3 months for 1 year before and after stopping treatment. When it was necessary an alpha-adrenergic blocker or a calcium channel blocker was introduced.

Results: 27 patients were included (7 females, 20 males), mean age 73.7 ± 9.4 years. The aetiology of CKD was: vascular nephropathy (n = 10, 37%), DN (n = 9, 33.3%) chronic glomerulonephritis (n = 2, 7.4%), chronic tubulointerstitial nephritis (n = 2, 7.4%), androgenic polycystic kidney disease (n = 2, 7.4%), and unknown aetiology (n = 2, 7.4%).

Three patients started RRT 1, 2 and 11 months after stopping RAAS inhibitors, and one was lost to follow-up.

MAP, GFRe and K level when ACEi/ARB were stopped was 50.6 ± 5.9 mmol/l and 12.9 ± 4.8 ml/min and 92.3 ± 8.7 mmHg respectively. MAP, GFRe and K levels 12 months before and after discontinuation of ACEi/ARB are shown in Figure 1.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
892A

Background: Obesity is a risk factor for the development of renal failure (RF). Proteinuria (P) is an independent determinant of the progression of chronic kidney failure. Adipose tissue is a recognized source of components of the renin-angiotensin-aldosterone system (RAAS). The use of drugs which block the RAAS is unable to inhibit aldosterone long term. The aim of our study was to analyze the renoprotective effect of mineralocorticoid receptor blockers (MRB) in combination with other drugs that block the RAAS in obese patients with proteinuric nephropathy.

Methods: In January 2004, we began a prospective observational study in our hospital-based consultation. The management of spironolactone (S) patients with P> 1 g/24 hours were divided according to body mass index (BMI) the group of obese (Ob) (BMI> 30 kg/m²) and a control group (C). Being treated with other drugs blocking RAAS were divided according to body mass index based consultation. The management of spironolactone (S) patients with P> 1 g/24 hours within the Ob group, and 39 in group C. Initially there were no significant differences in mean BP, proteinuria and blood pressure.

Results: Seventy-one patients were included. The mean age was 56.7 ± 15.1 years. The percentage of diabetics in both groups was greater than 50%. Thirty-two patients found patients with proteinuric nephropathy.

Conclusions: MRB treatment in obese patients with different proteinuric kidney diseases induces a significant slowing in the progression of renal failure associated with a remarkable and sustained reduction in proteinuria with a few adverse events.

PUB078
Preliminary Examination of Chronic Kidney Disease Shared Medical Appointment Outcomes. Molsen M. Elramah,1 Henry N. Young,2 Micah R. Chan.1 1UW Hospital and Clinics Dept of Nephrology; 2Univ of Wisconsin School of Medicine and Public Health.

Background: Chronic kidney disease(CKD) care can be challenging for multiple reasons. Our nephrologists implemented shared medical appointments (SMA) for CKD care in an effort to overcome such challenges. We examined if CKD SMAs resulted in similar outcomes in comparison to individual visits.

Methods: After IRB approval, we conducted a retrospective analysis of data from our database. Patients who received care in CKD shared medical appointments and individual visits from January 2011 to March 2013 were included. We compared the two groups on outcomes of;diagnosis, mortality, transplantation, the change over time in CKD stage, glomerular filtration rate, intact parathyroid hormone, creatinine, phosphorus, proteinuria, and blood pressure.

Results: We analyzed 75 records; 23 SMA and 52 individual visits. SMA patients had a greater mean difference in PTH (M=40.1, SD=98.3) compared to individual visits patients (M=4.9, SD=10.0) from 2011 to 2013 (t=-21, p=0.04).

Conclusions: Discontinuation of ACEI/ARB in patients with CKD stage 4-5 stabilized GFRs and improved K levels. There were no differences in MAP after stopping RAAS inhibitors.

PUB079
Chronic Kidney Disease (CKD) Is Distinct from End Stage Kidney Disease (ESKD). Helen G. Healy,1 Andrew John Mallett,1,2 Zaimin Wang,1,3 Anne Salisbury,1,2 Robert G. Fassett,1 Wendy E. Hoy.1 1CKD-GOL; 2Dept of Renal Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Queensland, Australia; 3Centre for Chronic Disease, School of Medicine, Univ of Queensland, Brisbane, Queensland, Australia.

Background: CKD is the most common chronic disease in Australia. Inferences about its natural history have largely relied upon hypotheses from mortality and Renal Replacement Therapy (RRT) datasets.

Methods: Aim: To describe how characteristics of Australian CKD patients differ from those of Australian RRT populations. Primary diagnosis, age and sex of the first 2139 patients from 5 sites in the CKD.QLD Registry (CKD.QLD) were analysed and compared with the 2005-2010 (n=15,514) and 2011 (n=2,760) Australia and New Zealand Incident RRT cohorts. (ANZ RRT 2005-10, ANZ RRT 2011). Comparison was also made with the Australian dataset of people dying with ESKD not on RRT (n=10421, AHW ESKD/nonRRT).

Results: The most common primary renal diagnoses in the CKD.QLD cohort were Nephrosclerosis (Misc, 26%), Diabetic Nephropathy (DN, 23%), Hypertension (HTN, 18%) and Uncertain (15%). In ANZ RRT 2005-10 and 2011 the most common primary renal diagnoses were DN (36%), Glomerulonephritis (GN, 23%, 22%), Misc (13%, 11%) and HTN (10%, 13%). Mean age in CKD.QLD was 65.5 years and in ANZ RRT 2011 it was 60.3 years. The most common age group in both cohorts was 55-74 years (47%, 47%) however in AHWW ESKD/nonRRT cohort it was ≥75 years (87%). 45% of the CKD.QLD cohort, 39% of the ANZ RRT 2005-2010 and 53% of the AJHW/nonRRT ESKD cohorts were female.

Conclusions: There are differences in proportion and ranking of primary renal diagnoses between these CKD and RRT/ESKD cohorts. CKD patients are older and more frequently female then those undergoing RRT. Extrapolation from RRT cohorts for characterisation of CKD should be replaced with direct study of CKD cohorts. When paired with RRT and mortality cohort data this will provide information of greater accuracy and translational impact.

Funding: Government Support - Non-U.S.

PUB080
Left Atrial Volume Index as Useful Predictor for Decline of Kidney Function in CKD G3b and G4. Takeshi Yokoyama,1 Mikako Hisamichi,1 Masahiko Yazawa,1 Nagayuki Kaneshiro,1 Katsuomi Matsui,1 Yusuke Konno,1 Yugo Shibagaki,1 Kenjirou Kimura,2 1Nephrology and Hypertension, Kawasaki Municipal Tama Hospital, Kawasaki, Kanagawa, Japan; 2Nephrology and Hypertension, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan.

Background: Several studies have documented a strong relationship between CKD and accelerated cardiovascular disease. Although heart failure is known to associate with progression of CKD, little is known which parameters of ultrasound cardiography (UCG) are helpful to predict decline of kidney function (KF).

The aim of present study is to clarify the relationship between the rate of decline of KF and the parameters of UCG.

Methods: UCG was performed in 38 CKD G3b and G4 patients from April 2011 to December 2012, and the following parameters such as left atrial dimension (LAD), left atrial volume index (LAVI), end-diastolic wall thickness of the interventricular septum (IVSTd) and posterior wall (PWTd), and left ventricular mass index (LVMi) were measured. We calculated estimated GFR (eGFR) by the Japanese GFR equation, and defined the rate of decline of KF as [(the latest eGFR - initial eGFR) / follow-up period]. We examined the correlations between the rate of decline of KF and the parameters of UCG.

Results: Average eGFR at UCG was 29.23 ± 8.47 ml/min/1.73m² and average rate of decline of KF was -0.29 ± 0.74 ml/min/1.73m²/month. Rate of decline of KF was significantly correlated with LAD(r = -0.381), IVSTd + PWTd(r = -0.425), LVMi(r = -0.394) and LAVI(r = -0.455). Multiple regression analysis revealed that only LAVI was an independent predictor for decline of KF.

Conclusions: Among the parameters of UCG, LAVI was the most useful predictor for decline of KF in CKD G3b and G4.

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

893A

Adjusting for potential confounders, this difference was no longer statistically significant. There were no differences in the proportions of patients who were on dialysis, deceased, or received a transplant between the two groups in 2013. Results also failed to indicate any differences in the changes across time for any other assessed outcome between the two groups.

Conclusions: This study demonstrates that CKD shared medical appointment clinical outcomes may be similar to individual visit outcomes. Larger study designs are needed to confirm these initial findings.

PUB079

Methods: Aim: To describe how characteristics of Australian CKD patients differ from those of Australian RRT populations. Primary diagnosis, age and sex of the first 2139 patients from 5 sites in the CKD.QLD Registry (CKD.QLD) were analysed and compared with the 2005-2010 (n=15,514) and 2011 (n=2,760) Australia and New Zealand Incident RRT cohorts. (ANZ RRT 2005-10, ANZ RRT 2011). Comparison was also made with the Australian dataset of people dying with ESKD not on RRT (n=10421, AHW ESKD/nonRRT).

Results: The most common primary renal diagnoses in the CKD.QLD cohort were Nephrosclerosis (Misc, 26%), Diabetic Nephropathy (DN, 23%), Hypertension (HTN, 18%) and Uncertain (15%). In ANZ RRT 2005-10 and 2011 the most common primary renal diagnoses were DN (36%), Glomerulonephritis (GN, 23%, 22%), Misc (13%, 11%) and HTN (10%, 13%). Mean age in CKD.QLD was 65.5 years and in ANZ RRT 2011 it was 60.3 years. The most common age group in both cohorts was 55-74 years (47%, 47%) however in AHWW ESKD/nonRRT cohort it was ≥75 years (87%). 45% of the CKD.QLD cohort, 39% of the ANZ RRT 2005-2010 and 53% of the AJHW/nonRRT ESKD cohorts were female.

Conclusions: There are differences in proportion and ranking of primary renal diagnoses between these CKD and RRT/ESKD cohorts. CKD patients are older and more frequently female then those undergoing RRT. Extrapolation from RRT cohorts for characterisation of CKD should be replaced with direct study of CKD cohorts. When paired with RRT and mortality cohort data this will provide information of greater accuracy and translational impact.

Funding: Government Support - Non-U.S.
The “Opt-Out” Recruitment Strategy: The SNORE Study

Muna T. Canales,1,2 Nicole Kay,1 Arefe Ishani,1 I. David Weiner,1,2 Richard Berry,1,2 Rebecca Brycht,1,2 Malcom-Randall VAMC, Gainesville, FL; Univ of Florida, Gainesville, FL; Minneapolis VAMC, Minneapolis, MN.

Background: Recruitment in an unbiased fashion of adequate numbers of human subjects is key for scientifically sound and generalizable studies. We report initial results of an IRB-approved “opt-out” recruitment strategy that involves primary care provider (PCP) approval and easy “opt-out” options as part of the SNORE Study, an ongoing prospective study of sleep apnea and CKD progression.

Methods: With IRB approval, we identified veterans age 18-99 in the N. FL. GSVA Veterans Health System (NF/GSVHS) (2/12/2012-present) with at least 2 MDRD eGFR between 15-44, at least 3 months apart; target enrollment ~250 over 2 years. We excluded those with dialysis, kidney transplant, PAO or O2 therapy, active cancer, solid organ transplant or inability to give consent. Via e-mail, we requested permission from each PCP in the NF/GSVHS to contact their patient for enrollment; non-responders were contacted again by e-mail and then by phone. We invited eligible veterans in random order to participate via a letter with follow-up call within 1 week if no response. Letters stated that the PCP gave permission for us to contact them and provided a 1-800 number and an email to facilitate communication. Interested subjects presented for initial baseline visit during which they completed informed consent and baseline assessments.

Results: Of 141 PCPs across 13 clinical sites 103 gave approval, 6 refused, 11 wanted to be contacted for each patient, and 21 have not responded. To date 560 letters have been mailed. 130 veterans called in and, of these, 37 were interested in participation. We contacted the remaining 430 veterans and, of these, 222 were not interested, 105 were interested and 103 could not reach. 75 study visits have been scheduled (13% of letters mailed out). Of those who scheduled a study visit, 86% completed enrollment as planned, 8% rescheduled and 6% canceled before the visit. On average, 3-4 visits occur each week with anticipated completion of enrollment in ~2 years as planned.

Conclusions: An “opt-out” recruitment strategy with PCP approval and easy “opt-out” options met expectations of IRB and yielded adequate enrollment numbers for this study. Funding: Veterans Affairs Support

Wine Intake Is Associated with Fewer Cardiovascular Events in the National Heart and Nutrition Examination Survey (NHANES) Tapan Mehta,1 Pamela Mettler,2 Kim McFann,2 Diana J. Jalal.3 Div of Renal Diseases and Hypertension, Univ of Colorado, Aurora, CO; Colorado Biostatistics Consortium and Colorado School of Public Health, Univ of Colorado Denver, Aurora, CO.

Background: Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular disease. Wine intake is associated with a lower risk of cardiovascular disease in non-CKD populations. Although kidney and cardiovascular disease share many risk factors, such as insulin resistance and inflammation, no study to this date has examined the potential relation between wine intake and CVD in individuals with CKD.

Methods: This was a cross sectional analysis of 5876 participants in NHANES 2003-2006. Wine intake was categorized as: none, <1 glass/day, ≥1 glass/day. Cardiovascular disease (CVD) was defined as history of: cardiovascular disease, angina, myocardial infarction, or stroke. The analysis was then stratified based on presence of CKD defined as estimated GFR ~60 mL/min/1.73m2 or albumin/creatinine ratio >30 mg/g.

Results: Of the 5876 participants, 671 had a history of CVD, 187 ingested <1 wine glass/day, and 20 ingested ≥1 wine glass/day. The group with CVD was older, had lower HDL cholesterol, greater waist circumference, and a greater proportion of males, in addition to worse glycemic control, hypertension, and CKD. Those who drank less than <1 glass/day had 0.56 odds (95% CI 0.38, 0.82) of having CVD than those who drank ≥1 wine glass/day.

Conclusions: These data suggest that wine intake is associated with reduced odds of CVD in the general population with and without CKD. Further studies are needed to understand the mechanisms underlying this association in particular individuals with CKD. Funding: NIDDK Support

Study of Apolipoprotein E Polymorphism across Different Stages of Chronic Kidney Disease Marcelo Costa Batista,1,2 Andrei Alkmim Teixeira,1 Mauro Sergio Martins Marrocos,1 Maria Dalboni,1 Beata Marie Redublo Quinto,1 Maria Eugenia F. Canziani.2 Nephrology Div, Universidade Federal de Sao Paulo, Sao Paulo, SP, Brazil; Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil.

Background: The burden of chronic kidney disease (CKD) is epidemic. Apolipoprotein E (APOE) polymorphism has been associated with its progression although scarce data are available in South American ethnic groups. Objective: We aim to determine apolipoprotein E polymorphism (APOE) alleles and genotypes distribution across different stages of CKD patients.

Methods: In a single-center cross-sectional study, patients were divided into 3 groups. Group 1: estimated glomerular filtration rate (eGFR) higher than 60ml/min/1.73m2 (n=189); Group 2: eGFR between 15 and 60ml/min/1.73m2 (n=222); Group 3: patients on renal replacement therapy (RRT) (n=224). APOE alleles and genotypes distribution were analyzed in relation to the different stages of CKD. APOE genotypes were determined by Pyrosequencing fragment length polymorphism (RFLP).

Results: We studied 615 patients (317 men, 51.0%, 63.8% were white, 40.3% diabetic and 15.6% smokers. Mean age was 60 ± 14 years. The homoygosus genotype e3/e3 was the most frequent genotype in all three groups (Group 1: 121 (72.9%), Group 2: 161 (75.6%) and Group 3: 144 (71.6%), p: NS) and e4 allele was more frequent in just CVD patients (Group 1: 31 (72.1%), Group 2: 62 (73.8%), Group 3: 58 (69%), p: NS). We did not observe difference on alleles or genotype distribution among the studied population along the different CKD stages. However, among diabetic patients, e2 allele was negatively associated with more advanced stages of CKD (Group 1: 7 (13.1%) OR: 3.36, 95%CI: 1.15,9.77; Group 2: 8 (7.1%) OR: 1.19, 95%CI:0.41,3.43; Group 2: 3 (0%) OR: 0.9, 95%CI:0.36,0.95. This progressive inclination was demonstrated across the 5 CKD stages.

Conclusions: In diabetic patients, the authors demonstrated a negative association between e2 allele prevalence and more advanced stages of CKD.

A Phase IV, Randomized, Blinded Single-Center Study of the Effects of Calcitrol and Paricalcitol on Vascular Calcification in Chronic Kidney Disease Stages 3 and 4-Vitamin D and Coronary Calcification Study (VCOR) Sylvia E. Rosas,1 Wei Yang,2 Harold Litt.3 Medicine, Univ of Pennsylvania, Philadelphia, PA; Biostatistics, Univ of Pennsylvania, Philadelphia; Radiology, Univ of Pennsylvania, Philadelphia, PA.

Background: In animal models, calcitriol significantly increased the serum calcium-phosphate product and aortic calcium content, while paricalcitol had no effect. The objective of this randomized clinical trial was to determine the differential effect of calcitrol and paricalcitol on vascular calcification in patients with chronic kidney disease (CKD).

Methods: Inclusion criteria: All adults identified as having secondary hyperparathyroidism (SHPT) with any CAC naive to activated vitamin D therapy. We used the Wizardon scan-sum test to compare CAC progression between groups using the absolute change in Agatston unit (AU)/time between scans. We also evaluated the square root of change in CAC volume (sqrt post) - sqrt (pre). Progressors were defined as those with a difference in volume > 2.5.

Results: Forty-four participants were randomized. The mean age (standard deviation) was 56.5 (9.2). Fifty-nine were male and two-thirds were African American. Fifty-seven percent had a history of diabetes (DM). The mean and median CAC score were 318.2 (632.7) and 140.2 AU at baseline, respectively. We did not find any difference in the median CAC progression between the calcitrol vs. paricalcitol arms (33.7 vs. 64.1, 31.3, p=0.75). The square root of the difference method yielded similar results (13.4 vs. 1.56, p=0.75). There were no statistical differences between progressors vs. non-progressors (44% vs. 37%, p=0.7). The median CAC progression in non-DM was similar between the two arms (57.3 vs. 38.3, p=1.0). However, the median CAC progression in those with DM appeared higher in the paricalcitol group but did not achieve statistical significance. (31.6 vs. 111.1, p=0.2) (p=0.04 for test of interaction).

Conclusions: In CKD patients with secondary hyperparathyroidism naïve to activated vitamin D therapy, we were unable to detect differences in CAC progression between the two therapies. The effect of diabetes on treatment group needs to be explored in future studies. Funding: Pharmaceutical Company Support - Abilvix

Perceptions of Risks in Chronic Kidney Disease among Patients, Clinicians and Administrators Helen Chu,1 Navdeep Tangri,2 Ognjenka Djurdjev,3,4 Brenda Hemmelgarn,4 Francois Madore,1 Claudio Rigatto,1 Norman Muirhead,1 Manish M. Sood,2 Catherine M. Clase,5 Adrea Levin.6,9 1PHCRC, 2U of M; 3PHSA, 4BCPRA, 3MUN; 5U of C; 6U of M; 7U; 8UBC, Canada.

Background: Clinical trajectories of patients with chronic kidney disease (CKD) are highly variable. Understanding the appropriate risk thresholds and time horizons associated with predicting risks of key outcomes (renal failure, cardiovascular (CV) events & death) is important in facilitating decision-making and addressing the needs of the patients and care providers. We aimed to determine the importance of specific time frames for prediction of key outcomes from patients, nephrologists and renal administrators, and performed a needs assessment for risk prediction tools among these groups.

Methods: Online surveys were developed and deployed across all stakeholders and deployed nationally through the Kidney Foundation of Canada, provincial renal networks and the Canadian Kidney Translation and Generation Network. Anonymous responses gathered over a 4-month period were descriptively analyzed.

Results: Over 270 respondents across Canada participated in the surveys. Patients deemed personal risks of needing renal replacement therapy and developing heart disease as similarly important over all time horizons (1-15 years). Both nephrologists and administrators felt that the time horizons of 1-5 years are the most relevant. The majority of nephrologists were not satisfied with their current ability to predict the progression to renal failure, CV events and death, with the ability to predict CV events and death being the most dissatisfying. All groups indicated willingness to use risk scores with improved accuracy, if available, to predict specific outcomes.

Conclusions: Patients, clinicians and renal administrators have slightly different time horizons that they deem important for predicting outcomes in CKD; however, all agree that there is a need to improve risk prediction. These perspectives from patients and other stakeholders provide valuable information for developing future research and tools for predicting patient-centered outcomes in the CKD population.
Patient Centered, Multidisciplinary Clinic for Pre-End Stage Renal Disease Care: A Process Improvement Project  

Nicole Piero, 1 Julia Hennessy, 2 Loretta Simbalt, 2 Charuhas V. Thakar. 2 1 VA Medical Center; 2 Univ of Cincinnati.

Background: Changes in U.S. healthcare system necessitates creative resource use while providing patient-centered care. A gap analysis within our hospital (2006-2010) revealed that 700/42,984 patients, who had ≥ 1 outpatient creatinine, had glomerular filtration rate (GFR) < 30 ml/min/1.73m2. 335/700 (48%) were evaluated in renal clinics, and 116/333 (35%) were seen by one additional clinic (nutrition, education, vascular access, social work) after ESRD preparation. We report a process improvement initiative by converting the need for multiple appointments to a multidisciplinary, pre-ESRD clinic. Methods: Since Jan 2012, after a renal evaluation, patients with a GFR <30 are enrolled in the pre-ESRD clinic representing all disciplines, and led by a nurse practitioner. Patients learn about kidney disease, dialysis choices, transplant, nutrition, payment, advance directives, and conservative therapy. Since Oct 2012 patients also complete a quality of life (KDQOL) and nutrition evaluation. Results: In a sample of 56 males mean age was 69 years, mean GFR of 20.5 ml/min/1.73m2. After pre-ESRD assessment, of the 56 patients 64% favored hemodialysis, 5% peritoneal dialysis, 7% no dialysis or hospice, and 24% were undecided. Outcomes of all 56 were: 25% have started hemodialysis (incident fistula rate = 36%), 7% died before dialysis, and remaining 68% are under follow-up care. 19/56 completed the KDQOL of which 39% and 58% reported severe activity limitation or limitation to climb stairs respectively. 15/56 completed nutritional assessment: 67% ate out <2 times/week whereas 33% ate out 3 – 10 times per week; 34% ate >4 oz meat portions/meal; and 60% ate frozen or canned food > 3 times/week. 15/56 patients completed 24-hour urine collection: Urea ranged 4.7-14.3 g/24h, sodium ranged 67-294 mmol/24h, and protein ranged 0-9.3 g/24h.

Conclusions: Over 1-year, such an initiative could result in an efficient use of resources by reducing the number of required appointments by over 50%. Moreover, a patient-centered program provides individualized care, and an avenue for nutritional intervention in patients with advanced CKD.

Funding: Veterans Affairs Support

Primary Care Physicians’ Own Exercise Habits Influence Exercise Counseling for Patients with Chronic Kidney Disease  

Yoshivuchi Morishita, Yasuhito Ando, Shigeaki Muto, Eiji Kusano. Nephrology, Internal Medicine, Jichi Medical Univ, Shimotsuke, Tochigi, Japan.

Background: We investigated primary care physicians’ exercise counseling practices for chronic kidney disease (CKD), and the association of these physicians’ own exercise habits with exercise counseling. Methods: The population of this cross-sectional study was 3310 medical doctors who graduated from Jichi Medical University from 1978 to 2012. The study instrument was a self-administered questionnaire to investigate their age class, specialty, workplace, exercise habits, and practices of exercise counseling for CKD. Results: 581 (16.48%) medical doctors practiced the management of CKD among a total of 933 responses. These 581 medical doctors were defined as CKD primary care physicians. Physicians who had previously diagnosed CKD patients were defined as CKD primary care nephrologists. Their own exercise habits (frequencies and intensities) were as follows: frequencies: daily, 71 (12.1%); ≥2–3 times/week, 154 (26.5%); ≥1 time/week, 146 (25.1%); and ≤1 time/month, 176 (30.2%); intensities: high (≥6 MTS), 175 (30.1%); moderate (4–6 MTS), 132 (22.7%); mild (≤3 MTS), 91 (15.4%); and none, 172 (29.6%). CKD primary care physicians’ exercise recommendation (general) levels for CKD patients were as follows: high, 31 (5.3%); moderate, 176 (29.7%); low, 256 (44.0%); and none, 92 (15.8%). The details of exercise recommendations (frequencies and intensity) were as follows: frequency: daily, 23 (10.8%); ≥2–3 times/week, 144 (70.4%); ≥1 time/week, 25 (12.3%); and ≤1 time/month, 0 (0%); intensity: high (≥6 MTS), 1 (0.5%); moderate (4–6 MTS), 62 (30.5%); mild (≤3 MTS), 132 (66.0%); very mild (≤3 MTS), 3 (1.5%); and none, 3 (1.5%). The CKD primary care physicians’ exercise recommendations (general) for CKD patients were significantly related to their own exercise frequency (p<0.01), but they were not related to their age, specialty, workplace, or exercise intensity. Furthermore, the CKD primary care physicians’ exercise recommendations (frequency (p<0.01) and intensity (p<0.01)) were related to their own exercise frequency.

Conclusions: CKD primary care physicians’ own exercise habits influence their exercise counseling for CKD patients.

Kidney Health in Volunteers Recruited as Study Controls  


Samer Rateb Abbas, 2,3 Cassandra Cartagena, 1 Fansu Zhi, 2 Peter Kotanko, 1 \n\n1 Nathan W. Levin, 1 Mary Carter, 1 Stephan Thijsen, 1 Caroline M. Williams, 1 Cesar Flores-Gama. 2,3 Nephrology, Renal Research Institute, New York, NY; 2,3 Nephrology, Beth Israel Medical Center, New York, NY.

Background: Little is known about kidney function in volunteers recruited as healthy controls. Here we report kidney function in such individuals.

Methods: We solicited the participation of healthy volunteers using posters and newspapers. Telephonic volunteers underwent a structured 22 questions to explore their eligibility. Volunteers who passed the telephone interview underwent clinical assessment (height, weight, blood pressure) and measurement of serum creatinine, BUN, urinalysis (1-4 weeks later. Estimated glomerular filtration rate (eGFR) was computed with the CKD-EPI equation. Albumin-creatinine ratio (ACR) was calculated as urine albumin/urine creatinine (mg/g). Systolic blood pressure SBP was recorded three consecutive times in a seated position on average SBP > 140 mmHg were considered hypertensive.

Results: Based on the phone interview, almost 50% of 180 volunteers were excluded because of kidney, cardiac, or malignancy-related conditions. Ninety-one participants (age 57±10 years; 49 female) were eligible. Of these 18 participants were excluded, mostly because of absent blood and urine samples. Results obtained in the remaining 73 participants are shown in Table 1.

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

Underline represents presenting author.
A Screening Model of Correlation Factors for Type 2 Diabetes Mellitus with Massive Proteinuria


Background: To establish the logistic regression screening model of the DKD with massive proteinuria crowd, and validate the effectiveness of the model.

Methods: Collected 605 type 2 diabetes patients with microalbuminuria and massive proteinuria were treated during January 2008 to November 2012. 605 cases were randomized to the first group(404 cases) for modeling group, and the second(201 cases) to validation. The modeling group was including 292 cases with microalbuminuria and 122 with massive proteinuria. The eGFR was calculated (MDRD Formula, all more than 30 ml/min 1.73m²). Statistical analysis used the SPSS15.0 software. Univariate and multivariate Logistic regression analysis were used to establish regression equation.sensitivity and specificity of the model was analysed by ROC curves, diagnosis cut-off point was set on the maximum of youden index. Put the validation group into the model, to compare the difference of areas of ROC curve between model group and validation group with Z test.

Results: After multi-factor analysis, the duration of diabetes, DR, waist-to-hip ratio, postprandial blood glucose 2 h, Fb, ALB, TC, Scr, CysC were the 9 main relative factors for massive proteinuria. AUC of the combination of multiple main relative factors was largest (0.907), and the cut-off value was 0.551 (Sensitivity 82.1%, Specificity 87.3%). The data of validation group applied to the model, the AUC was 0.850. To Compare the areas of ROC curves, that were no statistical difference (P>0.05).

Conclusions: The combination of multiple factors screening model of DKD with massive proteinuria was effective. The performance of the screening was stable. It can be used in clinical according to validation. Early prevention could be implement in the patients who are close to the diagnosis cut-off point.

Funding: Government Support - Non-U.S.

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

896A
Conclusions: Adherence to many health behaviors were low for our cohort of Stage 1-5 CKD patients not on dialysis. Older patients were more likely and non-white patients less likely to report healthy eating behaviors. More work is needed to determine reasons for the racial differences in health behaviors and potential strategies to improve healthy behavior patterns. 

Funding: NIDDK Support, Other NIH Support - T32, Private Foundation Support

**PUB095**

Improving Care of Patients with Kidney Disease: Use of Mobile Telephony to Improve Lifestyle and Adherence 

**Alfonso M. Cucto-Manzano**, 1 Héctor Gallardo-ricono, 1 Héctor R. Martínez Ramírez, 1 Laura Cortes-sanabria, 1 Enrique Rojas-Campos, 1 Petra Martínez, 1 Jose I. Cerrillos, 2 Jorge Andrade-Sierra, 2 Miguel Medina Perez, 1 **UMER, Hospital Especialidades, CMNO, IMSS, Guadalajara, Jalisco, Mexico; 2Dirección de Soluciones Operativas, Instituto Carlos Slim de la Salud, Mexico, DF, Mexico; 3Dept Nephrology, Hospital Especialidades, CMNO, IMSS, Guadalajara, Jalisco, Mexico.**

Background: Opportunities for new technologies (as mobile phones) to play formal role in health services are increasing. However, no study has been performed in kidney disease (KD). Aim: To develop and test a mobile phone program to improve lifestyle, adherence and clinical outcome of KD patients.

Methods: In collaboration, and with technology developed by the Carlos Slim Health Institute, a program based on mobile phone text messages and reminders was developed, and tested in a pilot study (Jun-Oct 2012). Test messages about KD risk factors (50), healthy lifestyle (40), and to improve adherence and follow-up appointments (35) were generated and sent to patients agreed to participate (recipients of a functioning kidney transplant performed at our Hospital, included when they were discharged). Patients were treated by their nephrologists according to clinical practice standards. A satisfaction questionnaire was applied at end of follow-up.

Results: Twenty-three patients (age 33±13 yrs, 43% women) had a follow-up of 58 (41-76) days. Patients received 8.0 (3.0-1) test messages/day, 3 (2,3) medication reminders/day, and 1.1 (0.3-2) appointment reminders/month. Clinical and biochemical data are shown in the table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11 (10-13)</td>
<td>12 (11-14)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>9.9 (8.6-11)</td>
<td>10 (9.6-12)</td>
</tr>
<tr>
<td>Intensity Blood Pressure (mmHg)</td>
<td>130 (115-138)</td>
<td>120 (115-124)</td>
</tr>
<tr>
<td>Albumin Blood Pressure (mmHg)</td>
<td>80 (72-84)</td>
<td>100 (90-108)</td>
</tr>
</tbody>
</table>

*p<0.05 vs baseline

In a 0-10 scale, patients considered utility of messages as 9±6±0.7, medication reminders 9±8±0.5, and appointment reminders 9±8±0.6.

Conclusions: More than 100 mobile phone messages were successfully developed and tested to improve lifestyle, adherence and clinical outcome of KD patients. Future research should address scalability of this intervention and explore association with changes in attitudes and behaviors.

**PUB096**

Chronic Kidney Disease Education and Impact on Dialysis Modality Choice and Dialysis Access 

**Doris Sofia Galina Quintero**, Clara Nicholas Lyas, Russell Griffin, Jane S. Davis, Dana Rizik, Eric L. Wallace. **Univ of Alabama at Birmingham.**

Background: Despite the morbidity and mortality associated with the initiation of dialysis with intravascular catheters (IVC), IVC rates of incident patients remains over 60%. Home modalities utilization remains low despite the associated benefits. Perhaps a contributing factor for these data is patient education. There is limited information about how Chronic Kidney Disease Education (CKDE) affects modality selection and placement of permanent access. Although education may be documented, its effectiveness is unclear. We analyze the effects of the UAB CKDE class on modality selection and permanent access placement.

Methods: Clinical and demographic data on all patients who attended CKDE class from 2010 through 2012 were collected through chart review. Data on all dialysis accesses was applied at end of follow-up.

Results: 174 patients were included. At the time of class attendance, patients had a mean glomerular filtration rate (GFR) of 19 ml/min/1.73 m² (Standard Deviation (SD) of 6). 50.3% were diabetic. 70/174 (40.2%) had no access placed at the time of analysis. There was no difference in age, gender, or race with regards to type of access placed.

Conclusions: More than 100 mobile phone messages were successfully developed and tested to improve lifestyle, adherence and clinical outcome of KD patients. Future research should address scalability of this intervention and explore association with changes in attitudes and behaviors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11 (10-13)</td>
<td>12 (11-14)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>9.9 (8.6-11)</td>
<td>10 (9.6-12)</td>
</tr>
<tr>
<td>Intensity Blood Pressure (mmHg)</td>
<td>130 (115-138)</td>
<td>120 (115-124)</td>
</tr>
<tr>
<td>Albumin Blood Pressure (mmHg)</td>
<td>80 (72-84)</td>
<td>100 (90-108)</td>
</tr>
</tbody>
</table>

*p<0.05 vs baseline

In a 0-10 scale, patients considered utility of messages as 9±6±0.7, medication reminders 9±8±0.5, and appointment reminders 9±8±0.6.

Conclusions: More than 100 mobile phone messages were successfully developed and tested to improve lifestyle, adherence and clinical outcome of KD patients. Future research should address scalability of this intervention and explore association with changes in attitudes and behaviors.

**PUB097**

Cost Analysis of Participatory Educational Intervention for Prevention, Diagnosis and Treatment of Early Chronic Kidney Disease 

Laura Cortes-sanabria, Victor Omar Frias-navarro, Héctor R. Martínez Ramírez, Alfonso M. Cucto-Manzano. **Unidad de Investigación Medica en Enfermedades Renales, Instituto Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico.**

Background: Our group previously demonstrated that adequate training to family physicians (FP) successfully preserved renal function of patients with DM2. However, no previous study has evaluated the economic impact of such an educative intervention. AIM: To determine and evaluate the direct costs (DC) of an educative-participative intervention (EPI) to FP and a multidisciplinary team (MDT) addressed to increase their clinical competence (CC) in the management of patients with DM2 and early nephropathy (EN).

Methods: Economic evaluation study. EPI included review of Clinical Practice Guidelines of early CKD and discussion of real clinical cases, 5 wk/h during 3 months. CC was evaluated with a previously validated instrument, applied at the beginning and the end of the EPI (maximum value of CC 150 points). The pattern of service utilization was identified; costs were calculated for each activity, according to the Institutional Unit Cost System (IMSS). Only direct medical costs (DMC, all monetary costs incurred during the intervention) were considered, and they are shown in US dollar.

Conclusions: Implementing an EPI in the primary health-care is a cost-effective measure to reduce the burden of kidney disease.

**PUB098**

National Kidney Centre Report on Kidney Screening Program Risk Factor for Chronic Kidney Disease – A Survey from Ranibas, Gulmi Nepal

Rishi Kumar Kali. **National Kidney Center, Kathmandu, Nepal.**

Background: National kidney center is providing dialysis to increasing numbers of patients every year. Kidney disease screening program along with awareness campaign is carried out from time to time.

Methods: Team of experts from National kidney center visited village Ranibas of Gulmi district to conduct kidney disease screening and awareness camp. Information about camp was published through media before the team arrived there. On three consecutive days all who came for screening were evaluated. Every individual registered, his/her BMI, BP, was measured. Urine dipstick test for protein and sugar was done there only. survey form filled with the help of volunteers to know medical history, personal habits especially water intake; smoking; tobacco chewing; alcohol consumption and exercise done by that individual. All data were entered into register for evaluation.

Results: More than 33 % of 731 persons examined were overweight 17.5 % of examined had raised blood pressure around 5 % examined were suspected to have Diabetes around 6% examined had proteinuria majority had healthy kidneys 98% had access to aerated drinks and use it 94% do not exercise except their regular work.

Conclusions: Even in a remote village of Nepal there are enough risk factors for development of kidney disease. Program to educate not only about kidney diseases or other education to remain healthy is needed. Need to make people aware about their health and ways how they can prevent serious disease by simple screening method which is not costly.

Funding: Clinical Revenue Support

**PUB099**

High Self-Efficacy Is Associated with More Self-Care in Patients with Chronic Kidney Disease

H. Omer Ikizler, Jillian Molli Berkan, Kenneth A. Wallston, T. Alp Ikizler, Kerri L. Cavanaugh. **Vanderbilt Univ.**

Background: Self-care behaviors, dietary and medication adherence, physical activity, and health care engagement, are important to optimize chronic kidney disease (CKD) treatment. To identify potentially modifiable factors to promote effective self-care, we investigated the relationship between patients’ self-perceived efficacy and frequency of CKD self-management behaviors.

Methods: Adult patients with CKD (eGFR<60) from one academic nephrology clinic were enrolled in a cross-sectional study from May 2012 to July 2013. Patient surveys assessed kidney knowledge, health literacy, frequency of CKD self-care, and their self-perceived efficacy in managing their kidney disease using the Perceived Kidney Disease Self-Management Scale (PKDSMS).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: Among 252 patients enrolled, mean (SD) age was 58 (12) years. 42% were male, and 83% were Caucasian. Mean (SD) self-efficacy score was 2.58 (0.73) out of 5; mean self-care score was 26.7 (6.4) out of 39. In univariate analysis, higher subjective numeracy (r=0.15, p<0.05), and greater perceived (r=0.19, p<0.01) and objective kidney knowledge (r=0.23, p<0.01) were correlated with higher self-efficacy. Self-care behaviors were also correlated with higher self-efficacy: healthier food (r=0.22, p<0.01), physical activity (r=0.20, p<0.01), adhering to a kidney diet (r=0.14, p<0.05), not missing doctor visits (r=0.13, p<0.05), and taking medications as prescribed (r=0.22, p<0.01). Total overall self-care score was also positively correlated (r=0.33, p<0.01). In an analysis adjusted for age, gender, race, education, perceived and objective kidney knowledge, the association between self-efficacy and overall self-care behaviors persisted (β (95% CI): 0.21 (0.10 - 0.31), p<0.001). Furthermore, higher self-efficacy was also associated with greater satisfaction with physician communication (r=0.30, p<0.01).

Conclusions: Self-efficacy is easily assessed and is moderately to strongly associated with a variety of self-care behaviors in chronic kidney disease. Interventions to improve self-efficacy specific to CKD may increase participation and effectiveness of self-care, enhance patient-centered communication, and ultimately improve clinical outcomes.

Funding: NIDDK Support, Private Foundation Support

A Bioreactor as a Long Term Perfusion Model

Vera Jankowski,1 Horst-Dieter Lemke,2 Joachim Jankowski,1 Charity, Berlin, Germany; Excorlab, Obernburg, Germany.

Background: Metabolic stimuli, pressures and hemodynamic flows are major mediators of vascular plasticity. In this study, we have developed an in vitro bioreactor to investigate cell-specific interactions, molecular mechanisms as well as tissue specific effects under physiological hemodynamic flow conditions. This bioreactor termed "artificial artery" can be used for screening of potential arterio-protective substances, pro-arteriogenic factors, and for investigating biomarkers of vascular diseases in CKD.

Methods: The bioreactor is built up out of 4 hollow fibre membranes colonised with primary human umbilical vein endothelial cells (HUVECs) on the inside and primary human arterial smooth muscle cells (HUMSCs) on the outside. By means of fluorescent staining as well as immunocytochemistry of reference proteins for endothelial cells and smooth muscle cells, a hydrophobic polypropylene membrane was identified as being the optimal polymer for co-colonisation.

Results: Applying defined arterial flow conditions, metabolic exchange, and cross-talk of endothelial and smooth muscle cells through the microporous structure of the hollow fibre, capillaries mimic physiological in vivo conditions of the vasculature and is therefore of high relevance for further studies. Chromatographic methods and subsequently mass spectrometry analyses as well as expression analyses of shear stress regulated genes proved our system to be viable and functional up to five days.

Conclusions: The "artificial artery" provides a solid in vitro model to test pharmacological active compounds for their impact on arterio-damaging or arterio-protective properties on vascular response in CKD.

Renal-Coloboma Syndrome Associated with Arnold-Chiari Malformation

Type 2 and Proximal Renal Tubular Acidosis

Heino R. Anto, Tatyana Tolchinsky, Fnu Jaipal. Dept of Nephrology, St. John's Episcopal Hospital, Far Rockaway, NY.

Background: A 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admitted for corrective surgery involving Arnold-Chiari malformation type 2. Besides this malformation the patient also had optic disc dysplasia and syringomyelia and was treated with topiramate for seizures. On this admission a 28 y/o patient was admits...
**Results:** Immunofluorescence staining showed that diffuse WT1 expression was observed in the metanephric mesenchyme and then, in succession, in the renal vesicle, the comma-shaped body, the tail of the comma-shaped body, the lower aspect of the S-shaped body and the glomerular podocytes. CD31 was scattered throughout the fetal kidneys and then surrounded the developing renal vesicle and comma-shaped body. At the S-shaped body stage, CD31-positive cells migrated into the vascular cleft to form precapillary cords in the immature glomeruli and finally localized in the endothelium of mature glomeruli. α-SMA expression was not present in the early fetal kidney, renal vesicle or comma-shaped body, but appeared near the periphery of the S-shaped body at the early stage of the S-shaped body, streamed into the vascular cleft by the late S-shaped body stage, aggregated at the root of the developing glomerulus, migrated to the periphery of the glomerular tuft at the capillary loop stage, and finally localized to the mesentenium in the mature glomerulus.

**Conclusions:** Porcine podocytes arise from the metanephric mesenchyme and the development of podocytes and endothelial cells precedes the development of the mesangial cells. Cross-talk between cells in the glomerulus may be essential during the development of the porcine glomerular tuft.

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

**PUB105**

**Atorvastatin Improve Effects of Mesenchymal Stem Cells Treatment for Kidney Ischemia/Reperfusion Injury through Down-Regulation of TLR4 Expression**

**Jieru Cai, Xiaofang Yu, Bingyong Zhang, Yi Feng, Xiaoqiang Ding. Nephrology of Dept, Zhongshan Hospital, Fudan Univ, Shanghai, China.**

**Background:** Statin has been shown to attenuate ischemia/reperfusion (IR) injury and enhances the efficacy of mesenchymal stem cells (MSCs) treatment. However, the components of the mechanism remain largely unknown. We aim to investigate whether atorvastatin regulates the expression of Toll-like receptor 4 (TLR4), a potential mediator of innate inflammation, and facilitates therapeutic efficacy of MSCs in renal I/R injury.

**Methods:** The model of I/R injury was induced by bilateral renal pedicles clamp for 24h systemically administration following I/R. The combined treatment with Ator and MSCs (Ator+MSCs) markedly increased the level of serum creatinine and blood urea nitrogen, reduced the severity of renal damage. In addition, inhibited renal tubular cell apoptosis, and reduced oxidative stress were observed in the Ator+MSCs group compared with control or mono-therapy group. Furthermore, TLR4 expression and high-mobility group box 1 (HMGB1) were decreased and survivals of KS group were 4 days compared to I/R group (I/R group v.s. I/R-KS group: 4.43±1.76 v.s.1.36±0.99 U/L, p<0.01). The cell proliferation increased significantly in I/R-KS group (I/R group v.s. I/R-KS group: 24.3±7.9 v.s.43.9±5.9/×400fild). The apoptotic cells decreased in I/R-KS group (I/R group v.s. I/R-KS group: TUNEL(+)) cells: 46.4±14.5 v.s. 25.3±13.0 /×200fild, p<0.01). Moreover, we could observe significant inflammation suppression in I/R-KS group compared to I/R group (F4/80(+) area: 4476±2433 v.s. 1577±1042 pixel/×200fild, p<0.01). In addition, CS-KS significantly suppressed cisplatin-induced cell apoptosis in vitro. Immunoblot analysis revealed that CS-KS contained many factors, such as HGF.

**Conclusions:** Not only the direct cell differentiation but also secreted factors from adult kidney stem cells have the potential to protect against AKI and activate renal regeneration.

**Funding:** Clinical Revenue Support, Government Support - Non-U.S.

**PUB107**

**Acute Hemodialysis Therapy in Neonates with Inborn Errors of Metabolism**

**Israel Eisenstein,2,3 Mahdi Tarabeih,1 Daniella Magen,1,4 Shirley Pollack,1,4 Hanna Mandel,2,4 Gad Bar Joseph,1,3 Israel Zelikovic.1,4**

**Background:** Inborn errors of metabolism (IEM) can cause devastating damage to the neonatal brain if not promptly treated. The most efficient therapy for IEM-induced metabolic crisis is hemodialysis (HD). Data on the use of HD in neonates is scarce.

**Methods:** We analyzed the demographic, clinical, and biochemical data of all neonates with IEM who were admitted to our Pediatric Intensive Care Unit between 2004-2013 with a metabolic crisis necessitating HD.

**Results:** Fourteen neonates (MF 7/7; Arabs/Jews 13/1) with IEM (6- Urea cycle defects (UCD), 4- maple syrup urine disease (MSUD), 2- mitochondrial cytopathies (MC), 2 - other) had uneventful delivery, and were admitted because of metabolic/neurological deterioration starting at 48h -14 days of age. Median age and weight of the infants at the initiation of HD was 6.3 days and 2999 g, respectively. HD was performed through double-lumen, 6.5- French, Gamcath® catheterprocheted into the internal jugular vein; Gambro AK200 dialysis machine and tubing and Fresenius FXpaed® dialyzers were used. A total of 30 dialysis treatments (at least 2 per patient) were performed. The first (2 hrs) HD treatment markedly decreased (91.9%) mean plasma ammonia level in UCD and MC patients from 1071 to 86 µmol/L (nl: 53-90), and markedly decreased (90%) mean plasma leucine level in MSUD patients from 2408 to 230 µmol/L (nl: 70-240). The second (3-4 hrs) HD treatment decreased the mean rebounded ammonia and leucine levels from 433 µmol/L and 780 µmol/L to 69 µmol/L and 88 µmol/L, respectively. The HD procedure was free of complications, resulted in marked clinical improvement in 11 patients, and enabled the initiation of appropriate dietary/pharmacological therapy in all patients. Eleven (78.6%) of the infants survived, and 3 (21.4%) succumbed to their metabolic disease in the neonatal period.

**Conclusions:** HD in neonates with IEM is safe, very efficient, and life-saving when performed by skilled personnel and in the appropriate setting.

**Funding:** Clinical Revenue Support, Government Support - Non-U.S.

**PUB108**

**Predictive Factors of Graft Censored Failure in Pediatric Kidney Transplants**

**Ana Rocha, Liliana Rocha, Maria Faria, Conceição Mota. Centro Hospitalar do Porto.**

**Background:** Kidney transplant in children’s has shown steady improvement in graft survival outcome over the last decades. Using data obtained from the transplant registry of our centre between 1984 and 2012, we assessed the independent determinants of graft failure using the Cox proportional hazards regression.

**Methods:** Altogether, 128 recipients aged <18 years at the time of kidney transplant and who had > 3 months graft survival were studied. Over 9.95 years of medium follow-up, 27 censored graft failures occurred. Censored graft survival at five, ten and twenty years post-transplant was 93%, 82%, 70% and 63%, respectively. Studied factors included recipient and donor age, gender, dialysis vintage, donor/recipient CMV
serology, panel reactive antibody percentage, human leucocyte antigen mismatching, previous transplant number, donor type [deceased vs. living donation], cold ischemia time, induction therapy with antithymocyte globulin, occurrence of acute tubular necrosis and development of acute rejection.

Results: Using univariate analysis, the significant predictors for graft censored failure were adult donor (P=0.001), higher receptor age (P=0.035), human leucocyte antigen mismatching (P=0.025), antithymocyte globulin induction (P=0.03) and development of acute rejection (P=0.001). Two factors independently predicted graft censored failure in multivariate analysis. The odds ratios for graft failure in patients with acute rejection and in children who received an organ of an adult were 3.744 and 4.962, respectively.

Conclusions: Pediatric recipients should receive the first priority for allografts from pediatric donors and acute rejection should be meticulously prevented.

PUB109
Efficacy and Safety of Eculizumab in Children with Dense Deposit Disease Kian K. Upadhyay, Richard N. Fine. State Univ of New York at Stony Brook, NY.

Background: Dense Deposit disease (DDD) is a rare cause of glomerulonephritis and is believed to result from dysregulated alternative complement pathway. Treatment options are limited and there is a high incidence of end stage renal disease if untreated. Eculizumab, a humanized monoclonal antibody, binds to the terminal complement, C5, and prevents formation of membrane attack complex (MAC) - C5b9, a potent proinflammatory agent.

Methods: We describe a 6 yo male with biopsy-proven DDD who was treated off-label with eculizumab soon after the diagnosis. The patient presented with nephrotic range proteinuria, microhematuria, C3 hypocomplementemia, with normal renal function and mild hyperalbuminemia without edema. Baseline serum soluble MAC (SC5b9) was elevated. Other tests included negative C3 nephritic factor, normal factor H & I levels, no autoantibodies to factor H & I, and no CD46, C3 or factor H mutation. After initial Rx with biweekly intravenous eculizumab, the proteinuria decreased from baseline urine protein to creatinine ratio (U/P C) of 5.6 to 0.7. SC5b9 normalized when checked after 3rd treatment. Subsequently, when the treatment frequency was changed to monthly after 5th treatment, the proteinuria started rising to U/P C of 3-4, necessitating initiation of ACE inhibitor therapy. SC5b9 level increased to pretreatment value when checked again during 10th infusion. The frequency was then changed back to biweekly and the treatment is ongoing. Renal function remains normal but the C3 hypocomplementemia persists. Repeat renal biopsy after 7th treatment showed no interval histopathological changes but with de novo staining for IgG in the same distribution as C3 and C5b9. Patient was fully immunized including meningococcal vaccine prior to the treatment. No serious adverse effects have been observed so far. To the best of our knowledge, this is the first youngest pediatric patient to receive eculizumab for DDD. It is yet to be seen whether eculizumab continues to be effective in this patient.

Conclusions: We conclude that biweekly eculizumab effectively inhibits the terminal complement cascade and may be useful in preventing progression of renal disease in DDD, especially in those who have elevated SC5b9 level.

PUB110
Typical or Atypical Hemolytic Uremic Syndrome? This Is the Question Gianluigi Ardissino, Francesca Tel, Stefania Salardi, Sara Testa, Fabio Paglialonga, Nicolò Borsa, Ilaria Possenti, Silvana Tedeschi. Center for HUS Prevention, Control and Management, Fondaz. IRCCS Ca’ Granda Osp Maggiore Policlinico, Milan, Italy.

Background: Hemolytic Uremic Syndrome (HUS) is commonly classified into 2 forms: typical HUS (HUS) due to an infection by Shiga-toxin (Stx)-producing E. coli (STEC) and atypical HUS (aHUS), mainly caused by complement alternative pathway dysregulation. The classification relies upon the evidence or not of STEC infection: isolation of STEC, detection of Stx in stools and/or in blood and serotype specific LPS antibody. However, diarrhea can also represent a trigger for aHUS, leading to difficulties in identifying the most appropriate treatment. Herein, we report a case of HUS associated with bloody diarrhea, in which prompt lab investigations revealed a complement related protein gene mutation which guided the clinical choice of treating the patient with Eculizumab.

Methods: A 5-yrs-old girl, while on vacation on the Red Sea, was admitted to the local hospital with macrohematuria, severe bloody diarrhea and fever. Lab showed mild anemia, low PLT count and AKI. An antibiotic treatment was started. Two days later, for worsened clinical conditions, the child was referred to our Center. Bloody stools were negative for Stx 1 and 2. Due to low C3 level (40 mg/dl) molecular biology for complement related genes was started and on day 6, a novel variant on MCP gene (p.Phe175Val) mutation was identified. The same day Eculizumab (600 mg) was administered with a rapid remission of the thrombotic microangiopathy and recovery of renal function. During the following 8 mos, no relapse occurred, despite the single dose of Eculizumab. The child is well with normal renal function.

Conclusions: Pediatric recipients should receive the first priority for allografts from pediatric donors and acute rejection should be meticulously prevented.

PUB111
Epidemiology of Hemolytic Uremic Syndrome in Children in Northern Italy Gianluigi Ardissino, Stefania Salardi, Sara Testa, Silvana Tedeschi, Valentina Paracchini, Francesca Tel, Ilaria Possenti. Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca’ Granda Osp Maggiore Policlinico, Milan, Italy.

Background: HUS is a rare microangiopathy characterized by platelet (PTL) consumption, hemolysis and renal damage. The most frequent type of HUS in children is associated with shiga-toxin (Stx)-producing E. coli infection (STEC-HUS), but other atypical forms (aHUS) are occasionally seen, including those related to complement dysregulation. Despite the severity of the disease and the fact that it represents a leading cause of AKI in children, the general epidemiology of HUS is all but well documented. The aim of the study is providing reliable, population-based epidemiological evidence.

Methods: Between 2001 and 2011, all incident cases with a first episode of HUS<18 yrs who present these conditions, were included: 1. PTL<150,000/mm³ or evidence of PTL consumption; 2. Evidence of hemolysis; 3. Signs of renal damage. Overall and age-related crude incidence rates per 100,000 people were calculated from 2001 to 2011 using the population estimates issued by the Italian Institute of Statistics (ISTAT). The population at risk was defined as Lombardy residents aged ≤18 years.

Results: Ninety-eight HUS cases were identified during the 10 yrs; the overall annual incidence was 0.55/100,000 children ≤18 yrs of age (range 0.44-0.66). The incidence in patients aged <5 yrs was 1.2 cases per 100,000, aHUS accounted for 11.2% of the cases (incidence:0.069/100,000); among the 11 aHUS patients, 4 (36.4%) were caused by complement gene dysregulation (2 C2H, 1 MCP, 1 C3f), 3 (27.3%) were associated with methyl-malonic acidemia, 2 (18.2%) were associated with pneumonia, and 2 (18.2%) were of unknown origin. The overall case fatality rate was 4.1% (3.4% in STEC-HUS).

Conclusions: Our findings provide epidemiological data useful to healthcare planning in the area of HUS, particularly in relation to estimating the financial burden that health care providers might have to face for treating atypical HUS.

Funding: Private Foundation Support
The U.S. Pediatric Nephrology (PN) Workforce 2013

William A. Primack,1 Kevin E.C. Meyers,2 Suzanne Kirkwood,3 Holly S. Ruch-Ross,4 Carrie Radabaugh,4 Larry A. Greenbaum,4 1UNC Kidney Center, Chapel Hill, NC; 2CHOP, Philadelphia, PA; 3AAP, Evanston, IL.; 4Carrie, IL.; Emory Children’s Center, Atlanta, GA.

Background: A shortage of pediatric nephrologists exists, yet the PN workforce is poorly characterized.

Methods: The AAP is conducting workforce surveys of all pediatric subspecialists (PSS). The first 42 questions are asked of all PSS to allow comparisons. Then 44 PN specific questions were created with help of the ASPN. The survey was sent electronically to all physicians who are either working as pediatric nephrologists or were ever US board eligible in PN.

Results: 500 responses (response rate 65.8%): 51% male. 68% US graduates. 396 are ABP Certified in PN. 409 practice PN full or part time. They spend 57% of their time in direct patient care, 14% administration, 12% clinical research, 11% teaching, 9% basic research. Mean work week is 54.5 ± 15.7 hrs (n=470). Respondents (n=405) spend 84% of their time in all aspects of PN with the rest of their time spent in non-nephrology administration, general pediatrics, and in adult neph. 131 plan to decrease clinical work in the next 5 yrs due to or more of the following: 59 are dissatisfied with work-life balance; 70 plan to retire; 13 for family reasons; 49 to increase nonclinical activities. 65% would probably or definitely choose PN as a career if they could do it over again, but 22% would not and 14% were unsure (n=455). 49 think that there should be a 2 year clinical as well as a 3 year academic track for fellowship, 34% did not and 17% were unsure (n=452). PN Division chiefs (n=110) and solo PN’s (n=28) report that 52% have adequate PN staff, 47% inadequate. In the next 3 years, 92% anticipate recruiting for newly created PN positions, as well as 77% and 71% to replace retiring and departing PN’s respectively.

Conclusions: 409 PN’s spend 57% of their time in patient care, but 32% plan to decrease clinical work in next 5 yrs. Also 20% of trained PN’s do not practice PN. An ongoing national shortage of pediatric nephrologists is likely given the high numbers who will need to be replaced over the next 5 years. The PN workforce requires continuing needs assessment monitoring.

Fighting Bloody Diarrhea for Shigatoxin-Associated Hemolytic Uremic Syndrome. Prevention and Mitigation: North Italian HUS Network

Gianluigi Ardissino, Francesca Tel, Sara Testa, Stefania Salardi, Rosaria Colombo, Ilaria Ponsi. Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca’ Granda Osp. Maggiore Policlinico, Milan, Italy.

Background: Shigatoxin-associated Hemolytic Uremic Syndrome (STEC-HUS) still represents a major public health problem caused by an infection often presenting with bloody diarrhea.

Methods: Since May 2010 a Network connecting pediatric hospitals in Northern Italy (10 millions gp) was developed aimed at screening bloody diarrhea in children for Shigatoxin. Among the objectives of the Network is the early diagnosis of STEC-HUS thus reducing the time of referral to our Center and allowing the implementation of interventions measures to prevent or mitigate the renal complication. The present study compares the clinical characteristics at diagnosis of an equal number of STEC-HUS cases referred to our Center in the past (2007-2009) and during the last 2 years (2012-2013) in order to analyze the efficacy of the Network.

Results: Since Jan. 2012, 22 cases of STEC-HUS have been referred to our Center and these were compared to 22 historical cases (sequentially referred during 2007-2009). No significant difference was observed in gender and age at diagnosis as well as in mean haemoglobin, LDMI and platelet levels at onset while mean creatinine was significantly higher in the historical group (3.6 mg/dL vs 1.7 mg/dL with CI 1.8-5.4 vs 1.7 mg/dL with CI 1.1-2.4; p <0.05).

Conclusions: The screening of bloody diarrhea, together with the increased awareness among pediatricians towards STEC-HUS, led to a remarkable advance in the diagnosis of the renal complication which can be estimated, based on creatinine, in as much as 24-48h. The anticipation in the diagnosis is the prerequisite for testing early intervention measures for mitigating the severity of STEC-HUS.

Funding: Private Foundation Support

Coinfection in Children with Bloody Diarrhoea Caused by Shigatoxin Producing Escherichia coli

Miho Hatano,2 Bandana Paudyal,1 Anil K. Mongia,2 Morris J. Schoeneman,1 Vaishali Bansal,1 Scott Miller,1 Hanan K. Tawadrous1. 1Pediatric Nephrology, SUNY Downstate Medical Center, Brooklyn, NY; 2Division of Nephrology, New York University School of Medicine, SUNY Downstate Medical Center, Brooklyn, NY.

Background: Renal complications of sicle cell anemia (HbSS) include: a trend lower toward hyperfiltration in the HU group. 18.7% and 20.8% of patients have microalbuminuria and proteinuria, respectively, prevalences similar to that reported in untreated children.

Conclusions: Renal function is similar in children with HUS receiving either HU or CTx, and both groups have a high prevalence of SLCN progression in children with HBSS.

Fighting Bloody Diarrhea for Shigatoxin-Associated Hemolytic Uremic Syndrome. Prevention and Mitigation: North Italian HUS Network

Gianluigi Ardissino, Francesca Tel, Sara Testa, Stefania Salardi, Rosaria Colombo, Ilaria Ponsi. Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca’ Granda Osp. Maggiore Policlinico, Milan, Italy.

Background: Shigatoxin-associated Hemolytic Uremic Syndrome (STEC-HUS) still represents a major public health problem caused by an infection often presenting with bloody diarrhea.

Methods: Since May 2010 a Network connecting pediatric hospitals in Northern Italy (10 millions gp) was developed aimed at screening bloody diarrhea in children for Shigatoxin. Among the objectives of the Network is the early diagnosis of STEC-HUS thus reducing the time of referral to our Center and allowing the implementation of interventions measures to prevent or mitigate the renal complication. The present study compares the clinical characteristics at diagnosis of an equal number of STEC-HUS cases referred to our Center in the past (2007-2009) and during the last 2 years (2012-2013) in order to analyze the efficacy of the Network.

Results: Since Jan. 2012, 22 cases of STEC-HUS have been referred to our Center and these were compared to 22 historical cases (sequentially referred during 2007-2009). No significant difference was observed in gender and age at diagnosis as well as in mean haemoglobin, LDMI and platelet levels at onset while mean creatinine was significantly higher in the historical group (3.6 mg/dL vs 1.7 mg/dL with CI 1.8-5.4 vs 1.7 mg/dL with CI 1.1-2.4; p <0.05).

Conclusions: The screening of bloody diarrhea, together with the increased awareness among pediatricians towards STEC-HUS, led to a remarkable advance in the diagnosis of the renal complication which can be estimated, based on creatinine, in as much as 24-48h. The anticipation in the diagnosis is the prerequisite for testing early intervention measures for mitigating the severity of STEC-HUS.

Funding: Private Foundation Support

Coinfection in Children with Bloody Diarrhoea Caused by Shigatoxin Producing Escherichia coli

Miho Hatano,2 Bandana Paudyal,1 Anil K. Mongia,2 Morris J. Schoeneman,1 Vaishali Bansal,1 Scott Miller,1 Hanan K. Tawadrous1. 1Pediatric Nephrology, SUNY Downstate Medical Center, Brooklyn, NY; 2Division of Nephrology, New York University School of Medicine, SUNY Downstate Medical Center, Brooklyn, NY.

Background: Renal complications of sicle cell anemia (HbSS) include: a trend lower toward hyperfiltration in the HU group. 18.7% and 20.8% of patients have microalbuminuria and proteinuria, respectively, prevalences similar to that reported in untreated children.

Conclusions: Renal function is similar in children with HUS receiving either HU or CTx, and both groups have a high prevalence of SLCN progression in children with HBSS.
Development of Oxabact® for the Treatment of Primary Hyperoxaluria
Elisabeth Lindner, OxThera AB, Stockholm, Sweden.

Background: Primary Hyperoxaluria (PH) is a rare inborn error of the glyoxylate metabolism characterized by severe hyperoxaluria (10x >0.8 mmol/day/1.73m²) with clinical presentation of nephrocalcinosis with or without recurrent calcium–oxalate urolithiasis and deteriorating renal function leading to ESRD.

Methods: Oxabact® therapy consists of lyophilised Oxalobacter formigenes in an enteric-coated capsule for oral administration. O. formigenes is an anaerobic bacterium which only utilizes oxalate as its substrate and is naturally suited to degrade oxalate in the human GI tract. Based on extensive animal and clinical data it is hypothesised that Oxabact® treatment can remove endogenously produced oxalate in patients with PH by enteric elimination, thereby lowering the disease’s detrimental effect on kidneys.

Results: The Oxabact® treatment has been evaluated in a series of clinical studies in PH patients. Although earlier Phase I/II studies showed a significant reduction of urinary and plasma oxalate these results were not reproduced in larger multi-centric double blind placebo controlled trials. The outcome of the these studies was found to be related to significantly reduced biological potency of freeze dried bacteria used in said studies. Extensive research and improvement in the manufacturing process for Oxabact® was done in the last two years to produce the final formulation (OC5) which has a hundred fold improvement in its potency (increased concentration of live cells, faster regeneration from freeze dried state and higher oxidation degradation activity) as compared to the product used in unsuccessful studies.

Conclusions: OC5 has been tested for safety and efficacy in animal models and is currently being tested in a pivotal randomised, placebo-controlled, double-blind, multi-centre clinical trial in PH with type 1. Following screening and baseline evaluations eligible subjects have been randomised 1:1 to receive OC5 or placebo for a period of eight weeks. The study end points will evaluate reduction of oxalate in 24h urine and plasma; quantification of O. formigenes in the feces and the safety and tolerability of treatment. Successful outcome of this trial is expected to provide a significant annet medical intervention for PH patients.

Funding: Pharmaceutical Company Support - OxThera AB, Government Support - Non-U.S.

Possible Pathogenic Roles of Granzyme B in Peripheral Blood Mononuclear Cells in Pediatric Patients with Idiopathic Nephrotic Syndrome
Yuko Akioka, Tatsuo Asano, Keki Nishiyama, Noriko Sugawara, Kiyonobu Ishibashi, Yoshitaka Hisamoto, Motoshi Hattori. Pediatric Nephrology, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Granzyme B (GrB) is a serine protease released from cytotoxic lymphocytes. Recently, increased research has focused on extracellular GrB activity which contributes to a loss of structural integrity through the cleavage of extracellular matrix in a number of chronic inflammatory conditions. Several clinical studies showed a correlation between GrB expression and disease activity of the disease. The purpose of this study was to examine the possible pathogenic roles of GrB in idiopathic nephrotic syndrome (NS).

Methods: We examined 41 patients with steroid sensitive nephrotic syndrome (SSNS) and 10 patients with steroid resistant NS (SRNS). Sex- and age-matched 11 healthy subjects were also included. Peripheral blood mononuclear cells were isolated and polychromatolyzed lymphocytes. Recently, increased research has focused on extracellular GrB activity which contributes to a loss of structural integrity through the cleavage of extracellular matrix in a number of chronic inflammatory conditions. Several clinical studies showed a correlation between GrB expression and disease activity of the disease. The purpose of this study was to examine the possible pathogenic roles of GrB in idiopathic nephrotic syndrome (NS).

Results: In both SRNS and SSNS patients in relapse, the percentages of GrB-positive cells were significantly higher than those in healthy controls (11.6±9.0%, 15.6±10.2% vs. 5.1±3.1%, P<0.01, P<0.05, respectively). There were no differences in the percentages of GrB-positive cells in CD19 and CD56 cells between NS patients and controls. GrB vs. 5.1±3.1%, P<0.01, P<0.05, respectively). There were no differences in the percentages

Conclusions: In contrast to previous reports, hematuria and macroalbuminuria were rare in our patients with sickle cell disease and its variants while enuresis, microalbuminuria and hypertension were more common.

Do Immunosuppressed Renal Patients with Fever Need Routine Hospitalization?
Mauricio Romero Olvera, Rossana Baracco, Amrish Jain, Gaurav Kapur, Tej K. Mattoo. Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI.

Background: Immunosuppressed patients with high fever are often hospitalized until cultures are negative and temperature settles down. The objective of this study was to assess the need for such practice in our renal patients on immunosuppression.

Methods: This retrospective study included children 2 to 18 years old who were on immunosuppressive regimens due to nephrotic syndrome (NS), systemic lupus erythematosus (SLE) and renal transplantation (RT), admitted to Children’s Hospital of Michigan from 2009 – 2012 for fever >38.3°C. Patients with diabetes, cardiac–respiratory disease or lupus flares were excluded. Patients were considered as having a significant clinical deterioration (SCD) if emergency department evaluation revealed low blood pressure, tachycardia, abnormal cardiac or chest auscultation, abdominal tenderness, and abnormal test results. Those with normal examination except for high fever were considered as having insignificant clinical presentation (ICP).

Results: The study included 60 patients with 103 admissions. Mean age was 9.28 (SD=9.66) years; 59.2% were males. Of the 103 admissions, 52 were in patients with NS, 32 had RT, and 19 had SLE. Twenty four admissions had SCD (23.3%), which included 4 to PICU; 79 (76.6%) admissions had ICP.

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Sickle cell disease</th>
<th>Sickle cell trait</th>
<th>Sickle beta thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Microalbuminuria (albumin/creatinine ratio &gt;300 mg/g)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leukocytosis (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic kidney disease (defined as GFR &lt;60 ml/min/1.73m²)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions: In contrast to previous reports, hematuria and macroalbuminuria were rare in our patients with sickle cell disease and its variants while enuresis, microalbuminuria and hypertension were more common.

Primary Hyperoxaluria Presenting with Anemia, Thrombocytopenia and Acute Renal Failure
Luis A. Ortiz. Pediatric Nephrology - Pediatrics, Children’s Hospital of Georgia, Augusta, GA.

Background: Primary Hyperoxaluria (PH) is an AR inborn error of metabolism resulting in high oxalate production and excessive urine oxalate excretion, it is a deficiency in the liver peroxisomal enzyme alamine-glyoxylate aminotransferase that catalyzes the transamination of glyoxylate to glycine. Failure to detoxify glyoxylate results in its conversion into oxalate then the endogenous production and urinary oxalate and glycolate are elevated. It is 1% of pediatric ESRD.

Methods: Evaluation of a 5 y/o healthy w/g, she presented fatigue, abdominal pain and vomiting. Evaluation worked-up showed Hgb 6.7, platelets 133; K 4.2, HCO3 14, BUN: 210mg, Cr 11.67mg. She was drinking one gallon of milk/day for the last 3 years. Her physical exam was unremarkable with BP: 93/55 and UOP 2.3ml/kg/hr. CxR: bilateral nephrocalcinosis, 11.67mg Cr. DsDNAab, pANCA, cANCA were negative; Stool for E. coli 0157 H7 were negative; 902A and WBC 10,000.

The Oxabact® treatment has been evaluated in a series of clinical studies in PH patients. Although earlier Phase I/II studies showed a significant reduction of urinary and plasma oxalate these results were not reproduced in larger multi-centric double blind placebo controlled trials. The outcome of the these studies was found to be related to significantly reduced biological potency of freeze dried bacteria used in said studies. Extensive research and improvement in the manufacturing process for Oxabact® was done in the last two years to produce the final formulation (OC5) which has a hundred fold improvement in its potency (increased concentration of live cells, faster regeneration from freeze dried state and higher oxidation degradation activity) as compared to the product used in unsuccessful studies.

The study included 60 patients with 103 admissions. Mean age was 9.28 (SD=9.66) years; 59.2% were males. Of the 103 admissions, 52 were in patients with NS, 32 had RT, and 19 had SLE. Twenty four admissions had SCD (23.3%), which included 4 to PICU; 79 (76.6%) admissions had ICP.
Serum Alanine: Glyoxylate Aminotransferase (AGXT) mutation full gene analysis was (+). Bone marrow biopsy, bone serial x-rays, eye exam were negative. Treatment with Low oxalate diet, PO fluid intake of 2 L/m2 day, pyridoxine (B6) 5mg/kg and daily hemodialysis (3-4 hours/day) avoided extra renal damage, but renal function was not recovered.

Conclusions: Clinical presentation in PH was very atypical. Nephrocalcinosis was a significant finding for the diagnosis. Early kidney Bx was the best procedure for final diagnosis (<36 hours). There was a delayed in the crystal precipitation in other tissues/or organs because of the high amount of Calcium she was drinking with the milk. Aggressive dialysis with low oxalate diet was the best procedure to avoid oxalate precipitation.

**PUB123**

**Why Pedriatricians Fail to Diagnose Hypertension: A Multicenter Survey**

Arend Bokenkamp,1 Merijn Bijlsma,2 Hester Blufpand,3 Gert-Jan Kaspers.3

1Pediatric Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; 2Pediatrics, VU Univ Medical Center, Amsterdam, Netherlands; 3Pediatric Oncology, VU Univ Medical Center, Amsterdam, Netherlands.

**Background:** It has become clear that adult hypertension begins in childhood and contributes to the development of cardiovascular disease. Early recognition and intervention may slow down the progression of elevated blood pressure (BP) to cardiovascular disease. Recent studies indicate that the majority of hypertensive cases are unrecognized. The purpose of this study was to elucidate why pediatricians fail to diagnose childhood hypertension, with special emphasis to the use of reference data. We hypothesized that pediatricians frequently omit to measure BP and do not routinely relate BP measurements to reference data.

**Methods:** Multicenter questionnaire survey among 197 pediatricians, pediatric residents and medical students in the Netherlands about their daily practice of BP measurement and the use of pediatric BP reference tables. Furthermore, respondents were asked to estimate BP percentiles and classify BP readings in 12 short clinical cases (6 normal BP, 2 pre-hypertension, 4 hypertension).

**Results:** 71% of physicians only measure BP during ambulatory visits if a child has risk factors for hypertension. After measuring BP, 65% compares the reading to reference data only if they suspect it to be elevated. However, their ability to rate a reading at its true value was limited. Forty-seven percent of the physicians categorized one or more of the prehypertensive or hypertensive cases as normal.

**Conclusions:** Most pediatricians only measure BP in certain circumstances, contrary to recommendations. After obtaining a BP measurement, the majority does not compare the reading to reference standards. Without the use of reference data, however, they commonly underestimate the BP percentile and potentially miss childhood hypertension. The introduction of automated blood pressure monitors that directly report blood pressure percentiles might improve the recognition of childhood hypertension.

**PUB124**

**Genetic Control of Renin Angiotensin System and Extracellular Matrix-Related Protein Polymorphisms Obese Preschool Children**

Kei Hwan Yoo, Hyung Eun Yim, In Sun Bae, Young Sook Hong, Joo Won Lee. Pediatrics, Korea Univ Medical Center, Seoul, Korea.

**Background:** We have recently shown that postnatal overnutrition in male rats leads to obesity and the acquired reset of the intra-renal renin system (RAS) and of extracellular matrix (ECM)-linked moleculardauer renal maturation. Long-standing obesity, renal functional and structural impairment, and hypertension were programmed later in adulthood. This study was designed to investigate whether genetic polymorphisms of RAS and ECM-linked proteins were associated with the susceptibility to obesity in childhood.

**Methods:** We performed the genotyping of angiotensin converting enzyme (ACE), angiotensinogen (AGT), angiotensin type 2 receptor (AT2), matrix metalloproteinase (MMP-9), and plasminogen activator inhibitor (PAI-1) proteins in 46 obese, 48 overweight, and 96 control children using PCR-restriction fragment length polymorphism analysis.

**Results:** The mean age was 22.3 ± 1.5 months in controls, 17.3 ± 2.19 months in overweight children, and 24.2 ± 2.96 months in obese children. No differences among the groups were found with respect to age, sex, gestational age, birth weight, blood pressure levels, and serum levels of glucose and cholesterol. Obese children showed a lower incidence of ACE II genotype, compared to the controls (Control 46.8% Vs. Obese 15.6%, P < 0.05). Overweight children had a higher incidence of MM genotype in the AGT M235T polymorphism (Control 2.1% Vs. Overweight 16.7%, P < 0.05). In the case of combination of overweight and obese children, a higher incidence of MM genotype in the AGT M235T polymorphism was found compared to the controls (Control 2.1% Vs. Overweight + Obese 10.6%, P < 0.05). There were no genotype differences of the AT2 C3212A and the PAI-1 4G/5G polymorphism among the groups.

**Conclusions:** The ACE I/D, AGT M235T, and MMP-9 C1562T polymorphisms could be suitable genetic markers for development of overweight or obesity of childhood.

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

**PUB125**

**Eculizumab (Anti C5 Monoclonal Antibody) in a Child with Therapy Resistant Systemic Lupus Erythematosus**

Rosanna Coppo,1 Alessandro Amore,2 Lucia Peruzzi,1 Roberta Camilla,1 Maria Elena Donadio,1 Giuliana Guido,1 Luca Vergano,1 Silvana Martino,2 Pier angelo Tovo.1 Nephrology Dialysis Transplantation, Regina Margherita Hospital, Turin, Italy; 2Pediatrics, Univ of Turin.

**Methods:** A 4 y girl presented with extremely severe systemic lupus erythematosus (SLE) (SLEDAI score: 42; C4<4 mg/dl, C3 <20 mg/dl, ANA 1/640; anti DNA >400 UI/ml; lupus nephritis Class IV,C, e-GFR 120ml/min/1.73m2, UP/UCr 15mg/mg). The symptoms slightly improved after 3 MP pulses, prednisone, 9 plasmapheresis, cyclophosphamide (withdrawn due to leukopenia) followed by cyclosporine. Three months later she worsened: e-GFR 60ml/min/1.73m2, UP/UCr 6 mg/mg. In spite of Rituxumab 1g/1.73m2 and MP pulse, SLEDAI increased to 63 (hypertension, seizures, numbness, O2 desaturation, pleural effusion). Platelets (Plts) 55,000/mm3, aprotoglobin <10 mg/dl, neg LAC, e-GFR 60ml/min/1.73 m2, UP/UCr 7mg/mg. After eculizumab 20 mg/Kg, she had impressive improvement in general conditions with normalization of Plts, aprotoglobin and e-GFR increase to 140 ml/min/1.73m2. Eculizumab was repeated over 2 months, then stopped. Rituxumab was infused but immediately stopped for severe adverse reaction. A new attempt to use cyclophosphamide was interrupted because of leukopenia. 9 plasmaphereses were performed, but renal conditions worsened (e-GFR 50 ml/min/1.73m2, UP/UCr 8) with a new e-GFR 70,000/mm3, aprotoglobin 110 (LAC neg). A repeated bone marrow biopsy confirmed Class IV nephritis without any sign of thrombotic microangiopathy. However, when eculizumab was re-introduced (20 mg/Kg) a prompt improvement was observed with normalization of aprotoglobin level, Plts count and e-GFR. The child was followed for 4 months on maintenance treatment with cyclosporin, prednisone and eculizumab every other week. SLE data remained unchanged over the follow-up (C4 <4 mg/dl, C3 30 mg/dl, ANA 1/640, Anti DNA >400 UI/ml), however e-GFR is 138 ml/min/1.73 m2, UP/UCr 7mg/mg.

**Conclusions:** This is the first case reporting a beneficial effect of C5 inhibition as rescue therapy in a SLE refractory to the standard therapies.

**PUB126**

**Hydrothorax, a Serious Complication of Infants on Peritoneal Dialysis – Can We Identify Risk Factors**

Michaela Gossner, Christina Taylan, Gesa Schalk, Rasmus J.C. Ehren, Lutz Thorsten Weber. Dept of Child and Adolescent Medicine, Univ Hospital, Cologne, Germany.

**Methods:** Approximately 150 children suffer from end-stage renal disease requiring renal replacement therapy in Germany every year. Due to congenital kidney disease 2/3 of them are still in infancy at initiation of therapy, which is most commonly peritoneal dialysis (PD) in this age group. Besides infections another serious complication of this procedure is the development of a hydrothorax, possibly due to an embryonic remnant of a persisting pneumatoenteric recess or an infracardiac bursa, a passage connecting the peritoneal cavity to the right pleural space.

**Results:** In this single center analysis all infants that had started PD in their first year of life between 2002 and 2012 were included (n=19). Infants with short-term PD treatment due to acute renal failure were excluded. All infants had a minimal duration of PD of four months. PD catheters were inserted by laparotomy. Median initiation of PD was at the ninth day of life (range: second day to ninth month).

**Results:** 3 of 19 infants were symptomatic with a hydrothorax at a median of 49.5 weeks (range: 33.6-72.1) after start of PD treatment, finally leading to long-term change of treatment modality in 2/3. All affected infants had been born prematurely. However, another 11 premature infants in this group did not show this complication. There was no hydrothorax in 5 term deliveries. Hydrothorax occurred independently from previous abdominal surgeries, the occurrence of catheter obstruction, birth weight, mode of delivery, ARF, score, age at initiation or duration of PD. However, this complication appeared in 3/6 preterm infants of Turkish origin.

**Conclusions:** This analysis failed to determine risk factors for the incident of hydrothorax after initiation of PD treatment in infants. The overall risk in our cohort was 15% and 21% in preterm infants, respectively. This finding was reported in literature (3%), which reviews other cohort compositions regarding age of children. Since preventive actions do not exist, physicians must be aware of this serious complication for the purpose of early detection and treatment, especially in preterm infants.
Reducing Central Venous Catheters in Children on Chronic Hemodialysis

Maria Eugenia V. Bianchi,1 Gustavo A. Velasco,1 and without Overweight

Roberta A. Estrada,2 Allan D. Kirk,3 Sandra Amaral,1 Vikas R. Dhundharkar,4 Daniel Feig,5 Bishu Ganguly,6 Charlotte Jones-burton,6 UCLA, US; Emory Univ, Atlanta, GA; Children's Hosp Philadelphia, Philadelphia, PA; Washington Univ, US; Univ of Alabama, US; BMS, US.

Background: Belatacept (bela) is approved for use in prevention of acute rejection (AR) in adult EBV-seropositive(+) kidney transplant (TX) recipients. In 2 phases of trials, bela was associated with comparable pt & graft survival & superior renal function despite higher rates & grades of early AR vs cyclosporine. The current study, the first study of bela in children, will determine if similar results occur in pediatric kidney TX recipients. Study objectives are to establish dose & evaluate PK, efficacy, & safety in pediatric conversion.

Methods: In this global multicenter study, 54 kidney TX recipients, currently on CNI-based immunosuppression (IS), will be studied in 2 groups: adolescents (age 12-17y) & children (age<12y). Pts will be ≥ 1 yr post-TX, have ≥ 1 gFR of 45-75 mL/min/1.73m2 & be EBV+ both at TX & start of study. Study will be conducted in 3 phases: 1) uncontrolled single dose phase (SD) to determine PK parameters & appropriate dosing for bela in each age group; 2) multiple dose phase (MD): pts randomized 2:1 to convert from CNI to bela or remain on CNI for 12 months; 3) long term extension phase (LTE). Enrollment will be staggered, with adolescents (N=9) starting SD first; adolescent PK results will inform dosing in this group for MD & also in the younger group for SD (N=6). All pts in SD will continue to receive all maintenance IS (steroids optional). In MD, CNI will be discontinued for pts in the bela arm.

Results: PK & safety determinations will be assessed in all pts in SD & MD. Outcomes to be examined during MD & LTE include the evolution of the eGFR by the updated Schwartz formula, AR, graft loss, & safety (including PTLD) in bela & CNI arms. Maintenance adherence & quality of life will also be explored.

Conclusions: This controlled multicenter trial will provide dosing & PK information, as well as initial efficacy & safety information about bela in stable EBV+ children & adolescents following kidney TX.

PUB129

Relationship between Birth Weight and Renal Volume in Children with and without Overweight

Marilia E. Biasi,1 Gustavo A. Velasco,2 Daniel Fortino,3

Argentinian Northeast Kidney Foundation, Resistencia, Chaco, Argentina; 2Radiology, Facultad de Medicina Unne, Corrientes, Argentina.

Background: Determination of renal volume by ultrasound (ERV) is considered an indirect indicator of the number of nephrons. As it know the number of nephrons can be considered an independent risk factor for the development of hypertension, and taking into account that low birthweight has been associated with a low kidney volume, we evaluate differences in renal volume in schol children with and without overweight and its relationship to birthweight.

Methods: We performed a cross-sectional observational study with non-probability sampling, in children of school of the Province of Chaco, by his guardian consent. The variables considered were: Nutritional Status by BMI according to WHO tables (overweight and without overweight), referred Birthweight, and its relationship with SC and renal volume. We evaluated the differences in renal volume and SC by children with and without overweight and its relationship to birthweight.

Results: We evaluated 1,842 children, at least 1 gap >180 days between IR-C data collection. The mean age was 4.5 years, with an overall MPR of 79%. The MPR declined by age group: 88% (0-5 yrs); 80% (6-10 yrs); 74% (11-15 yrs); 67% (16-20 yrs). There was a higher MPR (95%) vs. those w/out this diagnosis (83%).

40%, respectively. In pts 0-5 yrs, a diagnosis of failure to thrive (22/34 pts) was associated with a higher MPR (95%) vs. those w/out this diagnosis (83%).
69 of 97 pts (71%) born before the approval of IR-cysteamine reached ESRD; 8 of 93 (9%) and 29 of 93 (31%) pts born from 1994 to 2006 achieved CKD stage IV and ESRD, respectively. The median age for ESRD post approval of IC-cysteamine was 12 yrs (range 1 – 16).

Conclusions: Claims data is a novel approach for assessing long-term adherence to cysteamine in patients with cystinosis. Adherence with IR-C according to IMS claims with cystinosis shows a low and declines with age. Future analysis will correlate adherence with health outcomes, and analyze changes in adherence following the recent introduction of delayed release cysteamine (q12h dosing formulation). Efforts to improve adherence in this population are needed.

Funding: Pharmaceutical Company Support - Raptor Pharmaceuticals

PUB132

Anhydramnios in Fetal Nephropathy: A Non Conventional Indication to Amnioinfusion. Second Work of Mercy: To Give Drink to the Thirsty Gianluigi Ardissino,1 Roberto Fogliani,2 Sara Testa,1 Nicola Persico,1 Francesca Tel,1 Simona Boi,2 Sarah Salmona,2 Fabietta Isabella,2 Maria albina Galli,3 1Pediatric Nephrology, Fondazione IRCCS Ca’ Granda Osp Maggiore Policlinico; 2Obettries and Gynecology, Fondazione IRCCS Ca’ Granda Osp Maggiore Policlinico; 3Pediatric Cardiology, Fondazione IRCCS Ca’ Granda Osp Maggiore Policlinico.

Background: Oligohydramnios, complicating 4-5% of all pregnancies, may occur in some fetal nephropathies. When present in association with fetal kidney diseases, it predicts a more severe postnatal prognosis for it anticipates congenital reduction of renal function. Most of congenital nephropathies are characterized, soon after birth, by significant poluria and, consequently, by increased needs of fluid which, if unmet, are responsible for worsening of renal function. In case of oligohydramnios the fetus might not count on an adequate amount of drinking fluid possibly leading to fetal dehydrosis and consequent further reduced renal function.

Methods: A pregnant woman who presented with anhydramnios from the 32nd wk of gestation, with severe fetal bilateral hypoplastic kidney and repeatedly documented empty bladder, was addressed to 2 amnioinfusions (saline total 750cc) for providing the fetus with the fluid normally swallowed during late pregnancy (around 100 cc/kg/day) with the working hypothesis of rehydrating the fetus, improving renal perfusion, preventing further deterioration of renal function and eventually for reversing fetal anuria.

Results: Soon after the amnioinfusion a significant increase in the bladder volume (from 18 to 54 mm3) was observed indicating that fetal diuresis had restarted; this was associated with a doubling of both right (from 0.6 to 1.4 mL) and left (from 0.4 to 1.1 mL) cardiac output.

Conclusion: It is speculated that anhydramnios in fetal nephropathies may be responsible for further reduction of renal function secondary to fetal dehydration and that amnioinfusion may revert this functional worsening.

PUB133

Nephrotic Medication Exposure in Very Low Birth Weight Infants Erika Rhone,1 J. Bryan Carmody,1 Jonathan R. Swanson,2 Jennifer Richardson Charleston,1 1Pediatrics, Div of Pediatric Nephrology, Univ of Virginia, Charlottesville, VA; 2Pediatrics, Div of Neonatology, Univ of Virginia, Charlottesville, VA.

Background: Nephrogenesis continues until 36 weeks gestation, meaning that many very low birth (VLBW) infants must complete development ex utero. While potentially nephrotic medications (NM) are commonly used in the neonatal intensive care unit, the extent of exposure among VLBW infants has not been established. We sought to quantify NM exposure among VLBW infants in a Level III NICU.

Methods: We retrospectively reviewed the electronic medical record of VLBW infants (n=107) admitted from April 2011 to March 2012, excluding those admitted at >2 d of age or who died during hospitalization. Exposure to the following was calculated in person days; median 244; range 1-3764). APPD measurement at baseline demonstrated positive predictive value (PPV) for surgery of 50.8% (sensitivity 55.2%; specificity 79.7%) and SFU grading demonstrated a PPV for surgery of 54% (sensitivity 81.5% and specificity 73.7%). Logistic regression showed no statistical significance between APPD and SFU grading for predicting surgery at baseline (APPD: OR 2.72, CI 95% 2.06-3.36, p value 3; SFU: OR 3, CI 95% 2.5-3.8, p value 1.3). Combined APPD and SFU grading (Group 1: APPD<12 mm + SFU 0-2; Group 2: APPD< 12 mm + SFU 2-4; Group 3: APPD>12 mm + SFU 0-2; and Group 4: APPD>12 mm + SFU 3-4) showed higher PPV of 60% (sensitivity 34.2% and specificity 91.3%) but did not improve accuracy for predicting surgery when compared to SFU and APPD alone (OR 3, CI 95% 2.5-6.1, p value 1.9).

Conclusion: These data suggest that neither APPD or SFU grading alone, nor a grading system which combines both methods are good predictors for surgery at baseline. Our future analyses are aimed at determining whether accuracy for predicting surgery is improved by evaluating interval changes in APPD and/or SFU over time.

PUB135

Successful Remission of Treatment-Resistant Minimal Change Disease with Adrenocorticotropic Hormone Gel M. Khurram Faizan,1 Ruchir S. Patel,2 1Dept of Pediatrics, Hasbro Children’s Hospital; 2Dept of Medicine, Rhode Island Hospital, Providence, RI.

Background: Adrenocorticotropic hormone (ACTH) has historically been used to treat pediatric nephrotic syndrome (NS) and also received FDA approval for the treatment of NS in the 1950’s. It fell out of favor with the advent of oral steroids. Recent case reports and small case series reporting the successful use of ACTH has rekindled interest in its use for treatment of NS resistant to conventional immunosuppression.

Methods: We report a 19 yr old Caucasian female with frequently relapsing, treatment resistant NS who achieved remission with purified porcine ACTH (ACTHAR Gel®) treatment. Patient was diagnosed with NS at age 10. Two renal biopsies 5 yrs apart showed minimal change disease. Clinical course was complicated by numerous relapses despite chronic steroid and CNI therapy, severe dyslipidemia, and episodes of anasarca requiring IV albumin and furosemide. PMH: Significant for splenic infarct at age 14 and restrictive eating disorder. ROS: Positive for intermittent swelling, fatigue, and anorexia. Medications: Prednisone 10 mg, Tacrolimus 4 mg BID, Losartan 25 mg, Lisinopril 10 mg, Simvastatin

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

Underline represents presenting author.
40 mg, Penicillin V 250 mg BID. Vital signs: BP 122/81, Pulse 104, afebrile. Weight 51 kg, BMI 20.64. Physical exam: No lower extremity edema. Table 1 shows labs at baseline and post-treatment. ACTH was started at 40 units SQ twice a week for 6 moths. Tacrolimus and prednisone were tapered.

Results: Our patient underwent prompt remission of proteinuria and marked improvement in lipid levels, did not experience any side-effects, and remains on ACTH (Table 1). Subjectively, she reported improvement in her mood, energy and self-esteem.

Table 1:

<table>
<thead>
<tr>
<th>Proteinuria (mg/dl)</th>
<th>Before</th>
<th>AT1H</th>
<th>8 Wks</th>
<th>12 Wks</th>
<th>24 Wks</th>
<th>30 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGC</td>
<td>9.82</td>
<td>1.82</td>
<td>0.60</td>
<td>0.18</td>
<td>0.08</td>
<td>0.02</td>
</tr>
<tr>
<td>TGFβ</td>
<td>306</td>
<td>10</td>
<td>0.10</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Interferon (ng/ml)</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Time Protein/ Treatment Ratio</td>
<td>1.55</td>
<td>0.16</td>
<td>0.62</td>
<td>0.18</td>
<td>0.30</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Conclusions: Our report suggests that ACTH may be an important alternative in patients with challenging and difficult to treat NS due to minimal change disease. However, long term efficacy and side-effects remain unknown. Large scale prospective studies are needed to further validate our observation.

PUB136

Effect of Angiotensin II Type 1 Receptor Blocker on the 12-Lipoxygenase Activation and Slit Diaphragm Protein Expression in Type 2 Diabetic Rat Glomeruli


Background: 12-lipoxygenase (12-LO) is implicated in the development of diabetic nephropathy, in which the proteinuria is thought to be associated with a decrease of glomerular slit diaphragm protein. Recently, it was demonstrated that nephrin expression, but not p-cadherin expression, varies among the different sizes of glomeruli under type 2 diabetic conditions. Furthermore, the decreased expression of nephrin in the hypertrophied glomeruli in diabetic rats may be responsible for the albuminuria at the early stage of diabetes. In this study, we investigated the effect of angiotensin (AngII) type 1 receptor blocker (ARB) on 12-LO activation and slit diaphragm protein expression in type 2 diabetic rat glomeruli.

Methods: Podocytes were stimulated by AngII for 24 hours. 12-LO product 12(S)-HETE and AngII were infused to rats by osmotic mini-pump for 1 week and 2 weeks respectively. Rats fed high fat diet were received low dose streptozotocin (STZ) to make type 2 diabetes and divided into 2 groups: low dose STZ(DN), low dose STZ+ARB treatment (Losartan). Rats fed regular chow were as control group (Ctrl). All rats were sacrificed after 25 weeks of the injection.

Results: Relative abundance of 12(S)-HETE expression in type 2 diabetic rats was 0.57±0.11 in Ctrl and 0.35±0.05 in Losartan group; collagen type IV expression was 3.57±0.7 in Ctrl and 2.51±0.3 in Losartan group; nephrin expression in control group was 0.67±0.15 and 0.34±0.09 in Losartan group.

Conclusions: Our results suggest 12-LO activation and nephrin expression are increased in type 2 DN rat.

PUB137

The Effect of High Glucose Exposure on Iron Induced Cytotoxicity and the Protective Role of Carnosine

Sibylle Jenny Hauske, Emmanouil Ntakis, Eleni Stamellou, Shiqi Zhang, Bernhard K. Krämer, Benito Yardi. Vih Medical Dept, Medical Faculty Mannheim, Univ of Heidelberg, Germany.

Background: It is generally believed that diabetic complications are oxidative stress mediated. The production of mitochondrial derived reactive oxygen species (ROS) seems to play a pivotal role herein. Recently it has also been discussed that increased intracellular iron accumulation, occurring under high glucose conditions (HGC) may lead to additional oxidative stress.

Methods: In keeping with the postulated protective role of L-carnosine (CAR) in diabetic complications we sought to assess in this study: 1) if HG exposure makes cultured HGC (30mM) in the presence or absence of 20mM CAR. Hereafter the cells were challenged with iron mediated toxicity. The protective effect was not related to quenching of ROS. In keeping with the poor expression of PEPT1 and PEPT2 on HUVVEC our data indicate that the protective effect of CAR most likely resides outside the cells, possibly via a mechanism that involves iron chelation.

Funding: Government Support - Non-U.S.

PUB138

Aggravation of Diabetic Nephropathy in OLETF Rats with thy-1 Nephrin Mutation

Motoo Watanabe, Hiroshi Nakashima, Kenji Ito, Yasuhiro Abe, Satoru Oghara, Takao Saito. Div of Nephrology and Rheumatology, Dept of Internal Medicine, Faculty of Medicine, Fukuoka Univ, Fukuoka, Japan.

Background: OLETF rat was established as an animal model of human type 2 diabetes. We previously reported increased expression of pgem regulatory factor , ICAM-1, MCP-1, Collagen type III, IV, VI, IL-6, TGF-beta, Angiotin III,VEGF, collagen type IV and type VI, CD68 and TGF-beta in the kidney with immunohistochemical technique. The same procedures were performed in 2 groups of LETO rats, a non-diabetic strain of OLETF rat.

Results: Relative abundance of ICAM-1 mRNA normalized by beta-actin were 0.52±0.03 in LETO rats and 0.26±0.02 in Groups T and C, respectively (p<0.05). The abundances of Collagen type III expression were 0.57±0.11 and 0.35±0.05; Collagen typeIV were 0.18±0.03 and 0.12±0.01 in LETO rats, 5.19E-5±2.00E-5 in Groups T and C, respectively (p<0.05 in all assays). In Group T, Smad1, NF-kB, GLUT1, RAGE were higher than that in Group C, but they were not significant between groups T and C. Histologically, collagen type VI collagen positive area were increased by OX7 administration.

Conclusions: The inflammatory changes induced by anti thy1.1 antibody may be irreversible in the diabetic conditions of OLETF rats and accelerate the production of collagen type III and IV for aggravating diabetic nephropathy. These mechanisms may be applied to the advance of diabetic nephropathy by glomerulonephritis in human, eg. IgA nephropathy.

PUB139

Activation of Renin-Angiotensin System Is Involved in Fatty Acid Induced ER Stress in the Kidney

Chunling Li, 1 Yu Lin, 2 Renfei Luo, 2 Moshe Lev1, Tianxin Yang, 1, 2 Yidong Wang. 1 Institute of Hypertension and Kidney Research, Sun Yat-sen Univ, Guangzhou, Guangdong, China; 2Renal Div, Univ of Colorado Denver, Aurora, CO; 3Dept of Internal Medicine, Univ of Utah and Veteran Affairs Medical Center, Salt Lake City, UT.

Background: Free fatty acids (FA) are critically involved in the pathogenesis of diabetic nephropathy, and renal proximal tubule cells are an important site for the onset of DN.

The objectives of this study were to elucidate the role of renin-angiotensin system (RAS) activation in FA-induced endoplasmic reticulum (ER) stress in cultured human proximal tubule epithelial cells (HK2) and in mice fed with high-fat diet.

Methods: Treatment with saturated FA palmitic acid (PA, 1mM) for 24h induced HK2 ER stress, leading to an unfolded protein response as reflected by increased expressions of the ER chaperone Bip (4.23±0.54 in PA vs. 1.00±0.20 in controls, p<0.05) and proapoptotic transcription factor CHOP (9.06±0.36 in PA vs. 1.00±0.26 in controls, p<0.05) as evaluated by immunoblotting. PA treatment increased induced protein expression of IRE1alpha (3.44±0.46 in PA vs. 1.00±0.16 in controls, p<0.05) and phosphorylation of eIF2alpha.

Conclusions: It was suggested that the intrarenal RAS activation may play an important role in renal injury via mediating ER stress induced by fatty acid.

Funding: Government Support - Non-U.S.

PUB140

mPGES-2 Deletion Improves Glucose Metabolism but Enhances Streptozotocin-Induced Liver Toxicity

Ying Sun, 1, 2 Zhanjuan Jia, 1, 2 Kevin Yang, 1, Mi Liu, 1 Tianxin Yang, 1, 2 Internal Medicine, Univ of Utah, Salt Lake City, UT; 1VA Medical Center, Salt Lake City, UT.

Background: Microsomal prostaglandin E synthase-2 (mPGES-2) deletion doesn’t influence PGE2 production in vivo and the function of this enzyme remains elusive.

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

Underline represents presenting author.
Methods: We examined a possible role of mPGES-2 in glucose metabolism using mPGES-2 KO mice. Results: The IOD of DH group were given Dan Hong-injection intravenously (2ml/kg) daily for two weeks, showed a decrease in proteinuria (P<0.05) compared to the NS group. Conclusion: The present study might show that down-regulated TRPM6 in DCT would be a principal cause of hypermagnesuria in diabetic nephropathy. Suppression of NNCC might be involved in the TRPM6 down regulation. The elevation Mg excretion in diabetes might be independent of renal interstitial damage.

PUBI43

Down-Regulation of TRPM6 and NCC in Diabetic Nephropathy as a Principal Cause of Hypermagnesuria Hypomagnesaemia in Diabetes


Methods: to investigate the molecular mechanism of the hypermagnesuria in diabetic nephropathy, and the involvement of interstitial damage because renal interstitial damage is not rarely associated with hypomagnesaemia.

Results: Absolute Mg excretion in F were significantly high in 24 and 34 weeks (0.16±0.01 in 24L, 0.28±0.01 in 24F, 0.18±0.02 in 34L, 0.29±0.04 μg/min/100g BW in 34F), showing significant hypermagnesuria from the early stage of diabetic nephropathy. Gene expressions of TRPM6 and NNCC were significantly reduced in F (reduction rate in TRPM6: 73.8% in 24 week, 78.3% in 34 week, 75.3% in 34 week, whereas the expressions of claudin-16 in TAL were not significantly changed. Expression of molecular markers for interstitial damage, such as MCP-1, α-SMA were not different between F and L in all experimental periods in compatible with the histological assessment of interstitial damage. Present study might show that down-regulated TRPM6 in DCT would be a principal cause of hypermagnesuria in diabetic nephropathy. Suppression of NNCC might be involved in the TRPM6 down regulation. The elevation Mg excretion in diabetes might be independent of renal interstitial damage.

PUBI44

Study of TGFBI -509C>T Polymorphism Association with Diabetic Nephropathy Development in TID Patients


Background: Diabetic nephropathy (DN) is the most common cause of end-stage renal disease. DN manifestations may be a consequence of transforming growth factor beta 1 (TGF-B1) actions, since it promotes renal cell hypertrophy and stimulates extracellular matrix production. In this way, we aimed to investigate TGFBI -509C>T polymorphism association with DN development patients with type 1 diabetes (TID) from Natal-RN/Brazil.

Methods: TGFBI -509C>T polymorphism was analyzed in 156 TID patients and 188 normoglycemic (NG) subjects, aged between 6 to 20 years. Glucose, glycated hemoglobin, creatinine, urea, albumin-to-creatinine ratio (ACR), serum lipids and TGFBI mRNA expression were evaluated.

Results: TID patients showed increased levels of urea (mg/dL) [NG: 22 (19-27) and TID: 29 (22-33); p<0.001] and ACR (mg/g of creatinine) [NG: 6 (4.7-9.7) and TID: 7.7 (5.2-16.1); p<0.001], compared to NG subjects. No association was found for TGFBI -509C>T with markers of kidney damage development in TID patients (Table 1).

Table 1 - Relationship between TGFBI -509C>T genotypes and biochemical parameters of TID patients

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Glucose</th>
<th>Hemoglobin</th>
<th>Creatinine</th>
<th>Albumin</th>
<th>ACR</th>
<th>TGFBI mRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>wild</td>
<td>4.8±0.40</td>
<td>139±10</td>
<td>1.8±0.2</td>
<td>10±5</td>
<td>0.02</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>509T</td>
<td>7.0±1.0</td>
<td>154±12</td>
<td>2.1±0.3</td>
<td>13±8</td>
<td>0.04</td>
<td>1.2±0.2</td>
</tr>
</tbody>
</table>

Results are mean±SEM.
Conclusions: Our results show no evidence of association between TGFBI -309C>T polymorphism and markers of diabetic nephropathy development.

Funding: Government Support - Non-U.S.

PUB145

Anti-Apototic Effects of Green Tea Extracts on Streptozotocin-Induced Diabetic Nephropathy in Mice

Byung Chul Shin, Jong Hun Back

Department of Internal Medicine, Chosun Univ Hospital, Gwangju.

Background: Diabetic nephropathy is the most common cause of end-stage renal disease and is characterized by glomerulosclerosis and tubulointerstitial fibrosis, associated with increased albuminuria. Green tea extracts (GTE) have antioxidant properties and is responsible for the renoproteinosis. We examined whether GTE could ameliorate the development of diabetic nephropathy and its role of antiprot改变了 effects.

Methods: The mice (n=40) were divided into 4 groups. Control group (n=10) was intravenously injected with 150mg/kg normal saline; Streptozotocin (STZ) group (n=10) was IP injected with STZ 200mg/kg and induced diabetic nephropathy. GTE group (n=10) was received 0.1% GTE by oral route from 4 weeks to 16 weeks. STZ plus GTE group (n=10) was received with same dose. Serum glucose, blood urea nitrogen, serum creatinine, urine volume and urine protein amounts were measured at 16 weeks. Western blot assay of p53, caspase-3, cleaved caspase-3, caspase-7 were compared for the different groups. Histopathologic examination and immunohistochemical staining of mice kidney were performed.

Results: Compared with control group, STZ-group showed an increase in blood glucose and albuminuria. GTE treatment significantly reduced albuminuria and urine protein amounts, and a decrease in body weight. All the above parameters were significantly reversed with GTE treatment. After STZ injection, there were a diabetic glomerulosclerosis with increased caspase-3 and caspase-7. In GTE-treated mice kidney, shown a reduced expression of above parameters and the reserved pathologic findings.

Conclusions: GTE can inhibit progression of STZ-induced diabetic nephropathy by reductions in caspase-3 and caspase-7 activities. These results suggest that GTE ameliorates STZ-induced diabetic nephropathy by apoptosis suppression.

PUB146

Remission of Diabetes and Hypertension Accompanying Rapid Weight Reduction following Bariatric Surgery

Anil K. Mandal,1 Linda M. Hiebert.1

1Univ of Florida, Gainesville, FL, 2Univ of Saskatchewan, Saskatoon, Canada.

Background: Obesity and diabetes go hand in hand. Diabetes control is difficult to accomplish because of insulin resistance. Hypertension control also requires many and high doses of antihypertensive drugs. Remission of diabetes following gastric bypass surgery is reported (Arch Surg 2011; 146: 744-750).

Methods: This study reports a 52y obese male with progressive weight increase and uncontrolled diabetes of 10-12 years, despite intensive insulin therapy and variable hypertension control despite 4 line therapy. Gastric bypass surgery was recommended. Baseline weight of 207 lbs.; increased to 356 lbs., fasting blood glucose (FBG) and 2h postprandial blood glucose (2PPG) increased from 131 and 181 mg/dL to 147 and 263 mg/dL, respectively, despite 60 units of glargine insulin twice daily and regular insulin 5 units with each meal. Blood pressures (BP) ranged from low 130/80 to high 180/100 mmHg. Roux-en-y-Gastric bypass surgery performed in November 2011.

Results: At last visit, 18 months later, weight was 230 lbs. with a total weight loss of 262 lbs. Sitting BP was 120/60 with reduced BP medication. FBG and 2PPG were reduced to 102 and 85 mg/dL, respectively without insulin therapy. HbA1C varied from 7.8% to 9.3% with a mean 8.3% before surgery to mean 5.5% 18 months after surgery. Renal function is maintained normal.

Conclusions: Massive weight reduction following gastric bypass surgery restores normoalbuminemia even in insulin treated, long-term diabetes and simplifies BP control. Gastric bypass surgery is not a conventional therapy but should be considered when weight reduction, diabetes and BP control are at a crossroad situation.

PUB147

Circulating Irisin Level in Human Diabetic Cohorts; 11 Year Retrospective Cohort Study

Jin Joo Cha,1 Mi Jin Lee,1 Young Youl Hyun,2 Dae R. Cha,1 Jung Eun Kim,1 Miwha Lee,1 Hye Kyong Song,1 Young Sun Kang.1

1Nephrology, Korea Univ Ansan Hospital, Ansan, Kyunggido, Republic of Korea; 2Nephrology, Sungkyunkwan Univ Kangbuk Samsung Hospital, Seoul, Republic of Korea.

Background: Irisin, a novel myokine, has been proposed to induce browning of subcutaneous adipocytes. In humans, circulating irisin level was significantly decreased in obese and diabetic patients. Therefore, examined circulating irisin level and its associations with various complications of diabetes.

Methods: We performed a retrospective cohort analysis of 161 diabetic individuals followed up for approximately 11 years. Baseline circulating plasma level of irisin was measured using commercially available ELISA kit. The associations between the circulating irisin with variable metabolic parameters, microvascular and macrovascular complications were evaluated.

Results: The 161 patients (n=14, type 1 diabetes, n=147 type 2 diabetes, mean age 43.6±14.6, BMI 30.1±0.4 respectively) were analysed. There were no significant associations between circulating irisin levels and gender difference, the type of diabetes, body mass index, age, Patients with hypertension (n = 66) showed significantly decreased level of circulating irisin (649.09 ±661.9 vs 884.01± 792.27, p<0.04). There was no significant difference in irisin level among the CKD stages (using CKD-EPI equation), however there was a trend toward decrement as the stage advanced. (stage 1(n=62) 806.97±793.70, stage 2(n=58) 925.31±849.83, stage 3a(n=20) 690.73±522.96, stage 3b(n=12) 547.5±460.7, stage 4(n=10) 207.86±75.89). Biochemical irisin assessment was performed to evaluate the relative risks of irisin level with the development of micro- and macrovascular complications. The irisin level did not affect the risks of macrovascular complications. However, ince! Aced level of irisin (log irisin) significantly decreased the risk of retinopathy (Unadjusted RR 0.688, 95% CI 0.516-0.918, p=0.01, Adjusted RR 0.677, 95% CI 0.487-0.942, p=0.02).

Conclusions: Circulating irisin level of diabetic patients was not affected by renal insufficiency nor did not affect diabetic nephropathy. It might have a predictive role in diabetic retinopathy.

PUB148

The Association of Glypican-4 with Diabetic Complications in Korean Population

Mi Jin Lee,1 Jin Joo Cha,1 Young Youl Hyun,2 Dae R. Cha,1 Jung Eun Kim,1 Miwha Lee,1 Hye Kyong Song,1 Young Sun Kang.1

1Nephrology, Korea Univ Ansan Hospital, Ansan, Republic of Korea; 2Nephrology, Sungkyunkwan Univ Kangbuk Samsung Hospital, Seoul, Republic of Korea.

Background: Glypican-4(Gps4) is an adipokine, which is known to be important for adipocyte differentiation by interacting with and regulating insulin receptor activation and its downstream signaling. Serum Gps4 is known as a marker for BMI and insulin sensitivity in mice and human. But it is uncertain that the association of Gps4 with diabetic complications.

Methods: We investigated the association of serum Gps4 level with diabetic complications in a prospective cohort of 161 Korean diabetic patients from 2002 to 2013.

Results: In Univariate regression analysis, glycemic variability, estimated GFR was negatively correlated with urine albumin excretion and use of ACE inhibitor was positively correlated with serum Gps4 level (all p<0.05). In multivariate regression analysis, the increase of serum Gps4 level was associated with the decrease of glycemic variability independently (p =0.05). And the increase of serum Gps4 level was associated with the increase of urine albumine excretion (p =0.02). The Serum Gps4 level was not associated with retinopathy, neuropathy, cardiovascular disease, cerebrovascular events. Also serum Gps4 level did not increase depending on the CKD-epi stage.

Conclusions: Taken together, there is no relationship between diabetic complications and serum Gps4 level. But more research is needed on the relationship between Gps4 and diabetic complications.

PUB149

Effect of Ultrafiltration on Plasma Hemoglobin Concentration in Patients with End-Stage Renal Disease on Chronic Hemodialysis

Subir K. Paul, Shejuti Paul, Rajesh Boorgu, Narasimha Rao Boorgu, Jamie N. Cockrell.1 Shoa's Kidney and Hypertension Center, Florence, AL.

Background: Anemia is highly prevalent in patients with end stage renal disease. It is common practice to measure plasma hemoglobin concentration in patients on hemodialysis before HD treatment begins. Therapeutic interventions including adjustment of Epoogen dose and intravenous iron administration are undertaken based on these measurements. We have found considerable variation in plasma hemoglobin level in these patients without any apparent non-technical change, except for interdialytic weight gain. We hypothesize that the pre-ultrafiltration hemoglobin concentration in this patient population is artificially low because of plasma volume expansion. We propose that plasma hemoglobin level should be measured after ultrafiltration is completed. This study compares the plasma hemoglobin level in patients on chronic hemodialysis before and following ultrafiltration.

Methods: Our study included twenty five patients with end stage renal disease on chronic hemodialysis for at least 6 months duration with minimum interdialytic weight gain of three kilograms. Mean age was 59.08 years. Twelve were male and thirteen were female. Ten were white and fifteen were African American. Pre and post hemodialysis plasma hemoglobin concentration was determined in a standard laboratory. Statistical analysis was done with student’s t-test.

Results: The mean interdialytic weight gain was 4.6 kilograms. Pre-ultrafiltration hemoglobin concentration was 11.32 ± 0.27 g/dL. Post-ultrafiltration hemoglobin increased to 12.14 ± 0.28 g/dL (P<0.04).

Conclusions: This preliminary data suggests that pre-ultrafiltration hemoglobin concentration in chronic hemodialysis patients may be artificially low because of plasma volume expansion associated with interdialytic fluid gain. Measurement of plasma hemoglobin in this patient population should be done after hemodialysis when ultrafiltration is completed and euvolemia is achieved. This strategy may reduce pharmacological interventions for anemia management in these patients.

PUB150

Effect of Ultrafiltration on Serum Albumin in Patients with End Stage Renal Disease on Chronic Hemodialysis

Subir K. Paul, Shejuti Paul, Rajesh Boorgu, Narasimha Rao Boorgu, Jamie N. Cockrell.1 Shoa's Kidney and Hypertension Center, Florence, AL.

Background: Malnutrition is prevalent in many hemodialysis patients with end stage renal disease. It is common practice to measure serum albumin concentration in patients on hemodialysis before the initiation of ultrafiltration and hemodialysis. Serum albumin has been found to vary considerably without any apparent clinical change except for interdialytic weight gain. We hypothesize that serum albumin in these patients is artificially low because of plasma volume expansion and should be measured following ultrafiltration.
Methods: Our study included 65 patients with end-stage renal disease on chronic hemodialysis for at least 6 months with minimum weight gain of 1 kg. Mean age was 61.17 years. Thirty two patients were male. Thirty three were female. Thirty two were White. Thirty two were black. Ultrasound was done to reach pre-dialysis dry weight for each patient. Serum albumin was measured pre and post ultrasound. Statistical analysis was done with student t-test.

Results: The mean weight gain was 3.66 kg. Pre-ultrafiltration albumin was 3.77 +/- 0.04 g/dL. Post-ultrafiltration albumin increased to 4.145 +/- 0.05 g/dL (P=0.0001).

Conclusions: This preliminary data suggests that pre-ultrafiltration albumin measurements in hemodialysis patients may be artificially low in patients with plasma volume expansion associated with interdialytic fluid gain. We propose that serum albumin should be measured after ultrafiltration when patients are relatively euolemic. This strategy may be valuable for assessment of malnutrition in patients of end stage renal disease on chronic hemodialysis.

PUB151
Clinical Factors and Renal Function at the Start of Dialysis: Impact on Mortality in Incident Hemodialysis Patients
Elvira Bosch,1 Eduardo Baamonde,1 German Perez Suarez,2 Cesar Garcia-canton,2 Rita Guerra,2 Dolores Checa,2 1Centro de Hemodialisis Averiscm, Las Palmas de Gran Canaria, Spain; 2Servicio de Nefrologia, Hospital Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain.

Background: The goal of this study was to analyze whether clinical conditions and renal function at the start of renal replacement therapy (RRT) are related with mortality.

Methods: Retrospective study with 220 incident hemodialysis patients between 2007 and 2010 in Southern Gran Canaria. Patients' demographic, clinical and laboratory data were analyzed at the start of dialysis treatment. Glomerular filtration rate (GFR) was calculated by using the MDRD4 and Cockcroft-Gault (CG) formula. Patients were classified into 3 different groups according to their GFR (MDRD4 > 15, 8-15 and < 8 mL/min). Survival rates were compared between groups.

Results: 65.5% male, 61.13 +/- 13 years old, 58.6% diabetic and 17.7% with cardiovascular disease; 65.5% started with catheter, the mean age-adjusted Charlson comorbidity index (ACCI) was 6.2 +/- 2.4 and the average MDRD4 at the start of hemodialysis was 10.67 +/- 3.25 mL/min. Patients who started with MDRD4 < 8 mL/min were (p=0.05) younger, with lower ACCI and higher incidence of catheter; they showed lower albumin and hemoglobin levels and higher urea and phosphorus levels. The median follow-up time was 30.9 months. Eighty patients died (17.7% of them with early start and 3.8% with late start). The risk of death was significantly higher for patients with hypoaalbuminemia, age > 65 years, higher ACCI, MDRD4 > 15 mL/min at the start, heart failure or history of ACH. After adjusting the model (Cox regression) the global risk of death was higher (p=0.05) for patients who started with catheter (HR: 2.4: 1.3-4.4), higher ACCI (HR: 1.16: 1.01-1.3), > 65 years (HR: 1.7: 1.01-3.08) and for those who started with GFR-MDRD4 > 15 mL/min (HR: 3.6: 1.03-13).

Conclusions: Patients with a late RRT start were younger, with lower ACCI and with lower albumin and hemoglobin levels. Factors affecting the survival of incident hemodialysis patients are: early start, start with catheter, older age, the GFR-MDRD4 and high ACCI.

PUB152
The Use of Continuous Measurement of Glucose Concentration in Intestinal Fluid in Hemodialysed Patients
Stanislaw Niemczyk,1 Wojciech Klimek,1 Kataryzna Piekacze,1 Bozena Pietrak.1 1Internal Diseases, Nephrology and Dialysis, Military Institute of Medicine, Warsaw, Poland; 2Information and Communication Technologies, Military Institute of Medicine, Warsaw, Poland.

Background: Fluctuations of glucose concentration in serum are an important problem in hemodialysed (HD) patients with and without diabetes. The aim of this study is to compare the fluctuations of the glucose concentrations in intestinal fluid in hemodialysed patients with and without diabetes assessed by the method of continuous measurement.

Methods: The study involved 22 HD patients (9 women and 13 men) in two groups: with diabetes (GDM): 4 women and 8 men; and without diabetes (GN): 5 women and 5 men. The concentration of glucose was measured using a Real Time Guardian (Medtronic) monitoring system every 5 minutes. The study assumed 4-day monitoring.

Results: In the 9319 measurements were performed (average 776.58/person). Total observation time was 752 hrs 35 min (average 62 hrs 42 min). In the GN the 7079 measurements were performed (average 707.9). Total observation time was 589 hrs 55 min (average 58 hrs 59 min). In the GDM the average value of glucose concentration was 137.58 mg/dl and was higher than the GN by 30.28 (p = 0.004). The maximum values of glucose concentration #8203; 4.19 #8203; and #8203; 4.19 (p < 0.008) compared with the GN. The groups of patients were analyzed for the frequency and the length of glycemia fluctuations. No differences in the number of hypoglycemia were observed.

Conclusions: Continuous measurement of intestinal glycemia seems to be a useful, accurate and safe method of the assessment of carbohydrate metabolism in HD patients. In patients with diabetes asymptomatic hypoglycemia are more frequent and longer. Episodes of hypoglycemia also occur in patients without diabetes.

PUB153
Lack of Effect of Standard or Adjusted Dialysate Potassium Concentration on Postdialysis Potassium Levels
Xenia P. Sumin, Michael F. Michelis, Maria V. Devita. Nephrology, Lenox Hill Hospital, New York, NY.

Background: Controlling serum potassium concentration (K) is an important goal in maintenance hemodialysis (MHD) patients. Intermittent hemodialysis results in rapid fluctuations of serum K that can extend from pathologically high to low concentrations. Pre-dialysis hyper- and hypokalemia have been implicated in increased death risk in MHD patients. Complications of dialysis in regard to serum K is largely a function of both K flux and the development of hypokalemia. The goal of this study was to examine the postdialysis serum K in patients with normal predialysis serum K when dialyzed against standard and adjusted K baths to assess the frequency and extent of postdialysis hypokalemia.

Methods: Monthly labs at a single outpatient dialysis center were screened to identify MHD patients with predialysis serum K in normal range (K<3.7 and K<4.5mEq/L). Of 72 such patients identified, 11 patients were on 3K bath. Twenty-two of the remaining 61 patients, all on 2K bath, were chosen at random to compare to the 3K group. Postdialysis serum K levels were collected on all patients. Patient data on treatment time (min), blood flow (ml/min), and URR was also collected.

Results: Mean pretreatment K (4.05+0.22mEq/L) in 2K dialyzed group was not different from the mean pretreatment K (4.00mEq/L #8211;0.35mEq/L) in 3K dialyzed group (p=0.59). Mean change between pre- and posttreatment serum K was -0.12+0.56mEq/L for 2K dialyzed group and -0.14+0.31mEq/L for 3K dialyzed group (p=0.94). Postdialysis K (3.93+0.60mEq/L) in 2K dialyzed group was not different from the mean posttreatment K (3.68mEq/L #8211;0.35mEq/L) in 3K dialyzed group (p=0.73). Treatment time was longer in the 2K group, 214 versus 195 minutes (p=0.04). There was no difference in blood flow or URR between the groups. Though the 2K group had significantly longer treatment time, there was no correlation between change in K and either treatment time or blood flow.

Conclusions: There was no significant difference in postdialysis serum potassium levels among the 2K and 3K dialysis groups. It appears patients with normal predialysis K can be dialyzed against 2K bath with minimal risk for the development of severe hypokalemia.

PUB154
Performances of the New Revaclear High Flux Dialyzers for Conventional HD Treatments
Fulvia Caligaris,1 Maria Roseo,1 Adina Misca,1 Francesco Guarnieri,2 Denis Steckhip.3 1ASL AT Ospedale, Asti, Italy; 2Gambro, Italy.

Background: High-flux dialyzers may delay long term clinical complications of dialysis. Aim of this study: to evaluate if standard HD with high-flux dialyzers Revaclear (Gambro) improves the removal of uremic toxin in stable HD patients respect to other low and high flux dialyzers.

Methods: ESRD patients on dialysis (Qb>250 ml/min) were retrospectively enrolled in a single center, controlled and observational study. The patients were treated on conventional HD (CHD: 19 low-flux, 5 high-flux; n=17,17m2, n=7,21m2) for 6 months and on high-flux HD with Revaclear dialyzers (RevHD: n=5,14m2, n=7,18m2) for further 6 months. Revaclear is equipped with a high water permeability PAES/PVP membrane, efficient and compact in size thanks to fiber microondulation and bundle density. Primary end-point: to evaluate the monthly pre-dialysis level of blood urea (Ur) and phosphorus (P). Secondary end-points: to evaluate the monthly pre-dialysis value of hemoglobin, hematocrit, Epo dose and 2-month eKt/V (Daugirdas).

Results: We analyzed 24 patients/10 F, age 68.4±12.0 years, HD vintage period 6.8±6.1 years vascular access:11 AV, 13 Tesio CVC). Mean Ur among the whole evaluation period was lower during RevHD (566±37 vs. 142±35mg/dl, p<0.05) and as time-related trend(p<0.05, Fig.1A). P was significantly lower during the RevHD period, both as mean value(4.6±1.81 vs. 4.19±1.88mg/dl, p<0.05) and as time-related trend(p<0.05, Fig.1B). Other parameters did not show any significant difference (Fig.1C).

Conclusions: Our findings in RevHD period were obtained with smaller surface filters about on 2/3 of the treatments respect to CHD, showing the high efficiency of Revaclear high-flux dialyzers on HD. Concerning the effect of Revaclear on hemoglobin levels and Epo dose, a further study on a larger population is needed.
PUB155

Is Aciddosis Associated with a Better Survival in Hemodialysis Patients? Bassam O. Bernieh, Yousef Boobes, Mohamed Raafat Al Hakim, Qutaiba Asmaa Y.M. Al-Chidadi, Abdelgalil Abdelrahman Ali, Broomfield Hospital, Chelmsford, United Kingdom.

Background: Association between acidosis and survival in hemodialysis patients remains controversial.

Methods: Correlation between 5-years survival and time-averaged S. Bicarbonate (HCO3) among 293 adults on maintenance hemodialysis was studied. Patients were categorized into four groups according to S. HCO3 levels.

Results: CRP correlated positively while S. Phosphate correlated inversely with S. HCO3. Normalized protein nitrogen appearance (nPNA) showed an inverted U-shape correlation with S. HCO3. The mildly acidic group were significantly younger and had a significantly higher BMI.

Conclusion: Survival was significantly higher among the acidic group, p<0.0001, despite a significantly lower Ks/V.

PUB156

Low Molecular Weight Heparin (LMWH) “Enoxaparin” as a Standard Anticoagulant in Hemodialysis Patients: A 15 Year Experience Bassam O. Bernieh, Yousef Boobes, Mohamed Raafat Al Hakim, Qutaiba Hussain Daood, Hanan Eljack, Nicholas T. Richards, Nephrology, Tavarem Hospital, Al Ain, United Arab Emirates; SEHA Dialysis Services, Abu Dhabi, United Arab Emirates.

Background: LMWHs are available since 25 years with wide use in the treatment and prevention of medical and surgical thromboembolic events. The use of LMWHs as anticoagulant in hemodialysis (HD) patients, is still not a routine or standard practice. We are using LMWH ‘Enoxaparin’ since 1998 as a standard anticoagulation in our HD unit, and in a previous publication (1), we defined the dose which would be used in HD (0.36 mg/kg), and the advantages of LMWH “Enoxaparin” over unfractionated heparin.

Aim of the study: In the current study, we are reporting our 15 years experience of using “Enoxaparin”, evaluating the current used dose, the dose according to the type of vascular access, etiology of kidney disease (diabetic, non diabetic), and dialytic mode (HD, HDF).

Methods: This study includes 252 HD patients, mean age 56.6 (17) year, Male 145 (57.5 %). Mean duration on HD 50 (44.5) months. 139 (55%) were diabetics, 138 (55%) had AVF, 28 (11%) had AVG, and 96 (34%) had tunneled catheter. The average dose used continued to be low and stable with time. Only the type of vascular access impact significantly the required dose.

Conclusion: To the best of our knowledge this study is the longest, and the largest experience ever reported with the use of LMWH “Enoxaparin” as a standard anticoagulant in HD. The average dose used continued to be low and stable with time. Only the type of vascular access impact significantly the required dose.

PUB157


Background: End stage renal disease patients on dialysis can suffer from metabolic encephalopathy. More often than not the reason remains uncertain. We report a case of a patient in which the encephalopathy completely resolved by switching from peritoneal dialysis to hemodialysis.

Methods: Our patient was a 65-year-old Hispanic male, with history of end stage renal disease, diabetes mellitus type 2, hypertension, coronary artery disease, gout and peripheral vascular disease. He was on peritoneal dialysis for last one year and had been compliant with his treatment with adequate dialysis. He was admitted to the hospital with change in mental status. Prior to this admission he was completely independent and worked as mathematicians teacher. As part of his work up, CT head did not reveal any new changes and lumbar puncture results were unremarkable. His ECG showed slowing of back ground activity suggestive of mild diffuse encephalopathy likely due to metabolic, toxic or infectious etiology. His TSH was elevated so he got IV syntheinid. He had culture negative peritonitis which was treated with IV antibiotics to resolution. Despite treatment of the metabolic and infectious abnormalities and providing adequate dialysis (Kt/V 1.7), his mental status did not improve. He remained hospitalized for two months, without any improvement in mental status until his renal replacement therapy was switched to hemodialysis. We used F 1800 dialyzer with Blood flow rate of 350 and Dialysate flow rate of 700 for his first session. Immediately after his first hemodialysis, a dramatic improvement of his mental status was noted. We continued hemodialysis and after his second session, he returned to his baseline, nine weeks after his initial presentation.

Conclusion: Although we do not have clear explanation for this but there is a possibility that hemodialysis may have some benefit in clearing middle molecules and some unknown substances in blood which may contribute to encephalopathy.

PUB158

Continuous Veno-Venous Hemodialysis (CVVHD) with Regional Citrate Anticoagulation (RCA) Is a Suitable and Safe Modality for Severe Acute Kidney Injury (AKI) Induced by Tumor Lysis Syndrome (TLS) Veronica T. Costa e Silva, Elerson Costalonga, Cilene Muniz de Alencar, State Cancer Institute - Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil.

Background: Continuous Veno-Venous Hemodialysis (CVVHD) with Regional Citrate Anticoagulation (RCA) has been shown to be a suitable and safe modality for severe acute kidney injury (AKI) induced by tumor lysis syndrome (TLS). It is a crucial modality for severe AKI induced by TLS, as it allows the removal of high volumes of fluids and electrolytes, including large amounts of sodium.

Methods: We report the case of a 64-year-old male with multiple myeloma who presented with hyperkalemia, hyponatremia, hyperphosphatemia, hypercalcemia, hypocalcemia, and hyperphosphatemia. The patient was started on CVVHD with RCA and was maintained on this modality for 91 days.

Results: The patient tolerated the procedure well and had a satisfactory outcome. The patient was eventually discharged on the 91st day.

Conclusion: CVVHD with RCA is an efficient and safe dialysis modality for TLS-induced AKI.

PUB159

Adjusting Effective Replacement Fluid Sodium Level in Continuous Hemofiltration Carl P. Walther, Amber S. Podoll, Kevin W. Finkel. Div of Renal Diseases & Hypertension, UTH ealth Science Center at Houston, Houston, TX.

Background: Management of dysnatremic patients with renal replacement therapy can be perilous because of rapid sodium correction if standard therapy fluids are used. We describe a means whereby patients receive CVVH with standard replacement fluid, and standard electrolyte- or hyperonosmolar fluids are infused into the patient, either post-filtrate or at a separate venous access site, to adjust the effective replacement fluid sodium concentration.
Methods: A model was developed for calculating the “effective” sodium concentration of the replacement fluid in CVVH as the mean of the sodium concentrations of the input fluids, weighted for fluid rate. \([Na_s]\) represents desired effective replacement fluid sodium concentration, \([Na_i]\) is the sodium concentration in the standard replacement fluid (usually 140 mEq/L), \([Na_j]\) is the sodium concentration in the “adjustment” fluid, \(Q_a\) is the standard replacement fluid rate, and \(Q_j\) is the rate of “adjustment” fluid. \(\frac{[Na_s] - [Na_i] \cdot Q_i + [Na_j] \cdot Q_j}{Q_a - Q_i + Q_j}\). The equation can then be solved for the “adjustment” fluid rate: \(Q_i = Q_a \cdot \frac{[Na_s] - [Na_i]}{[Na_j] - [Na_i]}\).

Results: By inputting values for the desired “effective” replacement sodium concentration, the replacement fluid flow rate, and the sodium concentration of the adjustment fluid used, the flow rate of the adjustment fluid is determined. As an example, the table below shows the calculated adjustment fluid rates for various desired effective sodium concentrations and CVVH replacement fluid rates where the adjustment fluid is 5% dextrose in water.

<table>
<thead>
<tr>
<th>Replacement fluid</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
<th>5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Dextrose infusion rate</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
<td>600</td>
</tr>
<tr>
<td>(Effective Na concentration mEq/L)</td>
<td>110</td>
<td>220</td>
<td>330</td>
<td>440</td>
<td>550</td>
<td>660</td>
</tr>
<tr>
<td>110</td>
<td>120</td>
<td>90</td>
<td>70</td>
<td>50</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: We propose that using standard CVVH replacement fluid, and standard additional “adjustment” intravenous fluids (e.g., 5% Dextrose, 3% saline), the effective sodium concentration for CVVH can be easily adjusted to avoid excessive correction in dysnatremic patients.

**PUB160**

Metformin Associated Lactic Acidosis (MALA): A Long Term Single Center Experience Andrea Angioi, Antonello Pani. AOB Cagliari.

Background: Metformin associated lactic acidosis (MALA) is a well-known side effect of Biguanides and in 13 years we observed an exponential increase in hospitalizations. Aim: investigate about the incidence in our area, the underlying causes, the survival in the short and long term.

Methods: We conducted a retrospective analysis retrieving 22 patients (pts) with MALA and acute renal failure admitted from Jan 2000 to Dec 2012. Inclusion criteria: MALA and acute renal failure admitted from Jan 2000 to Dec 2012. Inclusion criteria: We assessed available data to calculate whether MPHD, a batch system where the dialysate would require new dialysate.

**PUB161**

Multipass Hemodialysis (MPHD) – A Flexible Alternative in the ICU James G. Heal1, Mette K.M. Axelsen, Robert Smith Pedersen. 1 Dept of Nephrology, Copenhagen Univ Hospital at Herlev, Herlev, Denmark; 2Institute of Public Health, Aarhus Univ Hospital, Aarhus, Denmark; 2FlexiDialysis A/S, Rungsted, Denmark.

Background: Dialysis treatment of acute renal injury (AKI) varies between conventional HD for 4 hours to more gentle continuous renal replacement therapy (CRRT). We assessed available data to calculate whether MPHD, a batch system where the dialysate is recirculated, is a valid alternative.

Methods: Ten stable HD patients were dialyzed for 8 hours. The dialysate volume was 50% of the calculated water volume and the water flow 500 ml/min. Dialyse tests and blood tests before and after the filter, were taken at start and every hour thereafter. Dialyse volume and ultrafiltrate was measured continuously.

Results: The initial S-Urea was 20.5 ± 7.6 mmol/l. Minimal S-Urea levels of 13.0 ± 4.7 mmol/l occurred after 5 hours, and thereafter rose to 14.0 ± 4.8 mmol/l. A total of 316 ± 131 mmol urea was eliminated. The dialysate volume was 22.9 ± 4.8 liter. The rise in S-Urea from 5 to 8 hours was 1 mmol/l corresponding to 0.33 mmol/hour. If MPHD had been used for 24 timer (CRRT), assuming constant urea generation, s-urea would have risen to 14 ± (16 x 0.33) = 19.3 mmol/l. Assuming a terminal dialysate urea concentration of 19 mmol/l, a total of 435 mmol/day can be removed. In cases of extreme hyperkalemia, e.g. rhabdomyolysis, a water flow of 500-800 ml/min and blood flow of 300-350 ml/min, with a dialysate potassium concentration of zero, is recommended. This would rapidly permit the removal of approximately 100 mmol of potassium. Continuing potassium problems would require new dialyse.

Conclusions: MPHD can be used both as CRRT and for intensive toxin elimination, with a very low water consumption. The principle is also applicable to areas where sustained low-efficiency daily dialysis (SLEDD) is used. Thus MPHD is not a low-efficiency system. This has logistical advantages.

**PUB162**

Comparison of 15% and 4% Citrate Anticoagulation in Plasma Exchange N.Antoniuc, Juradka Buturac, Ponikvar, Jorg Guckel, Rafael Ponikvar. Dept of Nephrology, Univ Medical Centre, Ljubljana, Slovenia.

Background: To reduce infusion volume we introduced 15% citrate solution and compared (micro)anticoagulant effect with 4% citrate solution in plasma exchange (PE).

Methods: In 18 patients, PE was performed using 4% or 15% trisodium citrate. Anticoagulant effect was evaluated by postfilter ionized calcium (iCa) (target range 0.2-0.4 mmol/l), postfilter hourglass clotting time and visually by assessing circuit after the procedure (on a 5-excellent anticoagulation to 1-total clotting scale). Steieving coefficient (SC) for immunoglobulin G was measured at the start and at the end of all procedures; the reduction of SC at the end was indicative of microanticoagulation failure at plasmatfilter.

Results: 26 PE were performed. Postfilter iCa was in a target range in both groups and was significantly lower in the 15% citrate group (0.37±0.02 vs. 0.4±0.02 mmol/l, p<0.05). The mean hourglass clotting time was similar (19±5 min in 15% citrate group vs. 16±2.3 min, p=0.22). Visual assessment showed excellent anticoagulation at plasmatfilter and arterial bubble trap (score 4.9±0.3 in both groups) and almost excellent at venous bubble trap (4.6±0.8 and 4.7±0.6). On average, SC did not change significantly during the procedure in 15% citrate group (0.93±0.31 vs. 0.99±0.21, p=0.52) or in 4% citrate group (0.86±0.26 vs. 1.00±0.2, p=0.19). We observed a decrease in SC during 36% of procedures in 15% citrate group and during 50% of procedures in 4% citrate group (p=0.46). The infused volume of citrate per procedure was significantly lower in 15% citrate group (170±26 ml vs. 330±71 ml, p<0.001). No side effects were detected in either group.

Conclusions: 15% citrate showed similarly good anticoagulation as 4% citrate and allowed reduction of infused volume, which can be important in volume overloaded patients needing PE.

**PUB163**

Early Dialysis Initiation Based on Acute Kidney Injury Network Criteria in Critically Ill Asian Patients: A Prospective Cohort Cynthia Chew Lai Lim, Chieh-suai Tan, Manish Kaushik, Han Khim Tan. Dept of Renal Medicine, Singapore General Hospital.

Background: To compare patient mortality in intensive care unit (ICU) patients with acute kidney injury (AKI) and renal replacement therapy (RRT) initiated based on modified Acute Kidney Network (AKIN) creatinine and urine output criteria.

Methods: This was a single-center, prospective cohort study of medical and surgical ICU patients referred for AKI over 22 months. Indications for RRT were classified as Group A: "absolute" indications including serum potassium ≥6.0 mmol/l, serum urea ≥30 mmol/l, arterial pH <7.2, serum bicarbonate <10 mmol/l, acute pulmonary edema, acute uremic encephalopathy or pericarditis; Group B: modified AKIN stage 3 without "absolute" indications; Group C: AKIN Stages 1 or 2 without "absolute" indications. Demographic, clinical and biochemical data were collected prospectively from patient medical records. Patients with incomplete baseline data were excluded.

Results: There were 169 patients (mean age 59.2 ± 17.1 years; male 63.9%; diabetes mellitus 13.7%; hypertension 53.8%; ischemic heart disease 37.3%; medical ICU 72.2%; mean APACHE score 23.8 ± 6.0). Main AKI causes were sepsis (63.9%) and ischemia (34.9%). RRT was initiated in 121 patients. Complete data on RRT indications were available in 83 patients: Group A (n=26), B (n=26) and C (n=31). Those with RRT initiated in absence

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

Underline represents presenting author.

911A
of “absolute” indications were examined. Comparing Group B vs. C: baseline demographics and comorbidities were similar. There were no significant differences in premorbid MDRD eGFR (p=0.36); time from ICU admission to RRT initiation (p=0.51); CRRT modality (p=0.08); average CRRT effluent flow rate (p=0.23). There were no differences in ICU mortality (33.3% vs. 33.3%, p=0.85) or in-hospital mortality (35.7% vs. 28.6%, p=0.25).

Conclusions: In the absence of “absolute” indications, earlier RRT initiation based on early Cr/BSA criteria did not improve survival in critically ill patients. Controlled trials with well-defined dialysis criteria, including novel biomarkers, are required for further evaluation of optimal RRT timing.

Funding: Government Support - Non-U.S.

PUB164

Predictors of Mortality in Patients Treated with Continuous Veno-Venous Hemodialysis

Tanush Gupta,1 Sahil Agrawal,1 Jalaj Garg,1 Nikhil Agrawal,1 Savneek S. Chugh,1 Dipak Chandy,1 Internal Medicine, New York Medical College; Pulmonary and Critical Care Medicine, New York Medical College.

Background: Continuous Veno-Venous Hemodialysis (CVVHD) is a mode of renal replacement therapy utilized in critically ill patients when intermittent hemodialysis is contraindicated due to hemodynamic instability. The purpose of our study was to determine predictors of 7-day and in-hospital mortality in patients treated with CVVHD.

Methods: Study cohort included 60 consecutive adult patients (age≥18 years) requiring CVVHD in our Medical Intensive Care Unit (MICU). Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated at the time of MICU admission. Primary outcome of our study was in-hospital mortality.

Results: The mean age of our study population (65% males, 35% females) was 60.7±15.7 years. The mean APACHE II score was 23.6±6.6 with mean time to initiate CVVHD being 9.2±2.6 hours. Mean duration of CVVHD in our study cohort was 7.2±5.7 days. 77% patients were started on CVVHD due to Acute Kidney Injury while remaining 23% had pre-existing end stage renal disease. Only 17.3% patients eventually recovered their renal function. The 7-day mortality in our analysis was 28.3% while in-hospital mortality was 31.7%. A multivariable analysis, adjusted for CVVHD (OR 0.7, p = 0.004) and vasopressor support (OR 2.18, p = 0.01) were found to be predictors of 7-day mortality. However, only duration of CVVHD (OR 0.63, p = 0.007) predicted mortality in multimodel regression analysis. Similarly, recovery of renal function (OR 0.03, p=0.003) and APACHE II score (OR 0.12, p = 0.007) were found to be predictors of in-hospital mortality in adjusted analysis. But, only recovery of renal function (OR 0.01, p = 0.001) was associated with decreased inpatient mortality in multivariable regression analysis. Interestingly, time to initiate CVVHD did not predict both 7-day (OR 1.04, p=0.32) and in-hospital mortality (OR 0.99, p = 0.77).

Conclusions: Duration of CVVHD and recovery of renal function were found to be predictors of 7-day and in-hospital mortality in critically ill patients respectively. Time to initiation of CVVHD had no association with mortality.

PUB165

AKI Requiring Dialysis: Shift CVVHD Technique Does Not Affect Outcomes

Luis A. Concepcion, Medicine, Texas A&M Healthscience Center Scott&White Hospital, Temple, TX.

Background: The treatment of AKI requiring dialysis is controversial concerning the modality and dose.

Methods: Analysis of 18 month cohort of AKI patients treated with shift CVVHD (N=267) versus regular HD (4.6±6 Fresenius 4008Barbonate) demographics, laboratory data and survival obtained from the EMR, technical and monitoring details from the dialysis run sheets, pres/bpost BUN, Kt/V, Urea reduction (URR). CVVHD dose (ml/kg/hr), standardized Kt/V and EKR equivalent renal clearance per standard methods. Data as mean and standard deviation.

Results: 166 patients with AKI requiring dialysis (37.3% sepsis, 24% surgery, 38.7% other) Mortality 43.9% (48.3% sepsis 57.3% CV surgery 31.2% other 83.1) 91 days in dialysis received 6.06±0.05 dialysis, median of 23 days in the hospital. 800 treatments analyzed. 91.9% of treatments done in the ICU, 78.4% were CVVHD 21.6% conventional HD.

Conclusions: Duration of CVVHD and recovery of renal function were found to be predictors of 7-day and in-hospital mortality in critically ill patients respectively. Time to initiation of CVVHD had no association with mortality.

PUB166

Renal Replacement Therapy in the Setting of Orthotopic Liver Transplant – A Retrospective Descriptive Study

Adeokunbo A. Taiwo, Amishi S. Desai, Jay L. Koyner. Section of Nephrology, Univ of Chicago, Chicago, IL.

Background: Electrolyte and acid-base disturbances are common during the intraoperative course of orthotopic liver transplantation (OLT) and are magnified in those with chronic kidney disease (CKD) or acute kidney injury (AKI). Some have argued that utilizing intraoperative continuous renal replacement therapy (CRRT) attenuates these fluctuations and improves patient outcomes.

Methods: We performed a retrospective, chart review on all OLT recipients receiving intraoperative CRRT between Sept 1, 2010 and May 15, 2012 at the University of Chicago. Electrolyte and pH data were collected from different time points during OLT (the start of surgery (time zero), 25%, 50%, and 75% of the time into the surgery (time 25, 50, 75), pre-op and post-op. Data was analyzed using paired t-test.

Results: Data from 11 OLT recipients was available for analysis. Patients were predominantly male (9, 82%), mean age was 51.5 years (range 38-70). Indication for CRRT was as follows: 5 AKI (45.4%), 2 AKI on CKD (18.2%), 2 hyperkalemia (18.2%), 1 volume overload (9.1%) and 1 ESRD (9.1%). Type I hepatorenal syndrome was diagnosed in 3 (27.3%) patients prior to OLT. Nine of eleven (81.8%) patients died prior to hospital discharge. With the exception of comparisons between sodium at time 0 and time 75 (P=0.019), sodium at time 0 and post-op (P=0.001) and ionized calcium at time 0 and time 25 (P=0.016), there were no statistically significant difference between the other electrolyte and pH values measured at the different time points. Table 1 – Mean and SD values (± standard deviation).

PUB167

Improving AVF Rate: Effect on Hemodialysis Quality

Ayman Karkar,1 Ahmed Challaboul,2 Mohammed Abdelrahman,1 Maher Haj ibrahim,1 Mona Al Shubaili,1 ‘Kanoon Kidney Center, Damman Medical Complex, 1, Damman, Saudi Arabia; 2Kidney Transplantation Dept, Riyadh, Saudi Arabia.

Background: Vascular access (VA) is the life-line for patients on regular hemodialysis (HD), and the type of VA is associated with patient outcome. Tunneled catheters are associated with increased risk of laminar thrombosis, infection, hospitalization, and high cost. The native arterio-venous fistula (AVF) remains the best available VA option. The high catheter usage rate, increased incidence and prevalence of catheter-associated complications and the progressive increase in number of our ERSD patients in need for HD prompted us to follow the USA “Fistula First Initiative”. Our aim was to avoid or reduce the rate of catheter insertion and improve the rate of AVF use, and study that effect on quality of dialysis and patient’s outcome.

Methods: A vascular access program has been established in collaboration with an eminent professional vascular surgery team to manage 358 patients who have been on regular HD treatment for a period ranging from 1 to 252 months. The mean ± SD age of patients was 52±15 years with 62% male patients.

Results: Over a period of 2 years, 403 procedures were performed. These include 251 AVG, 151 AVF, 14 AVG+1AVF and 3 AVF+1 AVG. Other procedures include 35 permanent catheter insertion, 8 AVF aneuysmectomy, removal of 6 AVG, embololysis of 3 AVG, excision of 1 AVG lymphocele and ligation of 1 AVG. This program resulted in an increase in AVF rate from 35% to 82%, reduction in catheter rate from 62% down to 10%, reduction in infection rate from 6.6% to 0.6%, reduction in VA clotting from 5.1% to 1% and an increase in average blood flow rate from 214±32 to 298±37 ml/min (p=0.01). These results have been associated with improved average single pool Kt/V from 0.88±0.19 up to 1.28±0.2 (p=0.01), increased hematoglobin from 9.2±1.2 to 10.9±0.9 g/dl (p=0.01), improved serum albumin from 3.2±0.5 to 3.7±0.4 g/dl (p=0.05), reduction in administered erythropoirotin dose by 16% and a significant drop in hospitalization rate from 6.1% down to 3.8%.

Conclusions: In conclusion, these results confirm the great benefit of AVF on quality of HD and patient outcome, and clearly affirm that AVF should always come first.

Funding: Clinical Revenue Support

PUB168

Rates of Vessel Mapping Prior to Arteriovenous Fistula Placement Vary Across Mid-Atlantic United States

Jenten B. Lynch,1 W.G. Schekter,2 Kim Deaver,1 Ryan D. Evans.1 Mid-Atlantic Renal Coalition, Richmond, VA; 2University of Virginia; 3Valley Nephrology Associates.

Background: The Fistula First Breakthrough Initiative (FFBI) is a population-based intervention by the Centers for Medicare & Medicaid Services to increase appropriate arteriovenous fistula (AVF) use. Early referral for surgical evaluation and timely placement of a fistula, including prior vessel mapping, is encouraged. This study examines geographic variation in vessel mapping rates across the mid-Atlantic region. The relationship of vessel mapping to subsequent prevalent AVF use is examined in a sub-group of hemodialysis patients aged 66 years treated by large dialysis organizations.

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

Underline represents presenting author.

912A
Methods: Using Medicare Part B claims for Maryland, Virginia, West Virginia and Washington, D.C., we identified AVF placements in 2011, matched these with prior vessel mapping claims in 2010, and calculated vessel mapping in hospital referral regions (HRRs) defined by the Dartmouth Atlas of Health Care. To examine the relationship between vessel mapping and prevalent AVF use, we matched claims with April 2012 FFBI prevalent patient-level vascular access data from large dialysis organizations. These linked data were filtered using the following criteria: (1) 2011 claim for AVF placement, (2) matched with FFBI prevalent value access, (3) patient >= 66 years of age at access claim, and (4) patient started dialysis in 2011. Chi-square was used to examine association.

Results: 50.4% (1,990,348) of AVF claims were preceded by vessel mapping claims. Across HRRs within our geographic boundaries, the range was 23.3% to 85.8% for all patients (n=3,948) and 27.0% to 84.1% for patients >= 66 years (n=2,206). Four hundred eighty-six patients met all criteria for examination of association between prior vessel mapping and AVF use. Of these, 71.4% were using an AVF in April 2012. Those with prior vessel mapping and AVF use had 74.6% AVF use and those with no prior vessel mapping (n=226) had 67.7% AVF use (p<0.1).

Conclusions: There may be an opportunity to improve fistula prevalence both by increasing rates of pre-operative vessel mapping as well as by reducing geographic variation in AVF use.

Funding: Other U.S. Government Support

PUB169

Use of Gentamicin/Citrate Lock Solution Decreases Catheter Related Bacteremia

Grant Springfield, John Hergenrother. The Chrise Hospital, Cincinnati, OH.

Background: Infections remains a leading cause of morbidity and mortality in hemodialysis patients. Those particularly suscepible are accessed by tunneled hemodialysis catheters, which comprise a majority of the dialysis population. Antimicrobial lock solutions have previously demonstrated decreases in catheter related bacteremia (CRB) rates. An investigation of cetains related bacteremia rates with use of a gentamicin/citrate catheter locking solution (GCLS) was compared to the standard heparin catheter locking solution.

Methods: A prospective review evaluating all prevalent patients using a tunneled catheter for hemodialysis access was performed in an urban, tertiary care, hospital-based, outpatient hemodialysis unit from July 1, 2008 to December 31, 2008. Patients were assigned to the control group of the standard 2000 units/ml of heparin or the study group of a 5mg/dl gentamicin/4% trisodium citrate based on their dialysis schedule. Overall 53 patients were evaluated, 34 in the control group and 19 in the GCLS group. CRB was determined by positive blood cultures drawn on patients based on clinical suspicion for infection.

Results: The CRB rate of 5.3% (1/19) in the experimental group compared to 26% (9/34) in the standard group, an absolute risk reduction of 21% (p<0.05). Therefore, the GCLS was implemented for all patients treated in the hemodialysis unit. Data collection continued from 2009-2011, and CRB rates continued at low rates significantly less than historical controls. Rates decreased from 2.1 to 0.9 to 0.7 infections per 100 patient months of treatment, from 2009-2011 respectively.

Conclusions: Gentamicin/Citrate is an effective antiinfectious lock solution in tunneled hemodialysis catheters, significantly decreasing CRB rates.

Funding: Clinical Revenue Support

PUB170

Tunneled Dialysis Catheter Infection and Troponin-I Levels in End-Stage Renal Disease Patients

Kamel A. Gharabeih,† Mihaly B. Tapolyai,† Eva Csongradi,† Tibor Fulop.† 1Dept of Medicine, Univ of Mississippi, Jackson, MS; 2Dept of Medicine, Semmelweis Univ.

Background: Elevated troponin-I levels in end-stage renal disease (ESRD) patients on dialysis are commonly attributed to ESRD itself. Our hypothesis was that infection of tunneled hemodialysis catheters (TDC) may be associated with subtle troponin-I elevations.

Methods: We performed additional data analysis on our consecutive 3-year experience (2007-2009-2012) with bedside TDC removal at the University of Mississippi Renal Fellowship Program. Data was already collected for multiple patients and procedure-related variables. Data was analyzed with SPSS 19. and reported with means ±SD or medians 25-75% IQR for descriptive data; Pearson’s correlation and independent-samples T test was utilized for statistical comparison. The study was reviewed and approved by the University of Mississippi Human Research Office.

Results: Indication at the time of removal included bacteremia, fever or clinical sepsis with hemodynamic instability or respiratory failure. Of the 55 TDC removed, 63.6% took place on general floor, 12.7% in Emergency Department and 16.3% in Intensive Care Units, with a median time of 3 days [IQR 1-13] elapsed since admission or TDC placement. Four (7.2%) patients were hypertensive, 33 (60%) febrile or subfebrile (T>37°C) at time of removal; 7 (12.2%) on vasoactive pressors. Peak C-reactive protein (available in 63.6% of cohort) measured 12.9±8.4 mg/dl (0-149); mean troponin-I (34% available) was 0.534 ng/ml [IQR 0.3-0.9] (n=0.034) and they did not correlate with each other. Troponin-I had no association with temperature, systolic and diastolic BP or clinical sepsis. However, troponin-I, as a continuous variable had a strong trend of association with proven bacteremia (p=0.075) and the association of troponin-I (normal, abnormal) with bacteremia has reach significance (Pearson’s chi-square 0.049).

Conclusions: Our results strongly suggest that some of the elevated troponin-I levels in ESRD patients may be attributed to TDC-induced bacteremia. Additional investigations are warranted on this subject for definitive conclusion.

PUB171

Comparison of Survival and Hospitalization of Hemodialysis Patients Who Started Hemodialysis via Tunneled or Non-Tunneled Central Venous Catheter

Ji In Park, 1 Jung Pyo Lee, 2 Ji-Young Choi, 3 Yong-Lim Kim, 1 Yun Kyu Oh, 2 Dong Ki Kim, 1 Yun So Kim, 1 Chun Soo Lim. 1 Seoul Natul Univ College of Medicine; 2Seoul Natul Univ Borameal Medical Center; 3Kyungpook Natul Univ Hospital.

Background: Some of end-stage renal disease (ESRD) patients inevitably start dialysis via central venous catheter (CVC). Tunneled central venous catheter (TCVC) is well known to be better than non-tunneled central venous catheter (NTCVC) in terms of lower risk of infection and catheter failure. In this study, we investigated whether the difference in the use of these two different types of catheter shows difference in the survival and vascular access related hospitalization or not.

Methods: We enrolled new diagnosed ESRD patients and collected the data prospectively from August 2008 to March 2013. Laboratory and clinical variables with the type of catheter were documented, and hospitalization and mortality were recorded as the outcome events.

Results: Among 1770 patients, 810 patients started hemodialysis via CVC, 629 patients with TCVC and 181 with NTCVC. Hospitalization due to catheter-related infection were higher in NTCVC group (2.21%) than in TCVC group (0.47%) (p=0.048). TCVC group also showed significantly better survival rate than NTCVC. In the multivariate analysis adjusting for age, liver disease and congestive heart failure, the type of catheter was still significantly associated with survival (p<0.021).

Conclusions: The data demonstrate the TCVC has an association with the lower hospitalization rate due to catheter-related infection and has the higher survival rate than the NTCVC. TCVC should be firstly considered in the patients who start hemodialysis without functioning vascular access.

PUB172

Renal Outcomes in PICC Patients

Rita L. McGill, Takir Noureldine, Sushil Ratnaparkhe. Div of Nephrology, Allegheny General Hospital, Pittsburgh, PA.

Background: A 2012 quality-improvement study identified peripherally-inserted central catheters (PICC) in 85/375 (22.6%) of our inpatients.

Methods: The hospital data system was examined to identify renal outcomes in these patients over the next 365 days; external data was not sought. AKI events were defined by KDIGO criteria, with elevated serum creatinine for 3 days required. Outcomes were classified as: non-recovery with dialysis, recovery after dialysis, recovery/stabilization without dialysis, or indeterminate.

Results: At baseline, 7/85 PICC patients were in ESRD and 18/85 had acute kidney injury (AKI); 60/85 patients were at their CKD baseline or had estimated GFR 60 ml/ min/1.73m². At least one additional AKI was seen in 11/18 patients. 6/18 required dialysis for initial AKI and 1 for subsequent AKI: 3 of these recovered. 21/60 patients without AKI at baseline developed episodes of AKI over 12 months, 3 of which required permanent dialysis. Overall 39/78 (50%) non-ESRD patients had initial and/or subsequent AKI, and 10/78 (12.8%) required dialysis.

*patient lost to follow-up or early death. Among 39 patients with initial or subsequent AKI, recovery or stabilization with or without dialysis could be documented in 29 cases. Final serum creatinine was significantly higher than baseline for these patients, (0.95± 0.30 vs. 1.73 ±0.84, P-value=0.001 for paired t-test, 95% CI for difference: 0.48-1.09).

Conclusions: Inpatients requiring PICC have a 50% risk for AKI and a 12.8% rate of requiring dialysis within a 12-month time-frame, despite methodological potential for low ascertainment. PICC patients who sustain AKI are at risk for accelerated deterioration of renal function, even when dialysis does not occur. Given the negative impact of PICC placement upon future hemodialysis vascular access, it may be reasonable to place all PICC lines in dominant arm, even when advanced CKD is not present, especially in patients with AKI.

PUB173

Prospective Observation of Effect of Vascular Access Types on C Reactive Protein, ESR and Fibrinogen in 203 Hemodialysis Patients


Background: In this study effect of arteriovenous fistula (AVF) and Permanent hemodialysis catheters (PC) on inflammatory markers were observed in patients without any local or systemic infection.

Methods: Out of 350 patients dialyzing in Prince Sultan military medical city (PSMMC) 200 patients were included in this study. Patients with arteriogenous graft and who had documented local or systemic infection by repeated cultures were excluded from this study. The patients included in this study had monthly blood cultures. Total observation period was 180 days. The average of monthly C reactive protein (CRP), ESR and fibrinogen was taken for analysis. All patients were dialyzed with same dialyzer (Hemoflow FX0)

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

Underline represents presenting author.

913A
and heparin was used as anticoagulant. Patients with Hemoglobin above 12 or below 10 gm/dl were also excluded. Hemodialysis mode was used for all patients. SAS version 9.3 software was used for the data analysis.

**Results:** Mean age of observed group was 59.49 years. 55% were dialyzing with fistula and the rest with PC. Mean Kt/V in these two groups were statistically insignificant. There was no statistical significance between the PC and AVF regarding ESR and CRP protein level and fibrinogen. However fibrinogen level was significantly lower in PC group (p = 0.031 *).

**Conclusions:** In non infected patients, CRP and ESR are not affected by access types, if the patients are dialyzed by same dialyzer using same anticoagulant. Fibrinogen level is significantly lower in PC group.

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

**PUB174**

**Presentation and Complications of Non-Thrombus-Related Fibrin Sheath Pulmonary Embolus following Tunnelled Dialysis Catheter Removal**

**Background:** We report an unusual complication of tunnelled dialysis catheter removal. Fibrin sheath emboli have only previously been reported following line stripping, or in association with catheter related thrombus, whilst a prospective study has suggested that fibrin sheaths alone do not directly embolise following line removal.

**Methods:** A 25 year old male presented with advanced renal impairment of unknown cause. Dialysis was commenced via uncomplicated insertion of a right internal jugular tunnelled dialysis catheter. This remained his preferred choice of access whilst transplantation was pursued. After 9 months hemodialysis he presented with catheter sepsis. His line was removed without event. Temporary access was attempted via right internal jugular vein 24 hours later but failed; a temporary femoral dialysis catheter was inserted. Two days later he described left upper quadrant pain out of keeping with physical examination and observations. After several reviews, a computed tomography pulmonary angiogram (CTPA) was performed.

**Results:** CTPA demonstrated left sided pulmonary artery fibrin sheath emboli and no thrombus. Following involvement from the cardio-thoracic team he was managed conservatively and warfarinised. Within a week he reported new breathlessness. CTPA demonstrated unchanged sheath emboli, extended infarction and an expanded extensive pleural effusion. After a prolonged admission he recovered and was established on peritoneal dialysis.

**Conclusions:** Symptomatic non-thrombus-related fibrin sheath embolisation has not previously been reported. It is thought to be a rare complication; perhaps rarely diagnosed or clinically apparent. This episode may have been precipitated by access attempts at the site of recent removal. We recommend consideration be given to fibrin sheath embolisation in patients presenting with pleuritic chest pain, upper abdominal pain or new pleural effusions.

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

**PUB175**

**Importance of Monitoring and Immediate Intervention for Vascular Access Optimization**

**Background:** Programs of monitoring vascular access (VA), including angiographic and/or surgical intervention, have been performed in order to improve VA outcome. Our goal is to assess the impact of an immediate response from a vascular access center (VAC) and/or surgical intervention, have been performed in order to improve VA outcome. Our study retrospectively evaluates the clinical course and treatment outcome of performing PTA for dysfunctional, non maturing or thrombosed AVF in our experience.

**Methods:** Between Jan. 2008 and Dec. 2012, 101 PTA procedures were performed on 73 patients (49 men; median age 67 years, range: 27-89) with dysfunctional (63%), non maturing (7%) or thrombosed (30%) AVF. 63 wrist radiofocal [25 with latero-terminal (L-T), 38 with terminal-terminal (T-T) anastomosis] and 10 elbow fistulae with median age of 12 months (range 1 month-13 years) were treated.

**Results:** In radiofocal L-T AVF, stenoses were located in the ixia-anastomotic segment in 11 patients, in anastomotic area in 5, in the venous outflow in 5, in central vein in 1, in multiple areas in 3; in radiofocal T-T AVF the distribution was similar (ixia-anastomotic 47%, anastomotic 21%, outflow vein 16%, central vein 5%, multiple areas (11%). In elbow fistulae the stenoses were in the outflow vein in 7 patients (70%) and around the anastomotic region in 3 patients (30%). Angiographic and clinical success was 88%; 17 patients required 28 repeat PTA for recurrent stenosis/thrombosis. 8 patients had small extravasation that required no further treatment, 1 patient had microembolism in second interdigital artery. Excluding initial failure, mean primary and secondary patency for AVF were 34.3 months (95% CI:26.4-42.1) and 41.1 months (95% CI:37.9-52.4); the primary and secondary cumulative patency rates at 12 months were 59% and 84% respectively.

**Conclusions:** PTA can effectively salvage dysfunctional, non maturing or thrombosed AVF. Since repeat angioplasty is often necessary to maintain function, careful surveillance is necessary.

**Funding:** Other NIH Support - NIH grants 1R41HL110430 and 1R41HL112517, Private Foundation Support

**PUB176**

**Percutaneous Transluminal Angioplasty (PTA) for Dysfunctional, Non Maturing or Thrombosed AVF: A Local Experience**

**Background:** The arteriovenous fistula (AVF) is considered the vascular access of choice and stenoses are the major cause of its dysfunction. Our study retrospectively evaluates the clinical course and treatment outcome of performing PTA for dysfunctional, non maturing or thrombosed AVF in our experience.

**Methods:** Between Jan. 2008 and Dec. 2012, 101 PTA procedures were performed on 73 patients (49 men; median age 67 years, range: 27-89) with dysfunctional (63%), non maturing (7%) or thrombosed (30%) AVF. 63 wrist radiofocal [25 with latero-terminal (L-T), 38 with terminal-terminal (T-T) anastomosis] and 10 elbow fistulae with median age of 12 months (range 1 month-13 years) were treated.

**Results:** In radiofocal L-T AVF, stenoses were located in the ixia-anastomotic segment in 11 patients, in anastomotic area in 5, in the venous outflow in 5, in central vein in 1, in multiple areas in 3; in radiofocal T-T AVF the distribution was similar (ixia-anastomotic 47%, anastomotic 21%, outflow vein 16%, central vein 5%, multiple areas (11%). In elbow fistulae the stenoses were in the outflow vein in 7 patients (70%) and around the anastomotic region in 3 patients (30%). Angiographic and clinical success was 88%; 17 patients required 28 repeat PTA for recurrent stenosis/thrombosis. 8 patients had small extravasation that required no further treatment, 1 patient had microembolism in second interdigital artery. Excluding initial failure, mean primary and secondary patency for AVF were 34.3 months (95% CI:26.4-42.1) and 41.1 months (95% CI:37.9-52.4); the primary and secondary cumulative patency rates at 12 months were 59% and 84% respectively.

**Conclusions:** PTA can effectively salvage dysfunctional, non maturing or thrombosed AVF. Since repeat angioplasty is often necessary to maintain function, careful surveillance is necessary.

**Funding:** Other NIH Support - NIH grants 1R41HL110430 and 1R41HL112517, Private Foundation Support

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

Underline represents presenting author.

914A
Use of Cefuroxime in Treatment of Methicillin Sensitive Staphylococcus aureus in Haemodialysis Patient – A Single Centre Experience Vijay Sundaram Thanaraj, Ajay Prabhakar Dhaygue. Dept of Renal Medicine, Lancashire Teaching Hospital, Preston, Lancashire, United Kingdom.

Background: Infection is one of the most common causes of mortality in haemodialysis patients especially in patients who dialyse via catheter. It is common practice to use Vancomycin in management of Methicillin sensitive Staphylococcus aureus (MSSA) infection because of the broad-spectrum cover and convenience of administration in haemodialysis patients. Flucloxacillin is an effective alternative but q.i.d. dosing poses compliance problem. Use of Vancomycin however is associated with number of limitations. The incidence of Vancomycin resistant Enterococcus is on the rise. It is less bactericidal compared with the cephalosporins and penicillins.Cefuroxime, a second generation Cephalosporin is effective against MSSA and offers advantage over Vancomycin as above.

Methods: We used intravenous Cefuroxime; 1.5 grams given at the end of each dialysis session for a period of four weeks in patients with MSSA infection in haemodialysis patients. Root cause analysis and appropriate investigations were done for all the patients with MSSA infection to exclude other potential sources of infection other than dialysis catheter. Repeat blood cultures and exit site swab were taken following treatment to exclude ongoing bacteraemia. Ten patients were diagnosed with MSSA infection between December 2009 to March 2013.

Results: None of the 10 patients, who were treated with Cefuroxime, relapsed following completion of the course of treatment. The mean follow up period was 398 days.

Conclusions: In this study Cefuroxime appears to be safe and effective alternative in management of MSSA infection in haemodialysis patients. First generation cephalosporin (cefoxolin) has been used successfully, use of second generation cefuroxime has not been reported before. Although small number of patients were treated with cefuroxime, unlike cefazolin, we did not find any treatment failure and it may be superior to 1st generation cephalosporin. Like most of the first generation cephalosporin, this study has shown that the number of patients however we are proactive with ‘fistula’ first policy and incidence of catheter associated infections are very low in our centre. Further large studies are recommended.

The Research of Anatomic Relationships between the Internal Jugular Vein and the Common Carotid Artery under CT Scan Yimin Zhang, 1 Div of Nephrology, The Sixth Hospital of Sun Yatsen Univ, Guangzhou, Guangdong, China; 2Div of Nephrology, The Sixth Hospital of Sun Yatsen Univ, Guangzhou, Guangdong, China; 3Div of Nephrology, The Sun Tatsen Memorial Hospital of Sun Yatsen Univ, Guangzhou, Guangdong, China.

Background: Central venous cannulation through the internal jugular vein is necessary for the management of a variety of clinical conditions. The aim of this study was to investigate anatomic relationships between the internal jugular vein and the common carotid artery under CT enhancement scan at a different plane.

Methods: A total of 226 patients who were checked the neck by CT enhancement scan since January 2010 to July 2012. All patients were supine position and the heads were normotopia. To collect the anatomic relationships between the internal jugular vein and the common carotid artery at the high plane(above the upper edge of the thyroid cartilage) and the median plane(above the level of the cricoids cartilage)of all patients.The relationships were classified as anterior,anterolateral,anteromedial,posterolateral,posteriomedial,median or parallel or overlap. Categorical variables were presented as counts and were compared by the chi-squared test.

Results: There were 116 male patients(mean age was 52.1±13.9) and 110 female patients(mean age was 49.5±14.5). No patients showed the image with the internal jugular vein and the common carotid artery placed conversely. Two cases were anterior complete overlap on the lefe side(0.9%). At the high plane, the internal jugular veins were mainly posterior and posterolateral position(78.6%±8.3%). The relationships with the common carotid artery were mainly partially overlap(70.5%±71.4%). While at the median plane ,the internal jugular veins were mainly anterior and anterolateral position(72.3%,P<0.00 for both), the relationships with the common carotid artery were mainly parallel(56.2%±63.4%,P=0.00 for both).

Conclusions: The relationships between the internal jugular vein and the common carotid artery at the median plane had more proportion of parallel than at the high plane.


Background: Catheter dysfunction and catheter-related infections remain a significant cause of morbidity in patients maintained on tunnelled central venous catheters. Turolidine-heparin-citrate line locks containing an antimicrobial (turolidine) could potentially reduce the risk of catheter-related bacteraemia, although there are concerns that the reduced concentration of heparin (500 units/ml vs 5000 units/ml) may result in acceptably high rates of catheter dysfunction. A small randomized control trial demonstrated increased catheter survival in the setting of catheter salvage, however, there is no published data relating to switching line locks in a prevalent haemodialysis population.

Methods: A retrospective comparison was performed of all patients in three dialysis units, who underwent a switch in their standard line lock from heparin to taurolidine-heparin-citrate. Patients who died or changed modality of renal replacement therapy were excluded. Comparison of a number of parameters including thrombolytic usage, line changes, catheter infection or line loss were compared between the two groups. This was undertaken for three months prior to and following the switch.

Results: Data from 225 patients were included in the analysis over six months. There was a trend to a non-statistically significant reduction in catheter-related bacteraemia (8 vs 3 [pre- vs post]; p=0.12) and reduction in individuals requiring thrombolytic line locks (25% vs 0.2%). There was also a low rate of catheter dysfunction requiring line change following the switch (2 vs 1). No difference could be demonstrated between any of the anaemia or dialytic parameters.

Conclusions: This retrospective study has not demonstrated any significant difference in a number of clinically relevant parameters following a switch from heparin to turolidine-heparin-citrate line locks in a prevalent dialysis population. This study has not demonstrated increased levels of catheter dysfunction but requires further analysis at twelve months following the switch.

An Unusual Turn of the Wire Roxana Neyra. Ambulatory Surgery Center, Arizona Kidney Disease and Hypertension Center, Phoenix, AZ.

Background: Every day, hundreds of hemodialysis (HD) catheters are inserted either electively or as an emergency to initiate HD and save patients from life threatening conditions. In the process, there are some immediate and long-term complications, such as...
as hemotoma, bleeding, pneumothorax, and central venous stenosis respectively. A case of subcapsular hepatic hematoma post HD catheter insertion is presented.

She was a 78-year-old female with past medical history significant for end stage renal disease on HD 3 times per week. She had refused arterio-venous fistula creation. Therefore, her vascular access was a right internal jugular hemodialysis catheter for about 4 years. Her catheter was exchanged about once a year. She presented to the outpatient surgery center in May 2009 for catheter exchange due to poor flows. The catheter was replaced successfully using two wires advanced to the Inferior Vena Cava (IVC). Shortly after the procedure she complained of abdominal pain, nausea and vomiting. At the same time hypotension and bradycardia was noted. Patient was immediately transferred to the hospital. She underwent emergent venogram of the IVC, and arteriogram of the hepatic artery that showed no bleeding or extravasation. A computerized tomography of the abdomen was performed and demonstrated a heterogeneous fluid collection in the right lobe of the liver suggestive of subcapsular hematoma. Patient was treated with supportive measures and was stabilized. Over the following days, she developed a myocardial infarction, sepsis and was transferred to hospice.

Results: An autopsy was performed, and showed no liver laceration, hepatic artery or IVC laceration, but confirmed the subcapsular hepatic hematoma.

Conclusions: a) Nontraumatic subcapsular hepatic hematoma is a rare complication of insertion of dialysis catheters due to the wire advancing through the hepatic veins. It can be managed by observation and supportive measures. It can be life threatening. b) There is a relative safety in advancing the wire to the IVC when inserting a catheter. The position of the tip of the wire needs to be monitored at all times during the procedure to prevent complications, like the one described here.

**PUB184**

Use of Rivaroxaban to Rescue Vascular Access in Hemodialysis Patients

Fabian A. Ortiz-Herbener, Dept of Nephrology, Instituto Ecuatoriano de Dialisis y Trasplantes, Guayaquil, Guayas, Ecuador

Background: Rivaroxaban is a direct inhibitor of factor Xa. This novel oral anticoagulant has substantial renal clearance, with half-life prolonged in patients with chronic kidney disease. There is no significant loss of clinical experience of rivaroxaban use in hemodialysis patients.

Methods: This study aimed to investigate the effect of rivaroxaban as a compassionate treatment for vascular access dysfunction. A cohort of 5 patients with a history of at least four previous vascular access thrombosis was selected. Two patients received 10 mg QD and three patients received 15 mg QD with a follow up of four months. The INR was measured in a monthly basis, and the results were categorized as: “Good” (improvement in vascular access permeability), and “No Response” (when there is no improvement at all, and the patient required a new access). In addition, major side effects (bleeding from any cause) were stated as “Present” or “Not present”.

<table>
<thead>
<tr>
<th>Floor (mg)</th>
<th>Baseline INR</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Response</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>female (10)</td>
<td>1.05</td>
<td>0.93</td>
<td>0.86</td>
<td>0.86</td>
<td>Good</td>
<td>No Response</td>
</tr>
<tr>
<td>male (15)</td>
<td>1.15</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>Good</td>
<td>No Response</td>
</tr>
<tr>
<td>female (15)</td>
<td>1.15</td>
<td>1.03</td>
<td>1.06</td>
<td>1.06</td>
<td>Good</td>
<td>No Response</td>
</tr>
<tr>
<td>male (15)</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>Good</td>
<td>No Response</td>
</tr>
</tbody>
</table>

Conclusions: To our knowledge, this is the first clinical experience of Rivaroxaban in hemodialysis patients. Although it is a small number of cases, we found three patients with good response and no patients with major side effects. Larger studies are required to establish the safety profile of the drug in hemodialysis scenario.

**PUB185**

Persistent Variation in the Frequency of Payment for More Than Thrice Weekly Home Hemodialysis (HHD)


Background: Regional fiscal intermediaries (FIs) and Medicare Administrative Contractors (MACs) that pay Medicare claims can authorize payment for >3 weekly treatments. Previous work showed FIs/MACs may contribute significantly to variation in HHD payments (Richard Hirth et al. 2011). Due to bundling of drugs and lab tests on a flat rate basis, each additional paid treatment results in greater incremental revenues under the expanded bundle dialysis prospective payment system (PPS) than under the prior system. Due to bundling of drugs and lab tests on a flat rate basis, each additional paid treatment results in greater incremental revenues under the expanded bundle dialysis prospective payment system (PPS) than under the prior system.

Methods: We examined trends in HHD payments and evidence that dialysis facilities established the safety pro

<table>
<thead>
<tr>
<th>Floor (mg)</th>
<th>Baseline INR</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Response</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>female (10)</td>
<td>1.05</td>
<td>0.93</td>
<td>0.86</td>
<td>0.86</td>
<td>Good</td>
<td>No Response</td>
</tr>
<tr>
<td>male (15)</td>
<td>1.15</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>Good</td>
<td>No Response</td>
</tr>
<tr>
<td>female (15)</td>
<td>1.15</td>
<td>1.03</td>
<td>1.06</td>
<td>1.06</td>
<td>Good</td>
<td>No Response</td>
</tr>
<tr>
<td>male (15)</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>Good</td>
<td>No Response</td>
</tr>
</tbody>
</table>

Conclusions: To our knowledge, this is the first clinical experience of Rivaroxaban in hemodialysis patients. Although it is a small number of cases, we found three patients with good response and no patients with major side effects. Larger studies are required to establish the safety profile of the drug in hemodialysis scenario.

**PUB186**

A New System for the Short-Daily Hemodialysis Using Slow Sterile Dialysate Flow Rate

Wael Arkoache,1 Jacky Potier,2 Maurice Laville,1 ‘AUVR, Lyon, France; ‘Centre Hospitalier, Cherbourg, France; ‘Univ de Lyon, Pierre Benite, France.

Background: PHYSIDIA S is a new system for hemodialysis using slow sterile dialysate flow rate, without needing of a processing of water treatment. The mechanical characteristics of this machine are based on a new concept for the control of a precise dialysate flow rate. This system is especially intended for the short-daily home hemodialysis and obtaining the marked by the European Community.

Methods: A clinical pilot multicentric trial is led in France before the marketing. The objective of this study is to control the clinical tolerance of the patients and to analyze the impact of low dialysate volumes on the removal of solutes of different molecules. The ethic committee approved the protocol.

Results: Four patients dialyzed in two different centers ended the study: mean age 53.3 ± 20.7 years (mean ± SD); dry weight 69.9 ± 11.9 kg; BMI 26.3 ± 4.7; dialysis protocol 6 times per week x 2 hours by session. Polyethersulfone membrane is used (surface 1.9m2; KUF 75 ml/h/mmHg). The results of 12 sessions by patient (total 48 sessions) are summarized below (mean ± SD).

- Dialysis session duration: 116 ± 56 minutes; the total of volume of spent dialysate and ultrafiltration volume by session 24.8 ± 11.1 L; flow rate of dialysate 195 ± 5 ml/min; total UF by session 1554 ± 437 ml; total of urea recovered in the dialysate 317 ± 62 mmol by session; spKt/V by session 0.71 ± 0.15; eKt/V by session 0.53 ± 0.11; Std Kt/V by week 2.66 ± 0.45; β2-microglobulin (β2m) Reduction Rate (RR) by session 49.3 ± 6.4%; total of β2m recovered in the dialysate 110 ± 32 mg by session; Phosphorus RR by session 50.0 ± 8.2%; total of phosphorus recovered in the dialysate 17.6 ± 5.2 mmol by session.

Conclusions: The patient tolerance is very satisfactory without particular event, with a clinical evolution as the well-known evolution of a short-daily hemodialysis. Results are satisfactory and correspond to the results described for the short-daily hemodialysis with low flow dialysate rate. The machine is easy to use, and was reliable for all the periods of the essays.

**PUB187**

Adequacy of Glycemic Control in Diabetic Dialysis Patients: A Single Center Prospective Observational Study Using Continuous Glucose Monitoring

Siddharth Sharma, Thomas T. Titus, Talib Kasim Aljumahy. Nephrology, Gold Coast Hospital, Gold Coast, Queensland, Australia.

Background: Most international guidelines recommend targeting HbA1c of <7% irrespective of the presence of chronic kidney disease. However, the correlation of HbA1c with glycaemic control in dialysis patients is contentious due to shortened red cell survival, frequent blood transfusions, iron deficiency and use of erythropoietins. Paradigmatically, a large retrospective analysis of diabetic dialysis patients has shown worse outcomes in dialysis patients with HbA1c <5%. Intestinal glucose measurements using Continuous Glucose Monitors(CGM) correlates well with blood glucose using a glucometer even in dialysis patients. Hence, Continuous Glucose Monitoring could identify periods of significant hypoglycemia in dialysis patients.

Methods: This is a single center observational study, conducted on all in-center diabetic dialysis patients. CGM was applied to each patient for a total of 6 days continuously. Patients underwent routine dialysis and kept a diary to record their food intake and episodes of hypoglycemia. HbA1c was measured along with routine monthly dialysis bloods on each patient.

Results: There were no episodes of asymptomatic hypoglycemia in the study patients. There appeared to be better correlation between regular venous blood sugar reading than with HbA1c.

Conclusions: Asymptomatic hypoglycemia does not appear to be a factor in this small study. Regular blood sugar monitoring may be better marker for adequacy of glycemic control than HbA1c, in diabetic haemodialysis patients.

Funding: Pharmaceutical Company Support - Medtronic- supplied Continuous Glucose monitors for duration of study only

**PUB188**

Increased Levels of Tissue Factor, Adhesion Molecules, Nitric Oxide and Adiponectin in End Stage Renal Disease

Vinod K. Bansal,1 Jawed Fareed,2 Kristiyana Kaneva.2 Adiponectin in End Stage Renal Disease

Increased Levels of Tissue Factor, Adhesion Molecules, Nitric Oxide and Adiponectin in End Stage Renal Disease

Vinod K. Bansal,1 Jawed Fareed,2 Kristiyana Kaneva.2 Adiponectin in End Stage Renal Disease

Increased Levels of Tissue Factor, Adhesion Molecules, Nitric Oxide and Adiponectin in End Stage Renal Disease

Vinod K. Bansal,1 Jawed Fareed,2 Kristiyana Kaneva.2 Adiponectin in End Stage Renal Disease

Increased Levels of Tissue Factor, Adhesion Molecules, Nitric Oxide and Adiponectin in End Stage Renal Disease

Vinod K. Bansal,1 Jawed Fareed,2 Kristiyana Kaneva.2 Adiponectin in End Stage Renal Disease

Increased Levels of Tissue Factor, Adhesion Molecules, Nitric Oxide and Adiponectin in End Stage Renal Disease
Methods: This study included 119 ESRD patients on maintenance hemodialysis in conjunction with an ongoing IRB approved protocol on the profiling of inflammatory markers. Baseline plasma samples were collected from these patients prior to the routine dialysis session. Nitric oxide levels (NO) were measured using a commercial kit from R&D systems (Minneapolis, Minnesota) and ELISA based methods for TF, P-Sel, s-ICAM and adhesion protein were also purchased from R&D systems, Chromogenic and thrombin substrate method were used to measure the anti-Xa activity and thrombin generation.

Results: Tissue factor levels were found to be increased in the ESRD group (20.4±6.1 pg/ml) vs the control (11.2±4.1 pg/ml). The nitric oxide level was markedly higher in the ESRD group (12.1±7.4 M) vs the controls (7.3±4.3 M). The p-selectin levels were also elevated in the ESRD group (46.2±20 ng/ml) vs the control (31.3±4 ng/ml). The soluble ICAM levels were higher in the ESRD group (250.1±112 ng/ml) vs the control (180.1±17 ng/ml). Interestingly, the adhesion protein levels were also increased in the ESRD group (19.2±9.3/ mg/ml) vs the control (11.2±4.1 pg/ml). The pre-dialysis samples of the ESRD patients exhibited detectable levels of leptin.

Conclusions: These studies suggest that TF, NO, p-selectin and s-ICAM levels are increased in the ESRD patient. Despite the fact that a significant number of ESRD patients being anticardio, the AD levels were increased in this group. These results suggest that while ESRD represents a pro-inflammatory/hypercoagulable state, the repeated administration of heparin and other drugs may contribute to the regulation of the hemostatic process and inflammatory balance.

**PUB189**

Optimal Serum Phosphate and Calcium for Hemodialysis Patients Judging from Fibroblast Growth Factor-23 and Parathyroid Hormone Hiroshi Tanaka,1 Tomoyuki Kitai,2 Kumi Okamoto,2 Maki Mikami,2 Rumi Sakai,3 Ashiya Sakairumi Clinic, Ashiya, Hyogo, Japan; 2Sakairumi Clinic, Kobe, Hyogo, Japan.

Background: High dose hemodialysis, HDD improves mortality, blood pressure control, and life of hemodialysis patients. We have reported that HDD significantly decreased serum fibroblast growth factor-23, FGF-23, interleukin-6, IL-6, β2-microglobulin, β2-MG than standard dose hemodialysis, SDD. In this study we analyzed correlations between the above parameters including routine laboratory data of the patients with different dialysis doses.

Methods: We selected 206 hemodialysis patients, whose treatment modes were not changed at least 3 months. They were divided in two groups, whose hemodialysis product, HDD was higher or lower than 54 (ex. 6 hours/session and 3 times weekly). SDD patients were divided in two groups, whose hemodialysis product, HDD patients.

Results: Serum phosphates of SDD and HDD patients were 4.9 ± 1.3 and 4.4 ± 1.0 mg/dl, respectively with a significant difference. Their serum calciums were 8.9 ± 0.6 and 8.9 ± 0.6 mg/dl, respectively. Table shows correlation coefficients and p values of each laboratory data of all, SDD and HDD patients.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SDD patients</th>
<th>HDD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>0.533, P=0.001</td>
<td>0.564, P=0.001</td>
</tr>
<tr>
<td>P</td>
<td>0.529, P=0.001</td>
<td>0.525, P=0.001</td>
</tr>
<tr>
<td>Ca × P</td>
<td>-0.278, P=0.005</td>
<td>-0.278, P=0.005</td>
</tr>
<tr>
<td>Ca/P</td>
<td>0.200, P=0.005</td>
<td>0.200, P=0.005</td>
</tr>
</tbody>
</table>

Conclusions: In order to decrease serum FGF-23, serum phosphate should be as lower as possible avoiding morbid hypophosphatemia. Serum Calcium should be kept higher within the normal range regarding FGF-23 and parathyroid hormone, PTH.

**PUB190**


Background: Recent studies have demonstrated that cystatin C is cleared by hemodialysis. In this study, we assessed cystatin C kinetics during single hemodialysis treatments and estimated its volume of distribution.

Methods: Nine patients undergoing 10 hemodialysis sessions were studied. Each patient received a 3-4 hours hemodialysis session, which included a 1-hour dialysis only treatment, a 1-hour ultrafiltration only treatment plus 1-2 hours of combined dialysis and ultrafiltration. Arterial and venous blood sampling to measure cystatin C, creatinine, and urea levels at 2-hour treatment interval was done to calculate the diffusional, convective, and combined clearances of each solute. The clearance values of the three markers were compared with each other. The cystatin C clearance as calculated by solute clearance equations was compared with that obtained from a one-compartmental mass balance model. The cystatin C volume of distribution, its 30-minutes rebound ratio and its equilibration ratio were also calculated.

Results: The mean age ± standard deviation (SD) of the patients was 57 ± 9.3 years. The mean ultrafiltration volume (L) was 1.9 ± 1.0 L. There was a statistically significant difference between the cystatin C clearance values as estimated by the equations and by the model (p=0.014). There was also statistically significant differences between cystatin C, urea and creatinine clearances by all the treatment modes (p<0.05).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SDD patients</th>
<th>HDD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>0.533, P=0.001</td>
<td>0.564, P=0.001</td>
</tr>
<tr>
<td>P</td>
<td>0.529, P=0.001</td>
<td>0.525, P=0.001</td>
</tr>
<tr>
<td>Ca × P</td>
<td>-0.278, P=0.005</td>
<td>-0.278, P=0.005</td>
</tr>
<tr>
<td>Ca/P</td>
<td>0.200, P=0.005</td>
<td>0.200, P=0.005</td>
</tr>
</tbody>
</table>

Conclusions: Our relatively small study indicates disturbed metabolism of the essential amino acid tryptophan, poor sleep health, fatigue, and depressive symptoms. A larger sample size is necessary to more comprehensively explore the potential spectrum of interactions between TRP status and patient reported outcomes.
Levocarnitine Administration Can Improve Left Ventricular Systolic Function in Hemodialysis Patients Diagnosed with Car nitine Deficiency

Background: Since cardiac systolic dysfunction has been shown to be a risk factor for both mortality and the development of de novo CHF in patients on HD, a number of studies were performed to measure the effect of levocarnitine (LC) administration on systolic function in such patients. Cardiac dysfunction is also a contributing factor to the occurrence of dialysis-associated hypotension.

Methods: Over a three-month period, a daily dose of levocarnitine chloride (1800mg/day) was administered orally to 134 patients on HD who were diagnosed with cardi ovascular disease. At the end of the three months, the patients were divided into 3 groups according to the change in plasma free carnitine (FC) as follows: group1: FC=30±15μmol/L, N=22, group2:30<FC=72, N=13, group 3: FC=72, N=99. LDL and EF were measured by echocardiogram and PEP/ET was examined by systolic time interval using Varasen system in all patients before and after treatment. Blood pressure (BP) was measured at the start and the end of HD session and averaged for a week before and after 48 hours. The lowest positive blood pressure (BP) and maximum decrease of BP during dialysis were also measured. The frequency of use of vasopressors during the time of dialysis was compared among the patients in the groups.

Results: After administration of LC, the plasma concentration of FC increased in groups 2 and 3 significantly (from a mean ± SD of 22.5±4.7μmol/L to 45.8±11.3μmol/L in group 2, from 20.4±4.6μmol/L to 27.55.1±136.6μmol/L in group 3; paired t-test P<0.01). However, it did not increase significantly in group 1 (from 23.4±3.1 to 25.0 ± 4.6 μmol/L, n.s). PEP/ET improved significantly in group 3 (from 0.331 to 0.27, P<0.01), but remained unchanged in the other groups. LDL and LVEF did not change in any group. BP during dialysis did not show a significant change. The dosage of an occasional boosting agent to be used for dialysis hypotension significantly decreased in group 3, but remained unchanged in the other two groups.

Conclusions: Our study strongly suggested that levocarnitine administration can improve the left ventricular systolic function of patients on HD and reduce the frequency of HD-related hypotension.

Oral Iron Therapy Increases Serum Level of Hepcidin in Patients on Hemodialysis
Yuki Naito,1 Hiroki Takimoto,1 Masaaki Shimotori,1 Yutaka Tsubata,1 Kozo Mermel.1
1Dept of Medicine, Alpert Medical School, Brown Univ, Providence, RI.

Background: Patients receiving larger dose of ESA.

Methods: We studied 33 stable, dialyzed-patients transferred from CHD to ol-HDF. The mean values of laboratory tests at the initiation of HD treatment were: Hb, 9.1±1.0 g/dL; ferritin, 353±272 μg/L; HPC (ng/ml) was 0.6±0.8 at 0W in the HD, which was lower than 918A

PUB198
On-Line Hemodiafiltration and Control of Uremic Anemia
Ignace Mpio,1 Jean-christophe Szelag, Walid Arkouche. AURAL, Lyon, France.

Background: Control of anemia in chronic dialysis is a major regarding clinical outcomes. Nine months prospect over-cross study to determine if the advantages of the convective transfers of on line hemodiafiltration (ol-HDF) are associated with a better control of anemia than in conventional hemodialysis (CHD).

Methods: We studied 33 stable, dialyzed-patients transferred from CHD to ol-HDF (16 women (48%), mean age 73 ± 11 years, length of dialysis 7 ± 6 years, 24 (73%) were treated with erythropoiesis stimulating agents (ESA). Technical characteristics of CHD and of-HDF: ultra pure water, blood flow ≥ 300 ml / min and high membrane permeability (area ≥ 1.9 m² and ultrafiltration coefficient ≥ 40 ml/h · mmHg). HF was mainly used in the post-dilution mode (volumes of substitution of 18 to 24 l). Two phases were defined: phase A (CHD) and phase B (ol-HDF). Clinical and biological parameters of anemia were measured at Day 0 in phase A and after 9 months in phase B: ESA doses converted in dose of epoetin alpha (DA) per week, hemoglobin (Hb), albumin (Alb), iron saturation index (ERI) = weekly dose of DA in μg / Hb in g/dl, CRP, albumin, ferritin, and delivered dialysis dose (KT).

Results: After 9 months in ol-HDF, the comparative analysis of the results phase A and phase B reported: Hb (11.8 vs 11.7 g / dl; ERI (4.5 vs 4.1); doses of DA (53 vs 43 μg / wk, p<0.05); CRP (12 vs 9 mg / L; p<0.05); KT (47 vs 52 l); ferritin (353 vs 453 μg / L); albumin (39 vs 38 g / L). In Phase B the ESA dose was decreased by 10 μg (20%) associated with a reduction of CRP, maintaining Hb and ERI levels equivalent to phase A. A statistically significant difference in the nutritional and nutritional assessment. We found a significant correlation between delta DA and delta CRP but no correlation between KT and dose of DA.

Conclusions: ol-HDF is a non-pro-inflammatory dialysis mode as reported by other authors and facilitates the response to ESA. The properties of the convective purification have implications in reducing other causes of erythropoietin resistance.
Impact of Angioaccess Type in Hemoglobin Levels, Iron Kinetics and Erythropoietin Dose in Two Hemodialysis Units of Fresenius Medical Care in Puebla City, Mexico José Guillermo Pacheco Paredes, Carlos Colcher, Julio de León Ramírez Reyes, Karina Delfina Perez ayala. Fresenius Medical Care, Puebla, Mexico.

Background: An important issue in correcting anemia in hemodialysis patients is improving dialysis quality. It is demonstrated that in patients with chronic access has better outcome than patients with temporal access. The present study tries to demonstrate the relationship between hemoglobin levels, Epo alpha dose and iron kinetics with the type of angioaccess chronic or temporal in two separated units of hemodialysis in Puebla City, Mexico.

Methods: Data from medical files were analyzed that included hemoglobin levels, iron kinetics and concomitant erythropoietin (Epo) dose, by access type. STUDY DESIGN: Cohort longitudinal prospective study.

Results: 249 patients were studied in two-separated hemodialysis units with 6 months follow up from July 2012 to January 2013. The access type distribution was 47% with temporal angioaccess and 53% with chronic angioaccess. In patients with temporal access the hemoglobin levels were 10.6, g/dl serum ferritin were 434 and %transferrin saturation was 32%. For patients with chronic angioaccess the hemoglobin levels were 11g/dl, serum ferritin 396 and %ST 39. The distribution of Epo dose was not significantly different. 50 patients were lost for different causes. 209 patients with complete data were included in the study. The access type distribution was 75% with chronic angioaccess and 25% of the patients with temporal access. Hemoglobin levels for patients with temporal access were 10.9 ferrign levels 409 and %ST 32% was 32%. For chronic access hemoglobin levels were 11.6 ferrign levels 361 and %ST 31%, 33 patients dropped from temporal vascular access to chronic vascular access. These patients had an improvement in the hemoglobin levels and ferritin levels with no significantly change in Epo dose.

Conclusions: In our population the improvement of hemoglobin levels and the decrease in the ferritin levels were the most relevant factors associated to chronic angioaccess. Epo dose was not significantly changed during the 6-month follow up; nevertheless no patient with chronic angioaccess required an increase in Epo dose.

Funding: Private Foundation Support

Can the Use of a Novel Dialysis Bloodline Increase Haemoglobin and Reduce Erythropoietin Doses? Interim Results of an Ongoing Clinical Audit Iain C. Macdougall,1 Adam Rumjon,1 Emmanuel Mangahis,1 Thomas Rybczynski,2 Franz-Gerold Lindmayr,1 Thomas Kilgallon.2

Background: To evaluate liver disease progression, we retrospectively compared levels of Hepatitis C Cirrhosis and Iron Load in End Stage Renal Disease

Methods: A pilot audit was set up to test the hypothesis. Fifteen patients from the chronic haemodialysis unit were entered into a 12-month open-label, single cross-over, cohort prospective audit. The patients were all aged over 18 years, had been on HD for at least 3 months and all had A-V fistulae. Haemoglobin (Hb) was measured on a monthly basis and EPO doses were recorded. Clinical decisions regarding EPO doses were made independently in line with an established anaemia management protocol.

Results: Eight of the patients experienced concurrent problems which led to them dropping out of the assessment. Drop out events included renal transplantation, gastrointestinal bleeding, episodes of acute inflammation, hospitalisation, and non-compliance. The remaining 7 patients demonstrated increases in haemoglobin (Hb) over a six month period of 1 g/dl. In 4 of the patients EPO requirements were reduced by 33% representing a total reduction of 9,000 IU/week, and a mean of 2,250 IU/week. Two patients have had no reduction to-date while one had a small increase at the start of the audit and has maintained that dose to-date. The patients have now entered into the cross-over phase.

Conclusions: As a result of these encouraging preliminary results, a Prospective European Multicentre Audit (PEMA) has been initiated to further evaluate the hypothesis that the use of the Oxelys bloodlines can improve the half-life of erythropoietin in dialysis patients and thereby reduce the requirements for ESAs, iron and heparin.

Funding: Pharmaceutical Company Support - Oxelys Ltd

Hepatitis C Cirrhosis and Iron Load in End Stage Renal Disease Nancy M. Tran,1 Devasmita Choudhury,1 Geri Brown,1 Terri W. Crook.2

Background: Hepatitis C (HCV) in patients with end stage renal disease(ESRD) is associated with increased cirrhosis, carcinoma and all-cause mortality. Whether or not an iron load given as part of dialysis anemia management can exacerbate fibrosis is uncertain.

Methods: To evaluate liver disease progression, we retrospectively compared levels of aspartate aminotransferase(AST), platelet count(p), AST/pl ratio, albumin, and iron load over a period of 20 years, from January 1992 through July 2012, in patients with ESRD alone(group 1, n=18), ESRD and HCV(group 2, n=24), and HCV alone(group 3, n=20). Using SPSS, continuous variables were analyzed with t-test and ANOVA; non-continuous variables were analyzed with Mann-Whitney test. The 3 groups were matched in terms of age, race, and gender.

Results: No difference was found in AST/pl ratio within or between groups( p>0.06) at start of analysis initiation in group 1 and 2; liver biopsy in group 3. Over study duration, the pl count was lower( p<0.04) but other biomarkers remained stable within group 2. Over time, there was no difference in biochemical markers within group 1, and none except for albumin within group 3. At completion of study, the AST/pl ratio in group 2 was not statistically different than values in group 1(p<0.86) or group 3(p<0.13). The total amount of iron received (intravenously or via packed red blood cell transfusions) was similar between groups 1(mean 8.0g) and 2(mean 10.6g) (U=171, p=0.72).

Conclusions: Preliminary findings show that while plt count was decreased within groups, the remainder of the biomarkers was not significantly different between groups 1 and 2 even in the setting of similar iron administration, which suggests a stable level of fibrosis. This finding could indicate that, despite their pre-existing liver disease, patients with ESRD/HCV may be able to tolerate the iron load. However, a larger cohort and review of other parameters (i.e. years of HCV exposure, HCV viral load, stage/grade of cirrhosis) will need to be further investigated.
Conclusions: Hb variability is very common in MHD patients, and the consistently low (<110g/l) is the most common Hb level fluctuation pattern in our center. Hb level is a protective factor for total clinical adverse events and death; Hb standard deviation and coefficient variation are risk factors for CV events.

Funding: Government Support - Non-U.S.

PUB204

Inflammation and CRP Chronic Haemodialysis Patients Cristobal Santacruz Nefrologia, Clinica de los Rinones Menyrial, Quito, Pichincha, Ecuador.

Background: We know that patients with CKD 5D have some conditions that predispose to be chronically inflamed and by this way their moribundity is increased. Several markers of inflammation have been used to measure, but has not been able to determine which one of them are the best and which could be useful in our daily clinical practice to get decreased moribundity. The goal of our study is to study in the interpretation of PCR and to determine patients in high risk.

Methods: 144 non selected patients 82 men (60%) and 62 women (40%), with a mean age of 53 years (range 16 to 83 years) treated with HD 44 months on average (range 3 to 161 months) were included in a base data when they began their treatments and this personal data was fill in. They did treatments with standard bicarbonate, biocompatibility dialyzers, minimal heparinization. None reused dialyzer. We made some labs exams as ferritin, transferrin, albumin and quantitative CRP.EPO was used to maintain predialysis Hb level 11-12g%. For this observational study we divided the patients into two groups: 1. Not inflamed CRP <5 mg / L. 2. Inflamed CRP > 5 mg / L.

RESULTS: 133 patients (94%) when assessed clinically were in good conditions regardless of the level of CRP, while 8 ptes (6%) considered clinically bad had an CRP average of 23. Associated comorbidities were: active lupus infection, severe heart disease and ischemic stroke.

Conclusions: 1.- 49% of HD patients specially men over 50 years old had high CRP level P=0,0086; 2.- The time spent in HD treatment, BMI, albumin, transferrin, ferritin and EPO doses doesn’t have statistical significance to rise the CRP level; 3.- The clinical course of patients and complications are not related with CRP levels but help us to identify patients at risk.

PUB205

Anemia in Hemodialysis Patients: An Audit of Hemoglobin Targets and Erythropoiesis-Stimulating Agents Use Samantha Jayne Owen, Adil Hazara, Sunil Bhandari. Hull and East Yorkshire Hospitals NHS Trust, United Kingdom.

Background: The objectives of anemia management in hemodialysis dependent (HD) patients have changed recently. We have reviewed the impact of Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines on anemia management in our HD population.

Methods: Hemoglobin concentration (Hb), Serum Ferritin (Ser), Platelet counts (PLT), ESA doses and blood pressures (BP) were reviewed retrospectively in all HD patients with reference to two separate time intervals: the last quarter of 2011 (‘Oct-Dec 2011’) and the same period in 2012 (‘Oct-Dec 2012’). For Hb, BP and ESA doses, average values from multiple observations have been used whenever possible.

Results: 230 HD patients were studied. Mean age: 64 (range 19 – 91) years; Male 147 (64%); mean duration on hemodialysis: 7 (range 2 – 34) years. Averages of Hb, Fer, PLT, ESA doses, BP and Hb/EPO are presented in table 1. There were no statistically significant differences in average Hb, Fer, systolic and diastolic OBP between the two time periods. ESA doses were lower by 0.5 micrograms/mcg/patient/week. Reduction in PLT was statistically significant.

PUB206

Determining the Hemoglobin Target in Order to Avoid Transfusion Ronil Kumar Patel, Adam E. Gaweda, Michael E. Brier. Univ of Louisville.

Background: The package insert for erythropoietin and recent comments from the FDA state “The goal is to individualize therapy and use the lowest ESA dose acceptable to reduce the need for red blood cell transfusion. We evaluate this goal through computer simulation.

Methods: We performed a simulation of hemoglobin (Hb) concentrations through time using the computer program Matlab. The following assumptions were made: 1) Hb level is below transfusion trigger level of 11 g/dL, 2) Routine blood loss is in the range of 1-3 gms Hem 3) Patients Hb cycle over a period of 6 months 4) Patients Hb cycle with an amplitude of 0.5 to 1.5 g/dL and 5) Transfusion threshold is 7 g/dL. Hb concentration was simulated using a sin function with period 6 months and amplitudes of 0.5, 1.0 and 1.5 g/dL. Each week we applied a Hb drop of 1-3 g/dL and assessed the need for transfusion based on the Hb falling to the transfusion threshold. The probability of transfusion was then summed over 26 weeks.

Results: The results are shown in Table 1 as the Hb target needed to avoid any transfusion for routine blood losses.

PUB207

Playful Intervention Improves Nutritional Knowledge of Hyperphosphatemia in Hemodialysis Patients Carina Machado de Barros,1 Marina Pioltine,2 Tânia Maria Marsulo Franciozi,1 Thais Barca Morais,2 Edeli Simioni Abreu,2 Rosana Farah,2 Bárbara Margareth Menardi Biavo,1 Jacqueline Santos,1 Elzo Ribeiro Júnior,1 Carmen B. Tzanno-martins.1 Nutrition, Grupo CHR. Brazil; 2Nutrition, Universidade Presbiteriana Mackenzie, Brazil.

Background: Chronic Kidney Disease (CKD) is a major public health problem and the control of serum phosphorus in these patients is recognized as an essential goal to be achieved in medical and nutritional treatment. This is due to the participation of this nutrient in the pathogenesis of secondary hyperparathyroidism, as well as in bone metabolism and bone mineralization. Objective: To evaluate the effects of a playful nutritional intervention on the knowledge regarding phosphorus of hyperphosphatemics patients undergoing dialysis.

Methods: A longitudinal study of 187 hemodialysis patients with hyperphosphatemia. In three nephrology clinics, located in São Paulo, Brazil. A nutrition dynamic was applied in the form of musical parody, composed by the researchers. All patients received, at the beginning of a given dialysis session, a pamphlet with the lyrics. The song featured key words to rise the CRP level; 3.- The clinical

Conclusions: Defining the target Hb concentration for an individual patient requires the assessment of the patients viability in Hb concentration over time, likely blood loss one wishes to protect against, the threshold for transfusion for that patient, and for those patients with the highest variability, one must balance the risk of transfusion vs. high mean Hb concentrations. The results of this simulation can provide the necessary information to set individual targets.

Funding: NIDDK Support

PUB209

Quantifying and Predicting the Effect of Infection and Erythropoietin Usage on Hemoglobin Level in Dialysis Patients Jenny Feng, Adam E. Gaweda, Michael E. Brier. Univ of Louisville.

Background: Infection contributes to anemia in dialysis patients with End Stage Renal Disease (ESRD). Erythropoietin(EPO) is recommend for improving hemoglobin(Hb) levels in such cases. However, hypo-responsiveness to EPO is evident during infection and there is a lack of evaluation of appropriate EPO dosages during infection.

Methods: The Hb levels of 46 dialysis patients with ESRD at the University of Louisville Kidney Disease Program Dialysis Unit were studied. They had stable Hb levels pre-infection, had at least 1 infectious event, and received increased dosages of EPO following infection. Hb levels from pre-infection, infection, and post-infection were averaged for each time period. EPO resistance was calculated. Patients who were hospitalized for their infections were compared to non-hospitalized patients.

Results: There were 27 infectious events that resulted in hospitalization and 15 infectious events that were treated at the dialysis unit. Hb levels decreased in both groups

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

Underline represents presenting author.
with a greater degree of decrease in hospitalized, -2.01±0.92 g/dL, versus 1.67±1.32 g/dL, in non-hospitalized. Duration of decreased Hb level was longer for hospitalized, 66.7±27.07 days, when compared to 59.53±33.66 days in non-hospitalized. The amount of time it took for Hb concentrations to recover and reach peak Hb concentrations was also higher for hospitalized, 77.40±45.41 days, when compared to 69.23±20.93 days non-hospitalized.

**Conclusions:** Infection contributes to hypo-responsivity to EPO in both hospitalized and non-hospitalized patients. Compared to non-hospitalized patients, hospitalized patients suffered from greater Hb decline and longer duration of hypo-responsivity. Aggressive EPO dose adjustment during and immediately following an infectious event may lead to overcompensation post-infection and Hb overshooting the target range. EPO dosages may need to be held constant or at least limit the dose escalation that occurs due to anemia management protocol. Ongoing work involves identifying factors associated with poorer EPO response and clinical outcomes, and simulating patterns of high response to EPO in infection.

**Funding:** NIDDK Support

---

**PUB210**

### Dysregulation of Thrombotic and Hemostatic Factors in End Stage Renal Disease

**Vinoif K. Bansal,** 1 Debra Hoppensteadt, 2 Syed Mustafa Ahmed, 1 Jaweed Fareed. 1 Nephrology, Loyola Univ Medical Center, Maywood, IL; 2Pathology, Loyola Univ Medical Center, Maywood, IL; 3Medicine, Loyola Univ Medical Center, Maywood, IL.

**Background:** Increased cardiovascular events occur in ESRD patients on maintenance hemodialysis. The objective of this study was to utilize newly introduced cardiac biomarker chips and immunoenzymatic methods, profiling various biomarkers of inflammation and thrombogenesis in a defined ESRD patient population.

**Methods:** Blood samples from seventy two ESRD patients were drawn prior to maintenance hemodialysis. Commercially available ELISA kits for Tissue Plasminogen Activator – Plasminogen Activator Inhibitor Type-1 complex (TPA-PAI-1 complex), Plasminogen Activator Inhibitor Type-1 (PAI-1), Myeloperoxidase (MPO), Thrombomodulin, (TM), Interleukin-1 beta (IL-1β), Anti-Annexin V, human sL-selectin, and Inter-Cellular Adhesion Molecule 1 (ICAM-1). Functional methods were used for measuring Antithrombino and Von Willebrand factor (vWF) activity. The biochip arrays (Randox, Evidence System, United Kingdom) for cardiac markers, included creatine kinase-MB (CK-MB), Myoglobin (Myo), Heart-type fatty acid binding protein (hFABP) and cardiac troponin I (cTnI). The cerebral array included C-reactive protein (CRP), D-Dimer (DDMER), Neuron Specific Enolase (NSE), Neutrophil Gelatinase-Associated Lipocalin (NGAL), soluble Tumor Necrosis Factor Receptor 1 (TNFR1) and Thrombomodulin (TM).

**Results:** ESRD patients showed assay dependent decrease in markers such as TPA-PAI-1, Anti-Annexin V, L-selectin and Antithrombin activity (ranging from 18 to 46%). The levels for MPO, TM, CK-MB, MYO, FABP, CRP, DDMER, NSE, NGAL, TNFR1, and vWF activity all showed a significant increase in the ESRD patients (ranging from 25%-5587%). No changes were observed in the IL-1β, ICAM1, or cTnI in ESRD patients compared to normal groups.

**Conclusions:** Studies underscore the role of inflammatory and thrombotic mediators in ESRD. The cardiac biochip array revealed a remarkable elevation of the FABP and as well as a notable increase in MYO. The cerebral array revealed a remarkable elevation of the TNFR1.

---

**PUB211**

### Stable Serum Magnesium Levels in Chronic Hemodialysis Patients

**Eduardo K. Lacson,** 1 Weiling Wang, 1 Chinu M. Jani, 2 Franklin W. Maddux, 1

1 Fresenius Medical Care, North America, Waltham, MA; 2Spectra Laboratories, Rockleigh, NJ.

**Background:** Serum magnesium (sMg) has been reported to be stable within one year in Japanese patients. We investigated the stability of sMg and prescribed dialysate magnesium (dMg) in chronic hemodialysis (HD) patients.

**Methods:** All in-center HD patients treated as of 1/1/08 at Fresenius Medical Care North America facilities with Mg measured for period 1 (4/1 - 6/30, 2007) and period 2 (10/1 – 12/31, 2007) were included. The 3-month mean sMg and weighted mean dMg for both periods were calculated and age, gender, race, diabetes mellitus, vintage, vascular access and hospitalization from the prior 30 days for each period. SigmaEpi variability (represented by twice the SD) indicates that ~95% of re-test samples will fall between ±0.2 mEq/L.

**Results:** 16,768 patients had mean age of 61.9±14.6 years, 53.7% males, 46.2% whites, 46.6% blacks, 7.2% other races, and 52.8% with diabetes, and dialysis vintage of 4.1 ± 3.7 years. The interquartile range (IQR) of delta sMg was -0.1 – 0.2 (Table). Subgroup analyses for age (<45, 45-54, 55-64, 65-75, and > 75 years), gender, race, diabetes mellitus, vintage (~<120, 121-1095, and >1095 days) and prior 30 dialysis hospitalization did not reveal effect modification.

**Conclusions:** Contrary to other studies, our study did not show any statistical difference in treatment of MI among all three groups: patients with normal kidney function, with CKD or ESRD. We recommend that our finding should be verified in large multicenter study.

---

**PUB212**

### Are There Differences in Treatment for Acute Myocardial Infarctions among Patients with Chronic Kidney Disease Stage 3-5, End Stage Renal Disease, and Patients with Normal Kidney Function?

**Ninad D. Parekh,** Chadi Saifan, Elie El-Charabaty, Suzanne E. El Suyeh. Dept of Medicine, Div of Nephrology, Staten Island Univ Hospital, Staten Island, NY.

**Background:** Patients with CKD and/or ESRD have a higher risk of CAD and consequently higher morbidity and mortality from CAD. In this study, we aim to evaluate the differences in inpatient care of acute MI among patients with no CKD, patients with CKD and patients with ESRD.

**Methods:** All patient with ESRD on dialysis admitted with MI from 2007 to 2012 were matched with patients with CKD and patients without CKD. The patients’ characteristics including age, sex, risk factors, medications, length of stay, and need for a cardiac catheterization or CABG were collected.

**Results:** Mean ages were 68.2, 66.1 and 68.9 years, for the no CKD, CKD, and ESRD groups respectively. There were no statistically significant differences in medications, length of stay, and LVEF among all three groups. The admission diagnosis, the need for catheterization or CABG, and different risk factors are shown in table:

<table>
<thead>
<tr>
<th>Category</th>
<th>No CKD</th>
<th>CKD</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.2</td>
<td>66.1</td>
<td>68.9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of Stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A t-test of two-sample assuming equal variances were done for the all three groups including the need for CABG or cardiac catheterization, and showed no statistically significant differences.

**Conclusions:** There are differences in treatment for acute MI among all three groups: patients with normal kidney function, with CKD or ESRD. We recommend that our finding should be verified in large multicenter study.

---

**PUB213**

### Pulmonary Hypertension and Right Ventricular Dysfunction in Patients under Maintenance Hemodialysis

**Lijun Zhao,** Songmin Huang, Hong Tang, Ting Liang. West China Hospital, Sichuan Univ, Chengdu, China.

**Background:** When chronic hemodialysis treatment has been revealed to increased the systolic pulmonary artery pressure (sPAP), right ventricular dysfunction (RVD) is an important predictor of prognosis in patients with end-stage renal disease (ESRD). This study was to investigate the prevalence of pulmonary hypertension (PH) and RVD among patients and the possible contributing factors for these clinical features.
Methods: Study population consisted of 67 patients under long-term hemodialysis (HD) therapy via arteriovenous (A-V) access in our HD center. Doppler echocardiography including intradialytic blood pressure variability indices (MPVR), right ventricle and RV wall thickness were performed in all patients. The relationship of PHT and RV hypertrophy were analyzed by Pearson correlation analysis. The risk factors of PHT were analyzed by Logistic regression analysis.

Results: SPAp=35 mmHg which indicate PHT was found in 37.31% of patients, while 44.78% of patients had RVD. Patients were divided into non-PHT subgroup (n=42) and PHT group (n=25). Compared with the non-PHT subgroup, patients with PHT had a higher systolic blood pressure, while had lower levels of hemoglobin and Kt/V value. Patients in PHT subgroup demonstrated lower left ventricular ejection fraction (LVEF) than patients in non-PHT subgroup (65.5% vs. 60.1%, p=0.04). RVD assessed, by MPI, was higher in patients with PHT than those without PHT. Additionally, the former group showed a higher incidence of RV hypertrophy than those in non-PHT subgroup (9.5% vs. 32.5%, p=0.041). Pearson correlation analysis showed that sPAP was correlated with RV wall thickness positively (r = 0.394, p = 0.01). Logistic regression analysis revealed that LVEF contributed to the predictability of incidence of PHT (regression coefficient b = 0.096, OR=1.100, p = 0.01) as well as systolic blood pressure (regression coefficient b = 0.063, OR=0.949, p = 0.002). The respectively study demonstrated high incidences of PHT and RV dysfunction among ESRD patients under maintenance HD via surgically created native A-V access. The status of LV function, poor control of systolic blood pressure have played an important role in the mechanism of PHT in RVD in chronic uremia patients.

PUB214
The Association of Dental Health and All Cause and Cardiovascular Mortality in Hemodialysis Patients: ORAL-D Study

Aiqun Chen,1 Hua Wu,1 Ying Sun,1 Deping Liu.2

Background: It has been hypothesized that oral disease may be associated with increased risks of death due to inflammation or as a general indicator of healthcare practices. We evaluated the association between dental status and the risk of all-cause and cardiovascular mortality in adults on hemodialysis.

Methods: ORAL-D is a multinational prospective cohort study of consecutive adults on hemodialysis in 75 outpatient clinics selected randomly from a dialysis network in Europe and South America. A dental surgeon evaluated dental status by using the DMFT (decayed, missing, filled, permanent teeth) score. Quality of dental health was defined based upon WHO criteria as low, moderate and high DMFT scores of <2, 2-7, 4-4 >4.4. We assessed survival at 8 months using centralized mortality data. We conducted analyses using Cox regression controlling for age, gender, previous cardiovascular events, income status, clinical performance measures, dialysis prescription and performance indicators, and depressive symptoms. Complete follow-up data at 12 months will be available by September 2013.

Results: 4720 hemodialysis patients in the participating clinics received a complete evaluation of their dental status and completed follow up. Median follow up was 8.0 (6.5 to 8.7) months and 344 (10%) died during follow up. Dental health (DMFT scores) had uncertain associations with all-cause and cardiovascular mortality in patients on hemodialysis. ORAL-D will be completed at the end of 1 year and analyze the relationship between ADMA and the different intradialytic blood pressure variability factors were analysed and compared between the 3 groups.

Conclusions: ADMA are markedly elevated in MHD patients and with a significant fall in the end of the HD sessions. The plasma ADMA lever and hs-CRP in intradialytic hypotensive patients is the highest.

PUB216
Usefulness of NT-pro-BNP as a Marker of Overhydration and Alteration on Body Composition in Dialysis Patients. Effect of a Nutritional Intervention on NT-proBNP Levels

María José Fernández Reyes, Manuel M. Heras, Alvaro Molina Ordas. Nephrology, Hospital General de Segovia, Segovia, Spain.

Background: NT-proBNP is a powerful predictor of risk of heart failure (HF) and mortality in patients with chronic kidney disease. Elevated levels of NT-proBNP in dialysis patients have been associated with heart disease and with extracellular water excess.

Analyse NT-proBNP to detect extracellular volume overload dependent on alterations in body composition and independent of cardio-histological factors; nutritional intervention in malnourished patients would modify the body composition and NT-proBNP.

Methods: We evaluated the nutritional status in 40 stable dialysis patients, mean age 71±10 years, time on dialysis of 49±47 months, 40% with history of HF. Nutritional analysis included: biochemical parameters related to nutrition and inflammation; anthropometric parameters; body composition by electrical bioimpedance; and nutrient intake. In 16 patients with nutritional deficiencies we started nutritional supplements. Two months later, the initial evaluation was repeated (including NT-proBNP).

Results: NT-proBNP correlates with history of HF (r = 0.30, p = 0.05) and with some body composition parameters related to extracellular water such as phase angle (r = -0.39 , p = 0.01), Na K exchange (r = 0.49, p = 0.001) and extracellular water percentage (r = 0.40, p = 0.01). In multiple regression analysis the model that better explains the levels of NT-proBNP is the one that includes the Na K exchange and the history of HF. There is a strong correlation between the NT-proBNP levels at baseline and after 2 months (r = 0.9, p <0.0001). Overall NT-proBNP did not change after the redermination two months later. Excluding the 16 patients with HF history, we observed that proBNP levels in 10 patients with nutritional intervention significantly decreased, whereas in 14 patients without nutritional intervention remained stable.

Conclusions: NT-proBNP in dialysis patients is independently correlated with parameters of extracellular water overload. Nutritional intervention in malnourished patients without HF history can decrease the NT-proBNP levels.
Results: Of 15 patients with LS-300, 13 patients were diagnosed as SDB. The average AHI was 26.7 ± 10.3 (mean ± SD) hour. Obstructive apnea was main. The BNP level was 418.2 ± 434.2 (mean ± SD) pg / ml, 278.8 ± 280.1 pg/ml before and after dialysis, respectively. The coefficient of BNP and AHI was 0.38, 0.37, before and after dialysis, respectively. In the case of whose pre-dialysis BNP level was more than 400pg/ml, the correlation coefficient of BNP and AHI was 0.72 (p = 0.04). Three of these patients were received sleep test again after Dry Weight reduction. AHI and BNP of them were improved. Of 4 patients with conventional PSG, all patients were diagnosed as SDB. 3 cases were severe, 1 case was mild grade of SDB. Obstructive apnea is main in both the day before dialysis and dialysis day. The AHI was improved after dialysis in three case of four. The BNP levels of 2 cases were more than 300pg/ml even after dialysis. In these 2 cases, AH1, maximum apnea time, minimum arterial oxygen saturation was improved in dialysis day.

Conclusions: Elevated BNP level is related to SDB in dialysis patients. Extracellular fluid volume overload is associated with SDB and the BNP level. SDB in dialysis patients can be expected to improve after dialysis if heart failure is suspected in the high level BNP.

PUB219

Diagnosis of Autonomic Dysfunction in Hemodialysis Patients Using Heart Rate Related Parameters in the Exercise Test Jocemir R. Lugon, Maria A. Carrera, Marcio Galindo Kiuchi, Felipe M. Pena, Andre B. Nogueira, Ronaldo C. Rodrigues, Jorge F. Strogoff-de-Matos. Medicine, Universidade Federal Fluminense, Niteroi, Rio de Janeiro, Brazil.

Background: Hemodialysis (HD) patients have increased risk of sudden death probably due to impaired autonomic function. We aimed to evaluate the frequency of autonomic dysfunction in a cohort of HD patients in comparison to controls (C) employing the exercise test (ET).

Methods: Cross sectional study with HD patients from a single center. Sessions were performed thrice a week for 4 hours. ET was accomplished in a non-dialysis day using the treadmill ramp protocol. The test was symptom-limited with an active recovery period of 2 min. A set of heart rate (HR) related parameters were assessed at baseline, exercise and recovery.

Results: From 125 HD patients, 41 were selected for the study. They were 50±14 years old, 51% male, 66% non-white, and 7% diabetics. Forty-one non-dialysis C, age and gender matched were enrolled. At baseline, HR, systolic blood pressure (BP) and diastolic BP of HD and C patients were not different. At ET values were statistically different between HD and C groups for the following variables: chronotropic deficit (23.5±12 vs. 6.5±6.4%, P=0.001); chronotropic index (57.5±19.1 vs. 88.9±12.0, P<0.001); HR recovery (HRR) at the 1st min (11.9±9.1 vs. 19.6±8.6 bpm, P=0.001), 2nd min (21.3±12.3 vs. 34.1±10.5 bpm, P=0.001), 3rd min (33.8±21.3 vs. 53.2±18.0, bpm, P=0.001), and 5th min (40.8±21.3 vs. 60.2±21.4 bpm, P=0.001); and R-R variability (SDNN) either during exercise (33.7±12.2 vs. 50.4±21.3 msec, P=0.001) or recovery (20.1±9.8 vs. 26.5±16.9, P=0.001). When patients under betablockers (HD 34% and C 17%) were analyzed separately, chronotropic deficit (35.0±10.0 vs. 10.6±5.98rpm, P=0.001), chronotropic index (41.215±7. vs. 89.0±9.5, P=0.001), and 1st min HR recovery (HRR) at the 1st min (27.8±16.1 vs. 42.6±11.2 bpm, P=0.001) and 5th min (33.2±14.1 vs. 53.4±14.4, P=0.006) still discriminate between HD and C.

Conclusions: The ET was found useful for diagnosis of autonomic dysfunction in HD patients. The most discriminant parameters between HD and C groups were the chronotropic deficit, the chronotropic index and the HRR at the 3rd and 5th min, irrespective of the use of betablockers.

PUB220

Cinacalcet May Improve Oxidative DNA Damage in Maintenance Hemodialysis Patients – An Observational Study Elif Ari Bakir. Nephrology, Kartal Research and Training Hospital, Istanbul, Turkey.

Background: The aim of the study was to evaluate the impact of cinacalcet on oxidative stress biomarkers, oxidative DNA damage (8-hydroxy-2′-deoxyguanosine/deoxyguanosyne) (8-OHdG/dG) and endothelial function in HD patients.

Methods: Thirty chronic HD patients undergoing 60 mg/day cinacalcet treatment with a follow-up of 6 months and 30 healthy individuals were included in this prospective study. Plasma malondialdehyde (MDA) levels and 8-OHdG/dG were determined as oxidative stress markers. Superoxide dismutase (SOD), paraoxonase (PON), catalase (CAT), carbonic anhydrase (CAN) and glutathione peroxidase (GPx) activities were measured as antioxidants. Results: MDA levels decreased, SOD, PON, CAT, CAN and GPx activities were increased after 6 months of cinacalcet treatment. Although CIMT remained stable, there was a significant improvement in FMD% as well as a notable reduction trend in 8-OHdG/dG ratio after 6 months of treatment.

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

PUB221

Left Ventricular Hypertrophy in End-Stage Renal Disease: Determinants and Impact on Myocardial Mechanics Attila Kovács, Mihaly B. Tapolyai, Maria Faludi, Klara Berta, Bela Merkely. Heart and Vascular Center; Fresenius Medical Care.

Background: Left ventricular (LV) hypertrophy is a major predictor of mortality in end-stage renal disease (ESRD). We sought to reveal the causes of increased LV mass in ESRD patients and to assess its influence on LV deformation using 3D echocardiography.

Methods: Forty-four patients (mean age 48±13 years, 54% men) with ESRD on maintenance hemodialysis (HD), without diabetes and any significant cardiac disease were investigated just before and immediately after HD, and compared to 46 controls (NC, 48±12 years, 48% men). Beyond conventional echo, 3D parameters were obtained using multi-beat reconstruction from 6 cardiac cycles (GE Vivid E9). LV mass indexed to body surface area (LVMI) were measured, and 3D speckle tracking analysis was performed to assess global longitudinal (LS), circumferential (CS), area (AS) and radial (RS) peak systolic strain (4D Auto LVQ). We also measured serum FGF-23 levels (Merck Millipore). We also measured serum FGF-23 levels (Merck Millipore) and evaluated overhydration status by bioimpedance (Fresenius BCM). Data are presented as mean/median/intergroup range.

Results: LVMI was remarkably increased in ESRD patients [34.6±6 vs. 7.1±8 g/m², p<0.001]. By multivariate linear regression (R²=0.91, p<0.001), FGF-23 (β=0.4±1), total iron binding capacity (β=0.49), overhydration (β=0.29), systolic blood pressure (β=0.43) and bodyweight (β=0.39) were found to be independent predictors of LV mass. In ESRD patients, LVMI values in all directions improved after HD (pre- vs. post-HD; LS: -20.3±2.7, CS: -24±2.4, RS: -10.6±2.1). FGF-23 (β=0.64), CS (β=0.43), LVMI (β=0.38), systolic blood pressure (β=0.27), and overhydration (β=0.24) were found to be independent predictors of LVMI in ESRD patients.

Conclusions: Beyond the chronic volume- and pressure overload, LV hypertrophy is determined by the endocrine effect of FGF-23. HD results in immediate improvement of LV function. The increase of LVMI correlates strongly with the reduction of 3D deformation parameters.

PUB222

Does This Adult Hemodialysis Patient without SIRS Require Blood Culture? Daisuke Uchida, Sho Sasaki,Masahito Miyamoto, Kenichiro Koitabashi, Daisuke Uchida, Sho Sasaki, Masahito Miyamoto, Kenichiro Koitabashi, Daisuke Uchida, Sho Sasaki, Masahito Miyamoto, Kenichiro Koitabashi, Katsuaki Ishii, Hiro Kawarazaki, Yugo Shibagaki, Kenjiro Kimura. Internal / Div of Nephrology and Hypertension, St. Marianna Univ School of Medicine, Kawasaki, Kanagawa, Japan; Nephrology, Shonan Kamakura General Hospital, Kamakura, Kanagawa, Japan; Medicine / Div of Nephrology, St. Luke’s International Hospital, Tokyo, Japan.

Background: Bacteremia is one of the most common causes of death in hemodialysis patients in Japan, but it is often difficult to diagnose it at the first hospital visit. The systemic inflammatory response syndrome (SIRS) is one of the most widely accepted criteria for the diagnosis of bacteremia in general population. However, it is not known if SIRS is also predictive of bacteremia in patients with hemodialysis.

Methods: We designed a multi-center retrospective observational study of adult hemodialysis outpatients who had 2 sets of blood cultures drawn for suspected infection at their first hospital visit from August 2011 to July 2012. Antibiotics administered prior to first visit and access other than arterio-venous fistula (AVF), which is the main vascular access in Japan, was excluded. Bacteremia was diagnosed by positive blood culture after the exclusion of contamination by a pre-set criteria. Clinical, biological and microbial data were obtained to evaluate the usefulness of SIRS as a predictor of bacteremia at first visit to the outpatient setting.

Results: Data was obtained from 279 participants. Vascular access other than AVF (N=27) and antibiotics administered prior to first visit (N=36) were excluded. Mean age of participants was 70 years, 62.8% were male, 49.5% were diabetic, and 28.1% had indwelling artificial objects. Among the 192 participants, 17.7% (N=34) had bacteremia and the most common infectious sites were endocarditis, osteomyelitis and AVF infection (N=4). The most common microbe was Staphylococcus aureus (N=11). 22.9% of those who met the
criteria for SIRS, and 12.5% of those who did not meet the criteria for SIRS had bacteremia (p=0.09). SIRS had a low sensitivity for bacteremia in hemodialysis patients (sensitivity 64.7%, specificity 53.2%, positive LR 1.38, negative LR 0.66).

Conclusions: SIRS may not be helpful in distinguishing adult AVF hemodialysis patients to exclude bacteremia.

PUB223
Annual Update on Elimination of Hemodialysis Related Bacteremia and Vascular Access Infection Jafar Al-Said, Aimee Pagaduan, Soni Mudrakshah. Nephrology and Internal Medicine, Bahrain Specialist Hospital, Bahrain.

Background: Hemodialysis related bacteremia and dialysis blood stream infection are the major causes of morbidity and the second cause of mortality in ESRD population. Great efforts are spent to control and reduce hemodialysis related bacteremia and access infection. We have been following strict infection control protocol since the beginning of our hemodialysis service. The aims of this study were to update the prevalence of Hemodialysis Related Bacteremia and vascular access infection and to identify the outcome of the tight infection control protocol we have been following.

Methods: This study is a retrospective analysis for the outcome of hemodialysis infection protocol over 112 months from January 2004 till May 2013. All Hemodialysis sessions performed were included during that period. Patients’ demographic and vascular access types were collected from the electronic data. Hemodialysis induced bacteremia inflection per 100 patient month, admission rates for Hemodialysis related bacteremia per 100 patient year and infection rates for vascular access infection were estimated.

Results: Total Patients were 147. Total Hemodialysis sessions were 8641. Mean age was 57.6 years (SE 1.3). Male gender formed 55%. Types of vascular access were; 56.3% cuffed tunneled catheters, 19.5% AV fistula, 18.2% AV grafts and 5.8% venous. Estimated infection prevalence is shown below.

- **Hemodialysis bacteremic infection per month**: 0.001
- **Hemodialysis related blood stream infection per 100 patient month**: 0.001
- **Admission for Hemodialysis related bacteremia per 1000 patient year**: 4.0
- **Admission for vascular access infection over 112 months**: Zero

Conclusions: The tight infection control protocol followed in our unit has consistently eliminated HD related infection and vascular access infection. We are reporting significantly lower infection rate as compared to all published international data. We would like to present and share this infection control protocol with other HD centers.

PUB224
The Role of Pre-Dialysis N-Terminal Probranin-Type Natriuretic Peptide for Volume Estimation in Haemodialysis Patients Arkmongkron,1 Andrew Davenport.2 1Renal Unit, Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand; 2Centre for Nephrology, Royal Free Hospital, Univ College London, London, United Kingdom.

Background: N Terminal Probranin Type Natriuretic Peptide (NTproBNP) is used to aid the diagnosis of heart failure. In haemodialysis patients, NTproBNP could be increased due to pre-existent cardiovascular disease, volume overload, and reduced by residual renal function. We examined the effects of volume status on predialysis NTproBNP, by measuring body water with bioimpedance and estimating over hydration using the Fresenius BCM In Body manufacture’s equations.

Methods: We prospectively studied 158 stable chronic HD patients, attending their midweek dialysis session who had predialysis bioimpedance measured (In Body). Serum biochemistry, relevant demographic, biochemical and bioimpedance data was collected prior to the session.

Results: Predialysis log NT-proBNP was correlation with age, sex, race, dialysis vintage, history of valvular heart disease, myocardial infarction, coronary stenting, peripheral vascular disease, number of anti-hypertensive medications, predialysis systolic blood pressure, mean arterial blood pressure, haematocrit, albumin, CRP, B2 microglobulin and volume overload estimated by the In Body equation, but not diabetes, stroke, hypertension, ratio of predialysis ECW/TBW, and volume overload estimated by the Fresenius BCM equation. On multiple linear regression analysis, NTproBNP was significantly associated with history of cardiac valve disease, myocardial infarction, coronary stenting, number of anti-hypertensive medications, predialysis systolic blood pressure and log B2 microglobulin, and negatively with serum albumin and haematocrit.

![Parameters](image)

Conclusions: Predialysis NT-proBNP is associated with pre-existent cardiovascular morbidity, anemia and hypoalbuminemia rather than estimates of overhydration.

*Funding: Private Foundation Support*

PUB225
Birth Weight and End-Stage Diabetic Nephropathy in Later Life: A Japanese Multicenter Study Kei Natani,1 Chie Saito,1 Soh Suzuki,1 Masahiro Hagiwara,1 Hirayasu Kai,1 Joichi Usui,1 Keigyou Yoh,1 Shiuchi Tsuuroka,2 Kunihiro Yamagata.1 1Dept of Nephrology, Faculty of Medicine, Univ of Tsukuba, Tsukuba, Ibaraki, Japan; 2Dept of Nephrology, Faculty of Medicine, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.

Background: Low birth weight is a surrogate marker for low nephron number, and an important risk factor for both the progression of end-stage renal disease (ESRD). However, most participants of previous study have been younger than 40, because little well-organized information on birth weight is available for the old general population as comparison subjects.

Methods: In January 2010 in 9 centers in Japan, 1130 Japanese patients undergoing maintenance hemodialysis were identified. Data was obtained from 230 patients (20.3%) by using a self-completed questionnaire containing questions about birth weight. The race and age-matched mean birth weight was calculated by using well-organized data from nationwide surveys. We divided our subjects into those with and without DM and used the median ages in each group (53.0 y for DM and 43.5 y for non-DM) and birth weight of each group was compared with age-matched mean birth weight.

Results: Older patients with DM had significantly lower birth weight than age-matched mean birth weight ( 2963±674* vs 3129±28, means/SD, respectively, *P=0.05), whereas no significant differences between them existed in younger patients in the DM group (3191±697 vs 3145±54 ) or in any patients in the non-DM (younger; 3107±401 vs 3140±54, older; 3048±157 vs 3114±40) group which consists of 101 patients with chronic glomerulonephritis and 45 with miscellaneous diseases.

Conclusions: We considered older diabetic patients with a small number of glomeruli due to significantly lower birth weight may have more severe long-term nephron damage than older non-diabetic patients. It was also suggested that the patients with young-onset diabetic nephropathy may develop ESRD with birth weight-independent manner. Therefore, we propose to notice that lower-than-mean birth weight would be a risk factor for ESRD in DM patients in later life.

PUB226
Morbimortality in Incident Hemodialysis Diabetic Patients in Southern Great Canaria Elvira Bosch,1 Eduardo Baamonde,1 Germán Perez Suarez,2 Cesar Garcia-canton,3 Marta Riaño-ruiz,2 Ana Ramirez Puga,2 Batista Fatima Garcia,2 Agustin Toledo Gonzalez,2 Mar Lago alonso,2 Dolores Checa.2 1Centro de Hemodialisis Avericum, Las Palmas de Gran Canaria, Spain; 2Servicio de Nefrologia, Hospital Insular de Gran Canaria, Las Palmas, Las Palmas de Gran Canaria, Spain; 3Servicio de Bioquimica Clinica, Hospital Insular de Gran Canaria, Las Palmas, Las Palmas de Gran Canaria, Spain.

Background: To describe the characteristics and prognosis of patients with diabetes mellitus (DM) who are incident in hemodialysis and to compare them with those of non diabetic (NoDM).

Methods: Retrospective study of incident hemodialysis (2007-2010). Subjects’ baseline clinical and laboratory data, as well as data on preexisting comorbidity were collected. Hospitalizations, causes of admission and causes of death were compared between DM and NoDM patients.

Results: 220 patients (58.6% DM – 41.4% NoDM) were included. Diabetic patients had higher average age, BMI and adjusted Charlson’s index (ACCI); they started HD with higher GFR and incidence of catheter and with lower levels of albumin, proteins and creatinine; they showed higher prevalence of ischemic cardiopathy, cerebrovascular accident (CVA), peripheral artery disease (PAD) and heart failure. The median follow up was 31 months (DM: 30.1 vs NoDM: 32.7 months p: 0.004). No differences were found in hospitalization rate (DM: 2.23 vs NoDM: 1.84; p:ns) or in the number of days in hospital (DM: 17.4 vs NoDM: 24.7 days; p:ns). Admissions due to PAD were more frequent among DM patients (p:0.000). DM patients had shorter survival time (49.1 vs 57.2 months; p: 0.005) and higher rates of global mortality (45.2% vs 24.2%; p:0.002) and mortality of cardiovascular cause (47.3% vs 24%; p: 0.046). Preexisting cardiovascular disease (HR: 3.26 CI: 1.58-6.71), age > 65 years (HR: 2.53 CI: 1.15-5.56) and starting with catheter (HR: 2.6 CI: 1.42-4.91) were the main risk factors (p: 0.05).

Conclusions: Diabetic patients start hemodialysis with higher GFR, ACCI and poorer condition of catheter and with poorer nutritional control. They have poorer prognosis, mainly determined by preexisting cardiovascular disease, age and starting with catheter.

PUB227
Survival Analysis in Korean Elderly Patients Initiating Dialysis: A National Population-Based Study Jung-hwa Ryu,1 Shina Lee,1 Hyunwook Kim,2 Seung-Jung Kim,1 Duk-Hee Kang,1 Kyu Bok Choi,1 Dong-Ryeol Ryu. 1Dept of Nephrology, Faculty of Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea; 2Internal Medicine, Wonkwang Univ College of Medicine Sanbon Hospital, Iksan, Korea.

Background: Although the proportion of the elderly among incident end-stage renal disease (ESRD) patients has been increasing in Korea, there has been a lack of information on their outcomes. Furthermore, there are some controversies about the appropriateness of dialysis initiation in elderly patients due to the dismal survival. This study aimed to assess the survival and to delineate predictors influencing on the all-cause mortality among elderly Korean patients initiating dialysis.

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

924A
Method: We included 11,301 patients (6,138 men) aged 65 years or older who initiated dialysis from January 1, 2005 to December 31, 2008 and followed up (median 37.8 months; range 0-84.0 months). Baseline demographic data, comorbidities and the information on mortality were obtained using the database of the Health Insurance Review & Assessment Service. The survival rate and the factors associated with mortality were analyzed.

Results: Unadjusted 24-month survival rate was 59.3% in all subjects, and it was decreased with the increase of age: 66.5% among patients aged 65-69 years, 59.0% among patients of 70-74 years, 52.5% among patients of 75-79 years, 48.5% among patients aged 80-85 years, and 30.2% among patients of 85 years or older. In addition, the survival rate was significantly higher in female and in patients on hemodialysis than patients on peritoneal dialysis in intention-to-treat analysis. Multivariate Cox proportional hazards model revealed that age, sex, type of healthcare security system, and comorbidities: diabetes mellitus, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, hemiparesis, liver disease, and any malignancy were independent predictors for mortality.

Conclusions: The survival rate in Korean elderly patients initiating dialysis was significantly associated with age, sex, and various comorbidities. With these results, individual counseling to dialysis initiation could be possible in elderly patients with chronic kidney disease.

PUB228
Risk Factors and Outcomes of Unplanned Hospitalization in Haemodialysis Patients – A Prospective Study from Greater Manchester East Sector Renal Network, UK

Shiv Bhutani,1 Leonard Ebah,1 Emily R. Keating,1 Sheetal Atrani,2 Marie McNulty,3 Andrew Stevens,2 Arvind Punnam,2 Sandip Mitra,1 1 Renal Medicine, Manchester Royal Infirmary, Manchester, United Kingdom; 2 Stockbridge Village Health Centre, United Kingdom.

Background: Hospitalization is a key prognostic indicator in Hemodialysis (HD) patients and has significant financial burden on renal networks. Registry data has shown links of hospitalisation in HD to various modiﬁable & unmodiﬁable risk factors, however prospective studies are distinctly lacking. This study investigated risk factors, outcomes & ﬁnancial impact of Hospitalisation (HZ) & rehospitalization (rHZ) for HD patients.

Methods: HZ data were collected prospectively from 4 satellite & central hub HD unit (April–September 2012). Electronic notes were used to collect data on demographics, comorbidities, causes & outcomes for HZ episodes.

Results: Among 413 HD patients, 148 episodes of HZ were recorded in 92 patients, 56 rehospitalisation (rHZ) episodes observed in 36 patients. The annual HZ rate was 0.7 episodes per patient-year (ppy) & 0.27 ppy for rHZ. Cardiovascular (25.5%), Infections (20%), and access related comorbidities (13.5%) were the leading causes of HZ. 12.3% admissions (n=18) were due to diabetes as a comorbidity. The strongest independent predictor of HZ was female gender (OR 1.23). In addition, SLE was negatively associated with hazard of death (HR 0.753 95% CI 0.72, 0.77). The dry weight of 40% of patients was increased 3% before the discharge. The average hospitalization was 29.9 days. Post-surgical infection was found in 9 patients, which were not larger than those of non-dialytic population. Half of the advanced cases were also treated with chemotherapy with percutaneous cardiac intervention therapy prior to the operation. All patients were dialyzed the next day with intermittent or continuous blood purification. The most frequent cancer was derived from atrophic kidney and urinary tract (21.8%). The average dry weight was reduced approximately 3% before the discharge. The incidence of Bacteremia (BAC) and/or associated risk factors on survival remains to be determined.

Conclusions: Without adjusting for income, this racial disparity in the LN cohort was greater with an AHR 1.19 (95% CI, 1.12-1.25). Further analysis of interactions demonstrated that higher income quintiles were significantly associated with lower mortality rate in both LN and non-LN populations, regardless of race. This study demonstrated that the higher incidence of HZ among HD patients, with younger & diabetic patients most at risk. The Total HZ was associated with an increase in mortality and However, a proportion were due to potentially preventable causes, with significant outcome & cost implications.

PUB239
Cancer Treatment for Patients under Dialysis Therapy; Single Center Surveillance
Tatsuo Tsukamoto, Makoto Araki, Takeshi Matsubara, Motoko Yanagita. Nephrology, Graduate School of Medicine, Kyoto Univ, Kyoto, Japan.

Background: Cancer is the growing cause of death (approximately 10% of all mortality) in Japanese dialysis patients, whose population becomes older along the better survival rate.

Methods: In order to clarify the therapeutic choice of the cancer treatment and the outcome, we examined actual conditions of the therapy by retrospective chart review in Kyoto University Hospital, which possess both cancer center and dialysis unit. From 2007 to 2012, fifty-seven dialysis patients, who were 63±13 years and 63.2% was male, were admitted to our hospital for surgical operation, chemotherapy, or radiotherapy. The indication for cancer therapy was discussed in the dialysis center, and the patients continued dialysis during the therapy.

Results: 40% of cancers were found within 5 years after the initiation of dialysis therapy. The most frequent cancer was derived from atrophic kidney and urinary tract (19.4% of male and 19.0% of female). Fifty of 57 patients were undergone radical operations, whose performance statuses were mostly 1. 13 patients (26%) had been treated with percutaneous cardiac intervention therapy prior to the operation. All patients were dialyzed the next day with intermittent or continuous blood purification method without serious adverse effects, such as severe hypotension, thrombosis and bleeding. The dry weight was reduced approximately 3% before the discharge. The average hospitalization was 29.9 days. Post-surgical infection was found in 9 patients, which were not larger than those of non-dialytic population. Half of the advanced cases were also treated with chemotherapy after the operation, whereas others were avoided to prescribe the chemotherapy because of their dialysis dependency. Thus, most dialysis patients had been successfully treated with single or combination therapy with careful administration of blood pressure, fluid volume, and cardiac function under the co-operation of oncologist and nephrologist, instead of fewer clinical intervention of cancer treatment in dialysis patients.

Funding: Government Support - Non-U.S.

PUB230
The Impact of Race and Income on Mortality in Patients with Lupus Nephritis on Maintenance Dialysis Robert Neve,1 Jorge I. Martinez Osorio,2 Lawrence Agodoa,1 Christina M. Yuan,1 Kevin C. Abbott,1 1 Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; 2 NIDDK, National Institutes of Health, Bethesda, MD.

Background: An analysis of racial and income disparities on mortality in end-stage renal disease (ESRD) patients with lupus nephritis (LN) on maintenance dialysis has not been reported. We analyzed the United States Renal Data System database to assess the impact of race and income on mortality in the LN and non-LN cohorts.

Methods: We identified 12,352 patients with LN as the cause of ESRD in a retrospective cohort of 1,132,217 patients, initiated on chronic dialysis between January 1, 1995 to December 31, 2006, followed until December 2, 2010. We merged data on median household income from the United States Census based on the ZIP code.

Results: In multivariate Cox regression analyses, African-American (AF) patients with LN (vs. non-AF) had an increased risk of death (adjusted hazard ratio [AHR], 1.10; 95% confidence interval [CI], 1.04-1.17).

Conclusions: Furthermore, analysis of interactions demonstrated that higher income quintiles were significantly associated with lower mortality rate in both LN and non-LN populations, regardless of race. This study demonstrated that the higher incidence of HZ among HD patients, with younger & diabetic patients most at risk. The Total HZ was associated with an increase in mortality and However, a proportion were due to potentially preventable causes, with significant outcome & cost implications.

PUB231
Effect of Bacteremia and Associated Risk Factors on Survival in Hemodialysis Patients Puja Chetroori,1 Rhonda E. Colombo,1 Stephanie L. Baer,2 Mufaddal F. Kheda,1,1, Stanley Nahman,1 Kristina W. Kintziger,1,2 Georgia Regents Univ, Augusta, GA;1 Charlie Norwood Vet., Augusta, GA.

Background: Bacteremia (BA) is a major cause of morbidity and mortality in hemodialysis (HD) patients. We have previously shown that BA in HD patients is significantly associated with many access-independent risk factors. However, the effect of BA and/or associated risk factors on survival remains to be defined.

Methods: Incident HD cases from the United States Renal Data System for 2005-2008 were queried for a diagnosis of BA and several potential clinical covariates using ICD-9-CM codes billed to Medicare. Cox proportional hazards regression was used to determine hazard of death in bivariable models. Covariates were classified by time of occurrence in relationship to a BAC diagnosis and HD initiation, and grouped according to infectious events, immunosuppressed conditions, demographic factors, and other comorbidities.

Results: In the 4-year period, 355,084 patients were available for analysis, and BA was identified in 77,288 (21.8%). 208,397 patients (58.7%) were alive at the end of the median time to death for patients with BAC was 455.7 days. Hazard ratio (HR) for death for BA was 2.00 (95% CI 1.98, 2.02). Comorbidities which carried a higher HR (CI) was age ≥65 years (HR 2.54 95% CI 2.51, 2.57), TPN (HR 2.29 95% CI 2.19, 2.39), pancytopenia (HR 2.11 95% CI 1.98, 2.25), and cirrhosis (HR 2.07 95% CI 2.01, 2.13), as well as infectious comorbidities such as candidemia and decubitus ulcer. These infectious conditions had the highest relative risks of bacteremia in our previous analyses as well. Among immunosuppressed comorbidities, diabetes was associated with a slight increase in hazard of death compared to non-diabetic patients (HR 1.22 95% CI 1.21, 1.23). In addition, SLE was negatively associated with hazard of death (HR 0.753 95% CI 0.71, 0.80) but carried a high relative risk of bacteremia (RR 1.77) in previous analyses.

Conclusions: Bacteremia is associated with a high risk of death in HD patients. Older age, TPN, pancytopenia, cirrhosis, and candidemia may carry a higher risk for mortality than bacteremia. Risk of bacteremia did not correlate with risk of death in patients with SLE.
Can a Newly Started Dialysis Center Improve Patient's Quality of Life; Single Center Experience

**Background:** Chronic diseases like chronic kidney disease can have a significant impact on patients quality of life (QoL), particularly when dialysis is indicated.

In our study, we assessed the impact of multidisciplinary approach on the QoL of haemodialysis patients in a new dialysis unit.

**Methods:** A multidisciplinary renal team of doctors, nurses, social worker and dietitian managing patients in the newly started hospital. 13 patients were enrolled in the study in a newly established dialysis center in Al Wakraa Hospital, Qatar. All patients were assessed at the beginning of dialysis in the new unit using the WHOQOL-HRQOL questionnaire consisted of 26 questions representing 4 domains of physical health, psychological health, social relationship and environment. 7 patients reassessed after 3 months again.

**Domain** | Facts Incorporated within domains
--- | ---
Physical Health | Independence of daily living, Dependence on medicinal substances and medical aids, Energy and fatigue, Mobility, Pain and discomfort, Work capacity
Psychological | Positive feelings, Self esteem, Spirituality/Religion/Personal Beliefs, Thinking, Learning, memory and concentration
Social relationships | Marital relationships, Social support, Social activities
Environmental | Economic resources, Political environment (pollution/ noise/ traffic/ climate), Healthcare and social care; accessibility and quality, Financial resources, Sexual activity, Social support, Thinking, Learning, memory and concentration

**Results:** 7 patients who had the chance to be assessed twice, have shown a significant improvement in their QoL after three months of treatment.

The remaining patients have shown a satisfactory level of QoL with space for some further improvement.

**Conclusions:** QoL is an important health care issue for dialysis patients. Newly established renal unit in a new hospital can still play a big role in improving patient’s QoL.

**Impact of Changes in Dialysis Unit Structure and Procedures on Cather Related Infections**

**Background:** The Acute Dialysis Unit (ADU) at Parkland Health and Hospital System provides hemodialysis to patients unfunded for outpatient dialysis. Catheter related bloodstream infections (CRBSI) are a significant source of morbidity in this group. We conducted this study to determine the impact of changes in ADU operational structure and procedures that were created to improve care and to decrease rates of CRBSI and infectious complications in our patients unfunded for outpatient dialysis.

**Methods:** We retrospectively analyzed all unfunded patients undergoing HD via a cuffed tunneled catheter during the 6 months before (period 1) and after (period 2) changes in the operational structure of the ADU. Changes included extended hours of operation, creation of an extra shift, increased levels of nursing staff, and hiring of 2 faculty nephrologists primarily responsible for care of unfunded patients. There was also a policy change that all CRBSIs requiring intravenous antibiotics be completed while inpatient rather than providing antibiotics when returning for urgent HD. We assessed the rates of overall CRBSI, Gram negative and polymicrobial infections, and complications (death, endocarditis, osteomyelitis) per 100 patient weeks of ADU.

**Results:** There were 2392 patient weeks in period 1 and 2578 patient weeks in period 2. There was a trend of reduction in overall CRBSI (3.22 v 2.33) and a significant reduction in Gram negative (2.30 v 0.85) and polymicrobial infections (1.30 v 0.27). There was not a significant difference in rate of complications (0.38 v 0.35).

**Conclusions:** Changes in ADU structure and procedures were associated with a trend of reduced CRBSI rates and significant decrease in frequency of Gram negative and polymicrobial infections. These results support continued implementation of these practices and future study of other targeted interventions to further lower CRBSI rates.

**Symptom Cluster, but Not Single Symptoms, Predicts Mortality in Dialysis Patients**

**Background:** bothersome symptoms are frequent and often co-occur in dialysis patients. Symptom burden is related to both health related quality of life (HRQOL) and depression. As HRQOL and depression are associated with mortality in dialysis patients, our aim was to investigate if symptom clusters predicted mortality in prevalent dialysis patients in Norway.

**Methods:** In a prospective observational cohort study including 301 prevalent dialysis patients, Kidney Disease and Quality of Life Short Form version 1.3 (KDQOL), SF-36, and the depression inventory (BDI) questionnaires were used. Based on KDQOL, 11 kidney-specific self-reported physical symptoms were entered into principal component analysis with varimax rotation to generate symptom clusters. Patients were categorized using quartile limits of symptom scores. Kaplan-Meier and multivariate Cox regression analyses were used for the survival analysis.

**Results:** Three symptom clusters were identified. The “uremic” cluster (nausea, lack of appetite, dizziness, feeling squeezed out, shortness of breath and chest pain) and “skin” cluster (itching and dry skin) were associated with all-cause mortality (log-rank p<0.001 and p=0.043). In multivariable analysis the worse 11 symptom cluster had a higher mortality rates compared to the three quartiles with less perceived symptoms (HR 2.47, 95% CI 1.44-4.22, P=0.001). No single symptoms were independently associated with mortality, neither were the other two symptom clusters.

**Conclusions:** “Uremic” symptoms independently predicted mortality in prevalent dialysis patients. Assessing co-occurring symptoms rather than single symptoms might help to identify dialysis patients at high risk for all-cause mortality. Additional research is warranted to determine whether symptom treatment may affect mortality rate.

**Efficacy and Safety of Calcium Carbonate in Patients on Hemodialysis – A Pilot Study**

**Background:** Hyperparathyroidism is caused by secondary hyperparathyroidism, and is associated with vascular calcification. Calcium carbonate (CaCO₃) is used broadly in China as phosphate binder to control the level of serum phosphorus.

**Methods:** A total of 19 hemodialysis patients with hyperparathyroidism (serum phosphorus >7.0 mg/dl) were enrolled. All patients received a fixed dosage of CaCO₃ (3.0g/day, equivalent to 1.2g/day of elemental calcium). The effect and safety of CaCO₃ on serum phosphorus level were recorded at baseline and Weeks 4, 8 and 12. Statistical results are based on t-test (for one sample and two-group comparisons) and Fisher’s Exact Test.

**Results:**
Results: Five patients were excluded including four of poor compliance and one receiving surgery. 14 patients completed the analysis. 10 were men and 4 were women, with a mean age of 48.7 ± 13.0 years and who were on dialysis since 40 ± 26 months before the study. After 12 weeks of treatment, the mean level of serum phosphorus decreased significantly from 6.8 to 5.6 mg/dL (P < 0.05). Eight patients (57.1%) achieved the NKF Kidney Disease Outcomes Quality Initiative target (serum phosphorus ≤ 5.5 mg/dL) and 4 (28.6%) achieved the Kidney Disease: Improving Global Outcomes target (serum phosphorus ≤ 4.5 mg/dL). In the subgroup with moderate hyperphosphatemia, the decreases of serum phosphorus in weeks 4, 8, and 12 were significantly relative to that in week 0, whereas in the subgroup with severe hyperphosphatemia, the respective changes revealed no significant differences. No serious adverse events related to treatment were reported.

Conclusions: CaC03 controlled serum phosphorus effectively in chronic hemodialysis patients with hyperphosphatemia. It may require larger dose of CaC03 for the decrease of serum phosphorus in the subgroup with severe hyperphosphatemia. The adverse events were mild in short term. Baseline serum phosphorus level affected the efficacy of CaC03. HJM, YT, YXS, RLZ, HLG contributed equally to the paper.

Funding: Government Support - Non-U.S.

PUB237
Albumin and Age Are Predictors of Early Mortality in Incident Hemodialysis Patients André Fragoso,1 Ana Pinho,1 José António Lopes,2 Antonio Gomes da Costa,2 Neurology Dept, Hospital de Faro, Faro, Portugal; 2Nephrology Dept, Hospital Santa Maria, Lisboa, Portugal.

Background: Despite improvements in dialysis care, incident hemodialysis (HD) patients have the highest mortality in the first months, particularly, elderly patients with multiple comorbidities. Recent prognostic tools to estimate 6-month survival in elderly incident HD patients has been validated and showed that decreased albumin levels and older age are important independently factors. The purpose of this study was to evaluate predictors of early mortality in incident HD patients.

Methods: In this prospective cohort study we included 188 chronic kidney disease patients beginning, permanently or temporarily, unplanned HD after hospital admission in 2012. Clinical and several laboratory parameters were determined for each patient at admission and the follow-up period was timed for 6-months from the first HD session. Our population was divided in two groups accordingly to the mortality 6-months after beginning HD: G-I (n=55) non-survivors and G-II (n=136) survivors. Results: We found that G-I was older than 80 years old (p=0.001), showed more than six comorbidities (p=0.0001), higher occurrence of cardiovascular disease (p=0.001) and recent hospital admissions (0.002). G-I also showed albumin level below 2.5g/dl (p=0.010). No differences were found between the two groups regarding history of diabetes and analytic levels of Hemoglobin or C Reactive Protein. In a cox multivariate analysis, two variables were independently associated with early mortality: age more than 80 years (hazard ratio [HR] 2.375; p=0.002; 95% CI 1.36 to 4.14) and albumin levels below 2.5g/dl (HR 2.045; p= 0.013; 95% CI 1.16 to 3.60). Area under the curve for the resulting prognostic analysis of 6-months mortality was 0.68 (p=0.0001; 95% CI 0.59 to 0.78).

Conclusions: In our study, an integrated 6-month prognostic tool based on decreased levels of albumin (under 2.5g/dl) and older patients (above 80 years old) accurately estimate early mortality. The instrument may be of value for researchers and clinicians to identify patients who have poor prognosis and consequently provide better care.

PUB238
Mortality Risk by Early versus Late Start of Hemodialysis Bruce M. Robinson,1 Yun Li,1 Yan Jin,1 Alissa Kapke,1 Jeffrey Pearson,1 Friedrich K. Port.1 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2Univ of Michigan, Ann Arbor, MI.

Background: In the US there has been a trend to starting dialysis at a higher eGFR over the past decade and before. Observational studies have found a positive association between eGFR at dialysis start and mortality, perhaps due to confounding by indication (CBI). The IDEAL randomized trial showed no association of eGFR at start with mortality, but had limited separation between early vs. late start. We aimed to reduce CBI by studying the practice of early versus late start.

Methods: The US Renal Data System ESRD database was used to identify 163,424 patients who initiated hemodialysis at dialysis facilities with at least 10 new patients in each year between 2006 and 2009. Mortality risk by eGFR (adjusted for demographics and comorbidity) was assessed using standard Cox regression models and an instrumental variable (IV) approach using physician as the instrument. The IV first stage used a linear model of hospital eGFR using physician as an instrument variable. The IV first stage used a linear model of physician eGFR as a function of physician dummy variables; the second stage used a Cox model to explain mortality as a function of categorized predicted eGFR (from stage 1).

Results: The Cox models confirmed prior findings of a strong positive association of eGFR with mortality risk (higher mortality at higher eGFR); the IV approach showed an attenuated association, presumably by reducing CBI (Figure 1). Sensitivity analyses limited to patients with nephrology care for six months prior to starting dialysis and excluding patients who died in the first two months of dialysis were corroborative.

Conclusions: Contrary to US trends in increasing eGFR at dialysis start over time, no survival benefit could be detected to support a practice of generally starting dialysis earlier.

PUB239
Peritoneal Dialysis in Nursing Home. Over 10 Years Experience Valerio Vizzardi,1 Massimo Sandrini,2 Luigi Manili,3 Laura Econimo,1 Grazia Venistette,1 Giovanni Cancarini,1 1UO Nefrologia, Spedali Civili and Univ of Brescia, Brescia, Italy; 2Fondazione di Cara, “Città di Gardone Val Trompia” ONLUS, Gardone Val Trompia, Italy.

Background: Guests of nursing home (NH) often are extremely frail, poor self-sufficiency and high hospitalization rate. Hemodialysis (HD) in these patients faces several issues; e.g.: very old age, comorbidity, vascular access problems and logistic difficulties (mainly transportation). Peritoneal Dialysis (PD) is a possible treatment in not self-sufficient ESRD patients living in NH; in fact, trained health professionals are able to assist frail patients in these structures. In Italy there is a prevalence of about 40 patients 0.9% doing PD in NH.

Methods: Retrospective analysis of clinical course and outcome in patients on PD treated in 2001 to 2013 in NH and followed-up by our Center. Results: 24 (MF=8/16) underwent PD for 10.8 years. Mean age was 77±9 years (range 56-94), median time on PD in NH was 5.5 months (I and III quartile: 1.9; 16.8; range: 1-81) with a total follow-up of 237 patient-months. Peritonitis occurred in 9 cases with a peritonitis rate of 1/26 patient-months; the causative microorganism were Gram negative in 67%, Gram positive in 11% and fungus in 22%. The mean hospitalization was 10.8 days/patient/year, but fourteen patients had no hospitalization during PD; the remaining 10 had a median of 14 days (I and III quartile: 14 and 37). Outcome: 21 deaths (age: 78±9 years; range: 56-95), 1 shift to HD (ultrafiltration failure). Today, 2 patients are still on PD.

Conclusions: In patients on PD in nursing home, dialysis adequacy, nutrition and hemoglobin met targets acceptable for that kind of patients. Peritonitis rate was in the range suggested by ISPD. According to our experience, PD in NH is effective and safe. Moreover, PD allows the “home-management” of poli-comorbid and not self-sufficient ESRD patients.

PUB240
Intravenous EpoGEN in Peritoneal Dialysis: A Single Center Experience Abdullah Harad,1 Kelly S. Jarvis,2 Michelle G. Brickle,1 Tarek M. Sobeh,1 John Durham.1 1Palmetto Nephrology, Orangeburg, SC; 2Davita Dialysis, Orangeburg, SC.

Background: EpoGEN is commonly given subcutaneously (SQ) in Peritoneal Dialysis (PD) patients. The reason is being more potent and longer acting. We are reporting a retrospective evaluation of a single center experience with the use of Intravenous (IV) EpoGEN in anemia management in PD patients. The use of IV EpoGEN in anemia management has been the local practice at this center as a convenient way to deliver EpoGEN while having laboratory tests done with venous stick without having to do SQ stick. That practice provided an opportunity to evaluate its efficacy.

Methods: The records for all PD patients (total 34) were reviewed. 14 patients excluded (6 were not on any kind of erythropoietin stimulating agents and 3 had their EpoGEN on hold for over 1 month, 2 patients on PD less than one month, 2 patients on SQ EpoGEN). 20 PD patients were on PD more than a month and receiving IV EpoGEN weekly or every other week and included in the analysis. They were evaluated for EpoGEN dosing, Hemoglobin, Ferritin, Iron saturation, Albumin, Age and Sex.

Results: Their mean age was 48.3 years and were 9 males. Mean Ferritin was 683.6 mg/dL, iron sat was 41.5 % and albumin 3.52 mg/dL. Mean hemoglobin value for 1 month of follow up was 9.99 mg/dL, mean EpoGEN IV dose was 35400 units for PD patients on weekly dosing (7 patients) and 27600 units for the every other week dosing (13 patients).

Conclusions: It appears that IV EpoGEN provided for stable management of anemia and convenient dosing in PD patients. Most patients were maintained on an every other week schedule. Only one third of patients required more frequent and higher doses of EpoGEN. Despite what might be predicted, most patients can be successfully managed on every other week dosing regimen.
**PUB241**

**Kinetics of α-Amylase Activity in Mixture of Glucose Polymers: A Model for Degradation of Osmostic Agent**

Jan T. Poleszczuk, Elvia Garcia-Lopez, Bengt Lindholm, Jacke Waniekiewicz.

*Nałęcz Institute of Biocybernetics and Biomedical Engineering, Warsaw, Poland; Department of Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden.*

**Background:** Glucose polymers (GP, as Icdextrin) are used as osmotic agents in peritoneal dialysis, and therefore the activity of α-amylase, the starch degrading enzyme, may have a substantial impact on the efficacy of the treatment. The kinetics of α-amylase activity is not easily predictable and the development of an experimental and mathematical framework for assessing α-amylase characteristics was necessary.

**Methods:** The reaction of porcine pancreatic α-amylase (PAA of 0, 25, 50, 100 U/L) and maltolheptose (G7 of 2.5 and 5 mg/mL) in PBS was carried out in vitro. G7 and all its possible decay products were frequently measured by HPLC. Different hypothetical pathways of G7 decay were analyzed together with mathematical models for the second order reactions of PAA with GP and the derived generalized Michaelis-Menten equations. The model parameters were estimated.

**Results:** For all experimental conditions no trace of maltohexose (G6) and only small quantities of glucose (G1) were found, what allowed us to eliminate a possible G7 decay pathway. Further comparison of the experimental data with fitted model curves yielded a single decay pathway with maltotriose (G3), maltose (G2) and G1 as the final products and substrates for PPA. The corresponding mathematical model reproduced the experimental data with high accuracy. The cleavage of G4 was much slower than the digestion of higher oligosaccharides, G7 and G5, which had similar kinetic parameters. G4 was digested mostly to two G2 molecules, but also, with low rate, to G3 and G1. The intermediate products of the G7 decay (G5, G4), but not the final products, had substantial inhibition effect on PPA catalytic efficiency.

**Conclusions:** The proposed method with the application of mathematical modeling for describing the digestion of GP of arbitrary length. It is the primary cause of technique failure and it is associated with increased risk of death. According to the ISPD 2010 recommendations the most accepted empirical protocol includes a combination of Vancomycin/Cephalexin for Gram-positive organisms and third-generation Cephalosporin or Aminoglycoside for Gram-negative bacteria. Cure rate widely varies between 44% to 85% but the initial empirical treatment of PD-related peritonitis is still under investigation.

**Methods:** We retrospectively evaluated all records of patients on PD with peritonitis between 1995 and 2012 treated in our Department. The protocol used in most of patients included an initial intraperitoneal instillation of Cefazolin (500 mg) and Ciprofloxacin (200 mg) or Oflloxacin (200 mg), followed by intraperitoneal Cefazolin (250 mg/bag) and oral Ciprofloxacin (500 mg) or Oflloxacin (200 mg) once daily.

**Results:** Records of 323 cases of peritonitis episodes in 143 patients on either Automated PD or Continuous Ambulatory PD were reviewed. More than one event was reported in 71 patients (250 cases). A single peritoneal infection was recorded in 72 (50%). Bacteriological data of 93 cases are missing. In 222 cases (97%) a single organism was isolated: 127 of Gram positive (57%) and 57 of Gram negative (26%) organisms. Methicillin resistant germs were detected in 69% of Gram positive and Pseudomonas in 33% of Gram negative infections. Fungal peritonitis was recorded in 9 cases. Thirty five cases were culture-negative. Overall treatment success rate was 73%. Total mortality was 4% (57% related to the peritonitis). Recurrence rate was significantly different in 98 cases with the use of Aminoglycosides (76%) than in the 211 cases where Quinolones were used (75.8%).

**Conclusions:** Empirical treatment with oral Quinolones and intraperitoneal Cefazolin is at least as good as the widely accepted combination of Vancomycin/Cephalexin and third-generation Cephalosporin or Aminoglycoside in peritonitis catheter related.

**PUB245**

**Peritoneal Dialysis in HIV Seropositive End Stage Renal Disease Patients: Single Center Experiences**

Piyatida Chuengsaman, CAPD Service and Training Center, Bangphao Hospital (Public Organization), Prummitr Branch, Bangkok, Thailand.

**Background:** Our peritoneal dialysis program was established since 2008, now we have provided this therapy to about 1,500 end stage renal disease patients. In Thailand, HIV-seropositive end stage renal disease patients get limitation to access to hemodialysis, due to healthcare professional’s concern about chance of viral transmission. Because peritoneal dialysis is a home-based therapy, this make the provider of this type of therapy feel more comfortable, thus make this therapy be more accessible for this group of patients.

**Methods:** We retrospectively reviewed our database. We compared the survival data, PD-related infection data, and other clinical parameter, between HIV -seropositive PD patients and overall center data.

**Results:** From February 2008 till September 2012, there were 1,366 patients which we have provided peritoneal dialysis. In this group of patients, there were 38 HIV-seropositive patients. At the end of September 2012, there were 13 active HIV-seropositive patients. Data about HIV status was available only for the patients who alive according to HIV viral load, 11 out of 13 patients got very low copies of virus (less than 40 copies/ml). The patient’s data is shown in Figure.
We also compare our overall center data with HIV-seropositive patients’ data as shown in (Table 1).

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Overall patients</th>
<th>HIV-seropositive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,366</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>9%</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: HIV-seropositive ESRD patients, is an emerging problem in Thailand. Despite the concern about PD-related infections complication, our data did not support this. Due to survival data is not as good as in HIV-seropositive ESRD patients, our program need to focus more to improve the outcome.

Funding: Government Support - Non-U.S.

PUR246

Combination Therapy with Peritoneal and Hemodialysis from the Initiation of Renal Replacement Therapy Preserve the Residual Renal Function and Peritoneal Function; Case Report Atsushi Ueda,1 Aki Hirayama,2 Shigeru Owada,2 Kei Nagai,4 Kunihiro Yamagata.4 1Tsukuba Univ Hospital Hitachi Medical Education and Research Center, Japan; 2Tsukuba Univ of Technology, Japan; 3Asao Clinic, Japan; 4Univ of Tsukuba, Japan.

Background: In ASN 2012, we reported in a retrospective cohort study an advantage of the peritoneal and hemodialysis (PD-HD) combination therapy from the initiation of renal replacement therapy (RRT) on the patient’s survival compared to PD or HD groups. We concluded this beneficial result was caused from the preservation of residual renal function (RRF) and serum albumin level.

Methods: This was the typical valuable case, a 51-year-old woman with diabetic nephropathy selected PD-HD therapy as the first dialysis method 10 years ago. The dialysis schedule consisted of five PD days and one HD without fluid removal a week. The Kt/V of RRF, PD and HD calculated by equivalent renal urea clearance were measured, and peritoneal equilibration test was performed every six months.

Results: At the beginning of this therapy, Kt/V of HD, PD and RRF was 0.81, 1.29 and 0.52, respectively. Interestingly, Kt/V of RRF increased to 1.29 at six months, it kept absolutely stable within 96 months and 0.44 at 120 months. The mean Kt/V of RRF, PD and HD was 0.85, 1.32 and 0.83, respectively. The mean for 10 years urine volume was 943 mL/day and the peritoneal fluid removal volume was 733 mL/day. The mean D/P Cr ratio was 0.52, peritoneal permeability did not increase for 10 years. Albumin level maintained stably, in addition anemia, inflammation and nutrition status kept as good control.

Conclusions: Since this combination therapy started at the initiation of RRT, fluid control could be kept well by urine and ultrafiltration of PD. A stable PET data indicated peritoneal resting might be expected to be beneficial on the preservation of peritoneal function. Finally, these effects could bring not only the long-term continuation of dialysis but also the improvement in anemia, inflammation and nutrition status. This case demonstrated that this new combination therapy was extremely useful for preserving both RRF and peritoneal function, indicating a good prognosis.

PUR247


Background: Patients with multiple access failure on peritoneal dialysis (PD), surgical externalization of catheter cuff was done and outcomes were observed.

Methods: Study included four cases two of which were unfit for reininsertion (PD) catheter or fistula creation. Two patients refused for removal of catheter. All patients had positive cultures from exit site. Exit site of two patients were positive for Methicillin resistant staphylococcus aureus (MRSA). The exit site of other two were positive for methicillin-resistant staphylococcus aureus (MRSA) and Pseudomonas Aeruginosa respectively. External Cuff was removed surgically followed by oral fluclaxacillin for MESSA positive Patients. Intra peritoneal vancomycin was prescribed for the MRSA positive patient whereas ciprofloxacillin was prescribed for pseudomonas positive patient. Along with continuation of PD, twice weekly dressing with 3% saline was done for all patients. Three months prospective observation was made regarding wound healing, persistence of exit site infection and any episode of peritonitis. PD fluid cell count, culture and exit site swab culture was done weekly to diagnose any infectious episodes during this period. Additional cultures were taken in case of any suspicion of peritonitis or tunnel or exit site infection. Adequacy of dialysis was assessed monthly.

Results: Mean age of this group is 68 years and two of them were females. None of the 4 patients had wound healing within this observation period. Exit site cultures were persistantly positive for two cases who had MSSA in the exit site after 3 months. Exit site cultures were persistantly positive for two cases who had MSSA in the exit site after 3 months.

Conclusions: Catheter loss of this procedure is 100%. 50% patients with this procedure can remain in PD. Procedure can be used for patients with high co morbidity and with very poor life expectancy.

Funding: Government Support - Non-U.S.

PUR248

Urgent Start PD: Establishing a Center of Excellence as a Model of Delivery Heathery L. Henderson, Qureshi T. Khairullrah, Jukakah S. Tayeh, Robert Provenzano. Nephrology, St. John Hospital & Medical Center, Detroit, MI.

Background: PD is underutilized as a dialysis modality in the US. Currently ~7% of US dialysis patients use PD. First reported by Ghaffari and replicated by others, urgent start PD programs (catheter use ± 2 weeks post placement) have been shown to increase PD % with acceptable complication rates. Urgent start PD is difficult to deliver to all patients due to physician inexperience & commitment, adequate staffing (in hospital & PD units), and administrative burden. Additionally, many hospitals in the US is structured around in-center HD and this places an undo burden on the majority of PD programs as “of course entry”. To address this deficit, we developed a center of excellence (COE) to deliver urgent start PD and increase PD percentages in our region.

Methods: Successful PD program depends largely on the experience of the nephrologists and PD nurses, which are typically higher in PD centers with larger patient populations. Unfortunately small PD centers far outnumber large centers making urgent start PD a nonviable option in many regions due to cost and staffing constraints. Our community based PD unit provides intermittent peritoneal dialysis (IPD) to urgent start patients referred by community based hospitals and nephrologists. Once tolerating full fill volumes, patients may be transferred back to their primary nephrologist at smaller PD units for continued care and management. Our intention is to increase patients into our urgent start program with plan for transfer back to their primary nephrologist once they no longer require IPD.

Conclusions: As integrated care penetrates the ESRD market, growing and maintaining PD populations will be critical. We have shown that instituting a centrally located PD COE gives more patients the opportunity to initiate PD that may otherwise not be possible and grow smaller PD centers nationwide. Transferring patients back to their primary nephrologist allows physician ownership and continuity of care, critical in an era of patient centered medical homes. Also by networking larger PD centers with smaller centers this may improve patient survival, outcomes, and drop-out rates.

Funding: Private Foundation Support

PUR249


Background: Hunan is in the middle of China, the number of Continuous Ambulatory Peritoneal Dialysis(CAPD) patients here counted for more than 19% in China. This study is to to investigate the status of CAPD patients in 6 peritoneal dialysis centers in Hunan Province.

Methods: Cross-sectional study of general data, nutrition, inflammatory state and dialysis adequacy of 835 CAPD patients in 6 peritoneal dialysis centers in Hunan Province during July, 2012 to December 2012, and analysis the data.

Results: General data:sex ratio is 1.2:1, age is 51.9±14.27, dialysis age is 23.6±19.71 months, and the primary disease before dialysis were chronic glomerulonephritis (59.2%), diabetic nephropathy (15.6%), benign arteriolar nephrosclerosis (12.7%). 35.2% patients controlled their blood pressure under 140/90mmHg, and blood pressure of patients with dialysis age more than 36 months significantly higher than less than 36 months. 2. Nuture: the rate of anemia is 83.3%, hypoproteinemia is 55.7%, serum phosphorus beyond 59.2%, diabetic nephropathy (15.6%), benign arteriolar nephrosclerosis (12.7%). 35.2% patients controlled their blood pressure under 140/90mmHg, and blood pressure of patients with dialysis age more than 36 months significantly higher than less than 36 months.

Conclusions: As integrated care penetrates the ESRD market, growing and maintaining PD populations will be critical. We have shown that instituting a centrally located PD COE gives more patients the opportunity to initiate PD that may otherwise not be possible and grow smaller PD centers nationwide. Transferring patients back to their primary nephrologist allows physician ownership and continuity of care, critical in an era of patient centered medical homes. Also by networking larger PD centers with smaller centers this may improve patient survival, outcomes, and drop-out rates.

Funding: Private Foundation Support

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

929A
Background: Changes in residual renal function (RRF) may require changes in the peritoneal dialysis (PD) prescription. However, measuring RRF with a 24-hour urine collection is laborious for patients. In a prospective multicentre cohort, we studied whether simplified measures of RRF adequately predict renal Kt/V (Kt/V) or significant changes in Kt/V.

Methods: We studied prevalent PD patients who had Kt/V >0.3 and at least 2 peritoneal adequacy tests done between 3 and 15 months apart without a change in modality of fill volume. We attempted to predict the follow-up Kt/V using multiple linear regression in which patient demographics, serum creatinine, urea and baseline Kt/V were potent predictors. We assessed candidate models by calculating mean bias of predictions and accepted the simplest model with a mean bias ±0.2 as optimal. We also attempted to predict a clinically important change in Kt/V of 0.2 using only a change in serum creatinine using logistic regression.

Results: A total of 888 patients were eligible for study. When predicting Kt/V, no model resulted in a mean bias of ±0.2.

Conclusions: We were unable to identify a simple method for accurately predicting Kt/V or significant changes in Kt/V. Further research is required to simplify the identification of patients with changes in RRF.

Clinical Characteristics of Long-Term Survivors and Short-Term Survivors on Peritoneal Dialysis Yiwen Li. Kidney Disease Dept, ZheJiang Province Hospital.

Background: To evaluate the characteristics of patients on long-term and short-term peritoneal dialysis (PD).

Methods: Patients who be treated with PD since 2006 to 2011 and received PD for at least one year in our Department of kidney disease were included in this study. According to dialysis duration, patients were divided into two groups. Group A (long-term) was defined as patients survived on PD for more than 4 years. Group B (short-term) was defined as patients who died and Group C (short-term) was defined as switched to hemodialysis within less than 4 years. Demography, biochemical indexes, dialysis adequacy, residual renal function were compared between these groups.

Results: There were 50 patients in group A, 55 patients in group B and 90 patients in group C. Survival analysis showed that 38.7% in group A, 30.9% in group B and 35.6% in group C died during the follow-up period of group A; group B and group C was 58.3%±10.3 months, 93.1 ±20.0 months, respectively. Younger, fewer episodes of diabetic comorbidity (group A 4/50 vs group B 13/55, P<0.05) were found in group A. Compared to group B and group C, the level of serum albumin at the beginning of PD was much higher in group A ([38.7±4.6] g/L vs [36.15±4.85]g/L and vs [35.23±5.27] g/L, P=0.01)]. Compared to group A and group B, the levels of blood sugar in group C is lower. The levels of CRP in group B is higher than in group A and group C (P<0.01 and P= 0.05). The levels of nDNA in group A is higher than in group B (P<0.05). The levels of TC, TG, hemoglobin, calcium, phosphate and iPTH were not significantly different between three groups. Renal Kt/V renal Ccr and urinary volume at the beginning of dialysis were much higher in group A (P<0.05). Peritoneal membrane transport, increased blood sugar morbidity were not significantly different between three groups.

Conclusions: In comparison to short-term survivors, long-term PD patients are characterized by being younger, less diabetic disease, higher level of serum albumin and Hemoglobin, higher volume of urine, lower level of CRP, better residual renal function, less ultrafiltration volume and lower pulse pressure difference.

Planned Dialysis, Not Early Referral, May Improve Quality of Life and Depression in Newly Diagnosed End Stage Renal Disease Patients: Comprehensive Prospective Study of the Clinical Research Center for End Stage Renal Disease (CRC ESRD) in Korea Ji In Park, Jin Ho Hwang, Yong-Lim Kim, Chun Soo Lim, Jung Pyo Lee. Internal Medicine, Seoul National Univ College of Medicine; Internal Medicine, Hangang Sacred Heart Hospital; Internal Medicine, Kyungpook National Univ Hospital; Internal Medicine, Seoul Boramae Medical Center, Republic of Korea.

Background: Health-related quality of life (HRQOL) has recently become an important issue, which was revealed to affect survival of end-stage renal disease (ESRD) patients. Few studies reported that early referral and planned dialysis improves HRQOL. Here, we investigated whether referral time and planned dialysis affects HRQOL by nationwide prospective cohort study.

Methods: We enrolled newly diagnosed 670 ESRD patients who responded to the survey on the HRQOL and depression at post-dialysis 3 month. We got follow-up data of 298 patients at post-dialysis 1 year. Early referral (ER) was defined as meeting with a nephrologist more than a year before dialysis, and planned dialysis as starting dialysis with functioning arteriovenous fistula or graft. Kidney Disease Quality of Life Short Form 36 (KDQOL-36) and Beck’s Depression Inventory (BDI) were utilized to measure HRQOL and depression.

Results: Higher KDQOL-36 and lower BDI score correlate with significantly higher survival rate that of referral did not affect KDQOL-36 and BDI score at post 3 months and at post 1 year, neither. However, planned dialysis showed significant improvement in mental component score and symptom/problem list at 3 months (P<0.05). Furthermore, planned dialysis showed better quality of life at post dialysis 1 year in physical component score, symptom/problems list, and BDI (P<0.05). These associations were significant after adjusting for age, sex, laboratory results and social factors.

Conclusions: Planned dialysis significantly improved HRQOL and depression of ESRD patients in short and long period of time. However, timing of referral didn’t affect them. This suggests that nephrologists should prepare dialysis at proper timing and make an effort to improve HRQOL of early referred patients.

Clinical Characteristics of Long-Term Survivors and Short-Term Survivors on Peritoneal Dialysis Yiwen Li. Kidney Disease Dept, ZheJiang Province Hospital.

Background: To evaluate the characteristics of patients on long-term and short-term peritoneal dialysis (PD).

Methods: Patients who be treated with PD since 2006 to 2011 and received PD for at least one year in our Department of kidney disease were included in this study. According to dialysis duration, patients were divided into tree groups. Group A(long-term) was defined as patients survived on PD for more than 4 years, Group B(short-term) was defined as patients who died and Group C(short-term) was defined as switched to hemodialysis within less than 4 years. Demography, biochemical indexes, dialysis adequacy, residual renal function were compared between those groups.

Results: There were 50 patients in group A, 55 patients in group B and 90 patients in group C. Survival analysis showed that 38.7% in group A, 30.9% in group B and 35.6% in group C died during the follow-up period of group A; group B and group C was 58.3%±10.3 months, 93.1 ±20.0 months, respectively. Younger, fewer episodes of diabetic comorbidity (group A 4/50 vs group B 13/55, P<0.05) were found in group A. Compared to group B and group C, the level of serum albumin at the beginning of PD was much higher in group A ([38.7±4.6] g/L vs [36.15±4.85]g/L and vs [35.23±5.27] g/L, P=0.01)]. Compared to group A and group B, the levels of blood sugar in group C is lower. The levels of CRP in group B is higher than in group A and group C (P<0.01 and P= 0.05). The levels of nDNA in group A is higher than in group B (P<0.05). The levels of TC, TG, hemoglobin, calcium, phosphate and iPTH were not significantly different between three groups. Renal Kt/V renal Ccr and urinary volume at the beginning of dialysis were much higher in group A (P<0.05). Peritoneal membrane transport, increased blood sugar morbidity were not significantly different between three groups.

Conclusions: In comparison to short-term survivors, long-term PD patients are characterized by being younger, less diabetic disease, higher level of serum albumin and Hemoglobin, higher volume of urine, lower level of CRP, better residual renal function, less ultrafiltration volume and lower pulse pressure difference.
Methods: We investigated if hyponatremia is managed appropriately in our academic tertiary care center. We reviewed 1344 serial electronic medical records retrospectively on 30 patients with hyponatremia during a six month period. Hyponatremia was defined as a serum sodium (Na<135 mEq/L.

Results: 141 (10.5%) patients (85 M and 56 F, mean age 65.9 yrs) were found to be hyponatremic during their hospitalization. 84 (59.5%) had mild hyponatremia (Serum Na <137 mEq/L), 27 (18.7%) had moderate (130 mEq/L), and 20 (14.2%) had severe hyponatremia (Na<120 mEq/L). The hyponatremic group, mean serum sodium on discharge (133.8) was unchanged to admission (133.7, p<.56). Standard diagnostic criteria, serum osmolality, urine osmolality and urine electrolytes were not checked in 74/84 (88.1%), 34/46 (73.9%) and 61/54 (54.5%) of the hyponatric patients. No significant difference in the management and treatment was seen in the mild versus the severe groups. Length of stay was longer in the hyponatremic patients with management discordance than the patients without. Importantly, mean length of stay was 7.7 days in the hyponatremic groups compared to 4.3 days in the normonatremic group (P<.001).

Conclusions: Diagnostic workup was significantly less comprehensive for patients with mild hyponatremia compared to those with moderate or severe hyponatremia. Longer length of stay had both a positive correlation with lower serum sodium levels and with increased Na levels, indicating that larger fluctuations in sodium levels may be an indicator of disease severity. Hyponatremia management remains suboptimal and further studies are needed to understand it and possible educational avenues to improve it.

PUB255

Interim Analysis of a Multi-National, Observational Safety Study of Tolvaptan in the Treatment of SIADH

Duncan Gould,1 Robert Goedde,7

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

Funding: Pharmaceutical Company Support - Otsuka Pharma Europe Ltd.

PUB256

Aquaporin-10 May Not Be Physiologically Important in Mammals as Some Are Pseudogenes

Kenichi Ishibashi,1 Ryouya Koma,1 Kenma Nozaki,1 Yasuko Tanaka,1 Yoshiyuki Morishita,2 Medical Physiology, Meiji Pharmaceutical University, Tokyo, Japan; 2Nephrology, Jichi Medical School, Shimotuke, Tochigi, Japan.

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

Funding: Pharmaceutical Company Support - Otsuka Pharma Europe Ltd.

PUB257

Symptomatic Chronic Hyponatremia in a Young Female due to Nephrogenic Syndrome of Inappropriate Antidiuresis: Response to Tolvaptan

Vimal Chadha, Uri S. Alon.

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

Underline represents presenting author.

931A

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical-Us.
Inefficativeness of Volume Approach to Hyponatremia: Proposal of New Approach

Louis J. Imbriano,1 Dymphna Gallagher,2 Nobuyuki (Bill) Miyawaki,3 Joseph Mattana,1 John K. Maesaeka,1 Medicine, Winthrop-Univ Hospital, Mineola, NY; 2Body Composition Unit, St. Luke’s-Roosevelt Hospital, New York, NY.

Background: There is awareness that the volume approach to evaluation of HN has been unsuccessful. We present 4 cases of hyponatremia (HN) that support this viewpoint.

Methods: Two females, ages 64 and 84 and 2 males, ages 71 and 73 yrs. met criteria for SIADH and renal salt wasting (RSW).

Results: Serum sodium (Na+) ranged from 116-121 mmol/L, concentrated urine, urine Na+ 23-95 mmol/L, increased fractional excretion (FE) of urate, 16.8-22.7% (normal 4-11%) and normal renal, adrenal and thyroid function. Two non-edematous females, 1 had Lyme disease and the other had hypothyroidism. 1 male had edema of both legs due to inferior vena caval obstruction by stage IV B cell lymphoma. All 3 patients had postural hypotension and tachycardia. In 2 patients, saline infusion induced excretion of dilute urines, plasma ADH being appropriately undetectable in the edematous patient with lymphoma; FEurate remained elevated, indicating the persistence of HN in both females that was consistent with RSW as compared to normalization in SIADH. Total (TBW) and extracellular body water (ECW) as determined by deuterium and sodium bromide, respectively, were decreased in the 2 nonedematous females. The increased FEurate, which persisted after correction of HN, dilution of the urine, and subsequent normalisation of plasma ADH, was consistent with RSW.

Conclusions: RSW was noted in 3 patients -2 by critical volume studies and 1 had edema; SIADH can occur with edema and pleural effusion. None had clinical cerebral disease which justifies proposal to change cerebral to RSW. We demonstrate the superiority of determining FEurate to the volume approach in HN.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical-US

Cost-Utility Analysis of Tolvaptan versus Water Restriction for Euvolemic or Hypervolemic Hyponatremia

Robert Nee, Christina M. Yuan.

Background: Hyponatremia is associated with increased morbidity and mortality. Tolvaptan, an oral vasopressin (V2) receptor antagonist, increases serum sodium concentration and is recommended as second-line therapy for moderate/severe hyponatremia. Probabilities of resolving hyponatremia, and utilities for resolved (0.68) and unresolved (0.55) hyponatremia were obtained from the SALT trials (Cyr, et al. Abstract 25379. ISPOR. 2009). The primary endpoint was the incremental cost-effectiveness ratio (ICER) in dollars per quality-adjusted year of life (QALY) gained.

Methods: A longitudinal model was developed using TreeAge Pro software (Williamstown, MA) to represent the costs and effectiveness of tolvaptan 30 mg daily vs. water restriction alone for outpatient treatment of euvolemic/hypervolemic hyponatremia. Costs, utility indices, and probabilities were obtained from literature review. Model time horizon was 48 hours. Baseline day hospital admission was required for tolvaptan initiation. Probabilities of resolving hyponatremia, and utilities for resolved (0.68) and unresolved (0.55) hyponatremia were obtained from the SALT trials (Cyr, et al. Abstract 25379. ISPOR. 2009). The primary endpoint was the incremental cost-effectiveness ratio (ICER) in dollars per quality-adjusted year of life (QALY) gained.

Results: The ICER was $2,800,000 per QALY gained, using a cost of $250 per 30 mg tolvaptan. One-way sensitivity analysis, using an arbitrary willingness to pay (WTP) threshold of $1,000,000, demonstrated water restriction to be the cost-effective option unless the cost of tolvaptan was < $71.22/day. A high FEurate is very unusual in edematous patients, usually <4%. None of the patients had cerebral disease.

Conclusions: There was a trend for more rapid improvement of serum Li levels in lithium intoxicated patients with greater rates of saline administration although it was not statistically significant given our small sample size. Prospective studies are needed to re-examine the efficacy of forced sodium diuresis in Li intoxication.

Funding: Pharmaceutical Company Support - ZS Pharma, Inc.

Saline Diuresis for Lithium Intoxication Revisited 30 Years Later

Wei Boon Ooi, Francisco Hernandez Munoz, Alina Livshits, Monique Carreno, Alexander B. Knee, Anthony E. Poindexter, Gregory Lee Braden. Dept of Medicine, Baystate Medical Center, Springfield, MA.

Background: Reviews and textbooks do not recommend saline diuresis as therapy for lithium (Li) intoxication. Past case reports (“70s) showed forced saline diuresis (>250mL/hour 0.9% NaCl) may be helpful. We now describe patients with Li intoxication & correlate saline administration with clinical outcomes.

Methods: Patients were identified by ICD-9 codes from 2007-2012. Exclusion criteria included incomplete medical records & patients who were dialyzed. Time from admission to normal serum Li level (≤1.5mmol/L) was used as surrogate marker for Li clearance. Main outcomes were rate of Li clearance due to saline diuresis & potential complications of saline diuresis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
is most common in reset osmostat, while F2Earate is increased in cerebral-renal salt wasting (RSW) and SIADH.

Methods: We present a patient with Addison’s disease (AD) and another with myxedema (MX), where F2Earate provided insight into the pathophysiology of HN. A 51 year old female with AD was admitted with low blood pressure, serum sodium (SNa) 119, potassium 5.4 mmol/L, low AM cortisol 3.1ug/dl, high ACTH 865.1 pg/ml, urine (U) Na 116 mmol/L, urine osmolarity (Uosm) 537 mosm/kg and low F2Earate of 2 and 3% (normal 4-11%). A 74 year old male with MX was admitted with SNa 116, UNa 44 mmol/L, Uosm 300 mosm/kg, high F2Earate of 26.6%, TSH 39.7 mIU/L and free T4 0.53 ng/dL. Both had normal renal function.

Results: HN in AD is associated with an appropriate increase in plasma ADH secretion due to extracellular volume (ECV) depletion resulting from defective distal tubule (DT) Na transport with intact function of the proximal tubule (PT) where urate is exclusively transported. This induces a prerenal state with low F2Earate. In MX, high F2Earate is consistent with RSW and SIADH. Studies in MX rats demonstrate a 17.1% reduction in ECV as determined by inulin space and a 28% reduction in PT Na reabsorption by micropuncture methodology. These data are consistent with the increase in FEIiurium from 29 to 42% when plasma from patients with RSW was infused into rats. This suggests a major defect in PT Na transport in RSW since lithium is transported 1:1 with Na in the PT and no transport in the DT.

Conclusions: The HN in AD and MX is due to an appropriate increase in ADH induced by ECF volume depletion, defective Na transport in the DT and AD and PT in MX. The low F2Earate in AD is consistent with intact PT function whereas the high F2Earate in MX is consistent with a major defect in PT solute transport.

PUB264

The Implication of Overstimulation of Redox-Sensitive Na/K-ATPase Signaling in Dahl Salt Sensitivity

Yanling Yan,1,3 Anna P. Shapiro,2 Steven T. Haller,2 Muhammad A. Chaudhry,1 Jiang Tian,2 Zi-jian Xie,2 Deepak K. Malhotra,2 Nader G. Abraham,1 Joseph I. Shapiro,1,2 Jiang Liu.1 Marshall Univ JCE School of Medicine, Huntington, WV; 2Univ of Toledo College of Medicine, Toledo, OH; 3Yanshan Univ, Qinhuangdao, China.

Background: Impairment of renal proximal tubule (RPT) Na/K-ATPase signaling contributes to Dahl salt-sensitive hypertension, but there is no difference in α1 gene coding, ouabain-sensitivity, and α1 expression between Dahl salt-resistant (R) and salt-sensitive (S) rats.

Results: A high salt diet (2% NaCl for 7 days) significantly stimulated RPT Na/K-ATPase signaling, protein carbonylation (whole cell lysate and Na/K-ATPase α1 subunit) and heme-oxygenase-1 (HO-1) expression in isolated RPTs in Dahl R but not S rats (12-14 week old). Compared to age- and gender-matched S rats fed with a low salt diet (0.3% NaCl), isolated RPTs from the S rats have a significantly higher basal level of protein carbonylation and HO-1 that do not respond to a high salt stimulation.

Conclusions: Oxidative stress affects RPT Na/K-ATPase signaling and sodium handling. Overstimulation of ROS/carbonylation in the S rats at baseline might desensitize the Na/K-ATPase signaling that is no longer responding to a high salt diet or ouabain.

Funding: Other NIH Support - NIH RO1 HL-109015 to Z.X. and J.I.S.

PUB266

Ouabain-Induced Protein Carbonylation of the Na/K-ATPase α1 Subunit Is Reversible in LLC-PK1 Cells

Yanling Yan,1,3 Anna P. Shapiro,2 Muhammad A. Chaudhry,1 Zi-jian Xie,2 Deepak K. Malhotra,2 Nader G. Abraham,1 Joseph I. Shapiro,1,2 Jiang Liu.1 Marshall Univ JCE School of Medicine, Huntington, WV; 2Univ of Toledo College of Medicine, Toledo, OH; 3Yanshan Univ, Qinhuangdao, China.

Background: In LLC-PK1 cells, ouabain-stimulated c-Src activation, ROS generation and protein carbonylation of the Na/K-ATPase α1 subunit were significantly attenuated by the antioxidant N-acetyl-L-cysteine (NAC) and disruption of the Na/K-ATPase signaling. Interestingly, both ouabain and CoPP also significantly induced HO-1 expression in LLC-PK1 cells. To determine the role of the Na/K-ATPase and its signaling, we used three stable cell lines generated from LLC-PK1 cells, PY-17 (the Na/K-ATPase α1 subunit knock-down cells), C2-9 (caveolin-1 knockout cells), and AAC-19 (PV-17 cells only expressing α1 cells). Both PY-17 and C2-9 show disrupted Na/K-ATPase signaling. Both ouabain and CoPP significantly induced HO-1 expression in AAC-19 cells as seen in LLC-PK1 cells. However, depression of Na/K-ATPase expression and disruption of Na/K-ATPase signaling not only prevented ouabain-induced HO-1 expression, but also prevented CoPP-induced HO-1 expression.

Funding: Other NIH Support - NIH RO1 HL-109015 to Z.X. and J.I.S.

PUB267

Abnormal Urinary Excretion of ENaCα by Hypertonic Saline Infusion in Chronic Kidney Disease

Janni Majgaard Jensen,1,2 Frank H. Mose,1 Jesper N. Bech,1 Erling B. Pedersen,1 1Depts of Medical Research and Medicine, Holstebro Regional Hospital, Holstebro, Denmark; 2Aarhus Univ, Denmark.

Background: Patients with chronic kidney disease (CKD) have a diminished capacity to concentrate urine. We wanted to test the hypothesis that this phenomenon is caused by abnormal activity in the aquaporin2 water channels and/or the epithelial sodium channels in the distal nephron.

Methods: The study comprised of 23 patients with CKD and 24 healthy controls, who consumed a 4-day standardized diet (120 mmol sodium/day) prior to the study day. At baseline conditions and after 3 % hypertonic saline infusion, we measured urinary
concentrations of ΩP2 (u-ΩP2) and gamma sumbit of ENaC (u-ENaC γ) free water clearance (C_f), urinary osmolality (u-Osm) and fractional excretion of sodium (FE_{Na}), GFR was measured by constant infusion clearance technique using {^{131}I}-DTPA as reference substance. Plasma concentrations of vasopressin (AVP), renin (RPG), Angiotensin II (AngII) and Aldosterone (Aldo) were determined by radioimmunoassay (RIA). Extracellular body fluid volume (ECV) was calculated by Body Composition Monitor.

Results: At baseline, GFR was 34 ml/min in patients and 89 ml/min in controls. CKD patients had a high u-ENaC γ, FE_{Na}, PRC, p-Aldo and p-APV and a low C_f compared to controls. No differences in u-ΩP2 or ECV were measured between patients and controls. Hypertonic saline infusion caused an increase in u-ENaC γ in patients (p<0.05), but there was no change in u-ENaC γ in patients. Controls had a higher increase in u-osm and a larger decrease in C_f compared to patients, but the increase in u-ΩP2, FE_{Na} and p-APV were similar. PRC, AngII and Aldo decreased in both groups although levels were higher in patients. ECV increased to the same extent in both groups.

Conclusions: In response to hypertonic saline, u-ENaC γ increased in controls and did not change in CKD patients. This abnormal response in u-ΩP2 in CKD patients might be caused by a less efficient decrease in reabsorption of sodium in the proximal tubules and subsequently no need for adjustment in the distal nephron via ENaC.

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

Conclusions: Tolvaptan is effective diuretic even in severe CKD patient, resistance to conventional diuretic, without worsening renal function.

PUB270
A New Step-Ladder Approach to Treating Severe Symptomatic Chronic Hypernatremia to Mitigate Catastrophic Cerebral Events
Maaculy A. Onuogbu,1,2, Ngoc J. Achebe,3 1Medicine, Mayo Clinic, Rochester, MN; 2Nephrology, Mayo Clinic Health System, Eau Claire, WI; 3Internal Medicine, Capital Medical Center, Olympia, WA.

Background: Hypernatremia is associated with hyperosmolality and hypertonicity of plasma and intracellular space. The brain and other tissues therefore adapt to avoid pathologic cell shrinkage/dehydration by synthesizing idiogenic osmoles. Severe hypernatremia is much less common than hyponatremia so physicians are less aware of the implications of over-rapid correction of chronic hypernatremia. We describe a new step-ladder approach to managing severe hypernatremia.

Methods: Case report.

Results: An unresponsive 80 year old Caucasian male patient, a Group Home resident, with cognitive developmental delay from birth, central diabetes insipidus with chronic hypernatremia was admitted with fever, pneumonia, volume depletion and severe hypernatremia (179 mEq/L). In addition to intravenous antibiotics, he required daily intermittent guided free water repletion therapy with intravenous 5% dextrose (100-250 cc/hr) to achieve a step-ladder correction of Na over 72-96 hours. Inhaled DDAPV was added about hospital day 4. This way, the over-rapid correction of chronic hypernatremia by >10-12 mEq/L/day was avoided, thus mitigating the potential but often unrecognized risk of cerebral edema. He was later discharged at baseline mental status, with a Na of 146 mEq/L.

Conclusions: With adaptive processes in severe hypernatremia, over-rapid correction produces rapid fluid movement into the brain cells and the development of cerebral edema. Most experts recommend 10-12 mEq/L/day correction. We have described a step-ladder approach of safely managing severe hypernatremia using guided intermittent intravenous 5% dextrose in an unconscious patient. Acute hypernatremia (<12 hours) should be corrected quickly; however, when in doubt, go slow.

PUB269
Hypomagnesemia in Critically Ill Patients with Sepsis
Ashish Kataria,1 Daniel W. Ross,1 Nirav Mehta,1 Myriam Kline,2 Kenar D. Jhaveri,1 Steven Fishbane,1,3 Kidney Diseases and Hypertension, Hofstra NSLIJ School of Medicine, NY; 2Biostatistics, Feinstein Institute of Medical Research.

Background: Hypomagnesemia has been reported in 20% to 65% of patients in an ICU setting. Our study aimed to evaluate the frequency of hypomagnesemia in critically ill patients with sepsis, determine clinical predictors for its development, and to ascertain how hypomagnesemia affects patient outcomes in the ICU setting.

Methods: A single center, retrospective cohort study was conducted. All ICU patients with sepsis within the last year were evaluated. A group with normal Mg levels was compared to low Mg group. Baseline demographics, medications used, and lab data were collected. Primary outcome was the frequency of patients that developed hypomagnesemia. The adverse outcomes studied from were: ventilator requirement, days on ventilator, ICU length of stay and mortality during the hospital stay. Mg level of <1.6mg/dl was used as the cutoff level. Logistic regression was used to model hypomagnesemia as a function of key demographic clinical variables.

Results: Hypomagnesemia was observed in 23% of (n=99) studied patients. There were no significant differences between the groups at baseline on any demographic or laboratory variables. Risk factors in developing hypomagnesemia such as diarrhea, chemotherapy use, use of PPI’s and diuretic were not significantly associated with the development of hypomagnesemia. Nonetheless, 77% patients who had low Mg levels were administered PPI’s as compared to 53% in the normal Mg group, (p-value=0.06). The development of hypomagnesemia was not associated with ventilator use, length of ventilator dependence, or length of stay in ICU and mortality.

Conclusions: While low Mg was extremely common in the ICU patients with sepsis, it did not affect their overall ICU stay and mortality. Despite the absence of significant associations of low Mg levels with the studied risk factors and clinical outcomes, the development of hypomagnesemia in 23% of ICU patients having sepsis during their ICU stay warrants a prospective study with a larger sample size to ascertain its relationship to clinical outcomes in this specific patient population.

Conclusions: Tolvaptan is effective diuretic even in sever CKD patient , resistance to conventional diuretic, without worsening renal function.

PUB268
The Effects of Tolvaptan on Severe Chronic Kidney Disease Patients with Congestive Heart Failure
Kei Terakura,1 Kentaro Tanaka,1 Toshiyuki Tsuchiya,1 Aoki,1 Morisato Miyagi,1 Ken Sakai,2 Sonoo Mizui,2 1Dept of Nephrology, Saiseikai Yokohama-City Eastern Hospital, Yokohama, Kanagawa, Japan; 2Dept of Nephrology, Toho Univ School of Medicine, Ota-ku, Tokyo, Japan; 3Div of Diabetes and Metabolism, The Institute for Adult Diseases, Asahi Life Foundation, Chiyoda-ku, Tokyo, Japan.

Background: Tolvaptan is a selective vasopressin receptor 2 antagonist and dose-dependent drug used to treat congestive heart failure (CHF) as diuretic. It is known that tolvaptan increases excretion of excess fluids and improves blood sodium in patients with heart failure without affecting renal function compared to conventional diuretics. However, few studies examined the effects of tolvaptan for patients with severe chronic kidney disease (CKD). The aim of the study is to examine the effect of tolvaptan on patients with severe CKD.

Methods: We analyzed CKD patients with less than 30 of estimated glomerular filtration rate (eGFR) who had CHF. Those of all patients have already treated conventional diuretics, but CHF worsened. We administrated tolvaptan for the patients with CHF in admission. In order to examine the effect of tolvaptan, we examined age, body weight, serum sodium and eGFR for three days after administration. The patients who had undergone conventional diuretics in observation period were excluded.

Results: We evaluated 52 patients consisted of 32 men and 20 women with a mean age of 77 ± 10.9 years and a mean eGFR of 17.8 ± 7.4 ml/min/1.73m^2 at admission. The mean dose of tolvaptan was 12±0.40mg. The maximum volume increased from 114.1±539.5 ml/day to 1864.5±1088.2 ml/day (p<0.001, Wilcoxon signed-rank test). Body weight improved from 57.9 ± 17.6 kg to 57.8 ± 17.0 kg (p=0.01, Wilcoxon signed-rank test). Serum sodium level elevated from 132.6 ± 6.3 mEq/l to 139.8 ± 6.4 mEq/l (p<0.05, ANOVA and Dunnett’s testing). eGFR (17.6±7.4 ml at baseline) remained 17.1±8.7 after administration (p=0.34, Wilcoxon signed-rank test).

Conclusions: Tolvaptan is effective diuretic even in severe CKD patient , resistance to conventional diuretic, without worsening renal function.

PUB271
Aggressive Therapy Fails to Influence Outcomes in Hospitalized Hypernatremic Geriatric Patients
Muhammad R. Toog, Anjali Singla, Xenia P. Sumin, Maria V. DeVita, Michael F. Michels. Nephrology, NSLIJ-Lenox Hill Hospital, New York, NY.

Background: Hypernatremia is a common electrolyte disorder and is associated with adverse outcomes such as increased length of stay and increased mortality. Prior studies have suggested a variety of factors that may result in undesirable outcomes. Methods: A 3 month retrospective chart review was performed on hospitalized patients over the age of 18 with a serum sodium level >150 mEq/L. This study was designed to characterize the rate of sodium correction, the level of monitoring as indicated by ward setting, whether or not a nephrologist was involved in the case, the type of fluids used, and other relevant data and whether any of these variables influenced patient outcomes.

Results: Of 28 patients with hypernatremia, 5 were excluded because of data deficiencies. Of the remaining 23 patients studied, the mean age was 82.6 years old and the mean initial sodium level was 152.3 mEq/L (range: 151–156 mEq/L). Ten (43%) patients were demented and twelve (52%) were on tube feeding. The overall mortality rate was 65%, Sodium level was corrected (≤145 mEq/L) in 15 (65%) patients. Correction did not influence rates of survival (33% corrected vs. 38% not corrected, p=0.99). Seven patients corrected in ≤2 days and 8 in ≥2 days but these differences did not affect survival. Thirteen of 14 patients admitted to or transferred to the ICU expired whereas 2 of 9 patients not in the ICU expired (p=0.001, RR 6.93). Obtaining a nephrology consult did not affect patient mortality (p=0.69). The patients received fluids, including NS, dextrose, 5% NS, D5W, and oral water, which appeared appropriate to their clinical status. The mean length of stay for all patients was 20.4 days and longer for those who remained alive, 23.6 days.

Conclusions: While low Mg was extremely common in the ICU patients with sepsis, it did not affect their overall ICU stay and mortality. Despite the absence of significant associations of low Mg levels with the studied risk factors and clinical outcomes, the development of hypomagnesemia in 23% of ICU patients having sepsis during their ICU stay warrants a prospective study with a larger sample size to ascertain its relationship to clinical outcomes in this specific patient population.

Conclusions: Tolvaptan is effective diuretic even in severe CKD patient , resistance to conventional diuretic, without worsening renal function.
Conclusions: Hypernatremia is associated with a poor prognosis and outcomes are still disappointing despite appropriate rates of correction, intensive monitoring, and the involvement of a medical specialist. This indicates that the disease state associated with hypernatremia appears to be of paramount importance in regard to patient outcomes and early attention to the primary process is essential.

PUB272
An Unusual Case of Hyperkalemia Refractory to Hemodialysis

Sindhu Malik Arjun, Gary Noroian, Robert Mark Black. Div of Nephrology, Saint Vincent Hospital, Worcester, MA.

Background: Pseudohyperkalemia is typically caused by hemolysis, thrombocytosis or traumatic blood drawing. We report a case of a patient with severe hyperammonemia-associated hyperkalemia.

Methods: An 80 year old man presented to our institution with critical aortic stenosis. Before his aortic valve replacement, his serum creatinine was 1.02 mg/dL and his serum potassium concentration was 3.0 meq/L. His post-op course required pressor support and mechanical ventilation. He developed anuric acute kidney injury with a creatinine rise to 4.63 mg/dL. His urine sediment was consistent with acute tubular necrosis. Intermittent hemodialysis was initiated. His serum potassium level remained normal for the first two weeks of dialysis. It then rose to 6.1 meq/L. He was dialyzed, but his potassium level two hours after hemodialysis was 6.7 meq/L. A repeat potassium level was 7.3 meq/L. The plasma level was also high. He was dialyzed again that evening. One hour into the dialysis treatment, the K fell to 5.7 meq/L and it was 3.8 meq/L at the end of the treatment. Blood pressure was lower and he had a very mild rise in the hepatic transaminases. An ammonia level was 572 umol/L (normal ~19–87). His ammonia level fell during the dialysis treatment, correlated with his serum potassium level. While hepatic transaminases rose progressively over the next 24 hours, the acute hyperkalemia and hyperammonemia preceded these changes.

Conclusions: We hypothesize that the elevated ammonia (ammonium) level interfered with the serum potassium measurement in our patient. Extremely high serum ammonia levels (~4000umol/L), were found to interfere with serum potassium measurements obtained using the OsmetechOPTI critical care analyzer. The proposed mechanism is the cross reactivity of the NH4+ ions with the K+ selective ionophores. Pseudohyperkalemia should be considered in patients with refractory hyperkalemia and very high blood ammonia levels.

Caroline M. Williams,1 Nathan W. Levin,1 Peter Kotanko.1 Div of Nephrology, Saint Vincent Hospital, Worcester, MA.

PUB273
Factors Associated with Calf 100 kHz Impedance in Healthy Subjects

Samer Rateb Abbas,1,2 Fansan Zha,1 Cesar Flores-Gama,1 Cassandra Cartagena,1 Caroline M. Williams,1 Nathan W. Levin,1 Peter Kotanko.1 Nephrology, Renal Research Institute, New York, NY; Nephrology, Beth Israel Medical Center; New York, NY.

Background: Calf bioimpedance is used in hemodialysis patients to assess fluid status. Advantages of calf over whole body bioimpedance are ease of use and reliable evaluation of fluid status (Zhu, Physiol. 2008). This prospective study was to investigate associations between body weight, body mass index (BMI), age, gender and race and calf impedance (Zo) at 100 kHz in healthy subjects.

Methods: We measured Zo at 100 kHz (ZOE device; Noninvasive Medical Technologies; Las Vegas, NV) in adult subjects 40 to 80 years of age and eGFR > 60 mL/ min/1.73 m² to create reference values. Zo was measured with leg horizontal in sitting subjects 5 minutes after placement of 4 electrodes; measurement took 30 seconds. Simple linear regression analysis was used to quantify the associations between Zo and body weight, BMI, and age. Groups (gender; black vs. non-black) were compared by unpaired t-test.

Results: We studied 62 subjects (age 56±9 years; 31 males; 26 Blacks). Zo was not associated with body weight, BMI, age, gender and race figure A and B.

Conclusions: In healthy subjects calf Zo measurement at 100 kHz is unrelated to key anthropometric and demographic characteristics, thus allowing the construction of Zo reference values irrespective of age, race, gender, body weight, and BMI.

PUB274
Dialysis Improved the Survival Rate of Patients with Severe Hyperkalemia

Do Hyoung Kim,1 Jung Pyo Lee,1 Jung Nam An,2 Jin Ho Hwang,1 Yun So Kim,1 Yun Kyu Oh,2 Chun Soo Lim.1,2 1Dept of Internal Medicine, Chung-Ang Univ College of Medicine, Republic of Korea; 2Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Republic of Korea; 2Dept of Internal Medicine, Seoul National Univ College of Medicine, Republic of Korea.

Background: Severe hyperkalemia, with potassium levels ≥ 6.5 mEq/L, is a serious complication with high mortality in the hospitalized population. The purpose of this study is to evaluate the efficacy of renal replacement therapy (RRT) and the impact of the timing of RRT in patients with severe hyperkalemia.

Methods: We collected clinical data from 909 patients diagnosed with severe hyperkalemia. All were hospitalized between August 2007 and July 2010. The diagnosis of severe hyperkalemia was made either at the time of admission or during the period of hospitalization. Early dialysis (ED) was defined if RRT was started within 12 hours from the diagnosis of severe hyperkalemia. 135 patients (14.9%) who received RRT were compared with 774 patients who received only medical treatment.

Results: Of the 909 patients, 156 were end-stage renal disease (ESRD) patients with RRT and 753 were non-ESRD patients. The survival rate of RRT group was better than that of medical treatment group (Log Rank test, P=0.010). This association was also significant after adjusting for age, gender, disease severity, kidney function, and potassium level (HR 0.628, 95% CI 0.419-0.939, P=0.024). In subgroup analysis, RRT increased patients’ survival rate in ESRD patients, however, it could not improve survival rate in non-ESRD patients. In non-ESRD patients, RRT group had significantly higher potassium levels and more comorbidities than medical treatment group. The average time from diagnosis to dialysis was 9.1 ± 9.6 hours. Those in the ED group had a mortality rate of ED group was significantly higher than that of late dialysis (LD) group (P=0.007). Potassium level of ED group was higher than that of LD group (ED vs. LD, 7.15 ± 0.74 vs. 6.86 ± 0.53 mEq/L, P = 0.037).

Conclusions: Renal replacement therapy with medical treatment improved clinical outcomes in patients with severe hyperkalemia. But, timing of dialysis treatment could not affect the patients’ survival.

PUB275
AVP-Induced Increase in AQP2 and p-AQP2 Is Blunted in Heart Failure during Cardiac Remodelling and Is Associated with Decreased AT1R Abundance in Rat Kidney

Sophie Constantin Lütken,1 Jorgen Frokiaer,1 Soren Nielsen.1 1 The Water and Salt Research Center, Dept of Biomedicine -Anatomy, Aarhus Univ, Aarhus, Denmark; 2The Water and Salt Research Center, Institute of Clinical Medicine, Aarhus Univ Hospital, Aarhus, Denmark.

Background: The effects of early HF on a standard sodium diet, sodium restricted diet, and sodium restricted diet in combination with long-term 1-desamino-8-D-arginine vasopressin (DDAVP) treatment. Focus were the AVP-angiotensin II receptor (AT1R) interactions with the (pro)renin receptor in regulation of the water channels AQP2, AQP1, and AQP3 in the inner medullary (IM) collecting duct of rat kidney.

Methods: LAD-ligation was performed on male Wistar rats. 10 days after operation the rats were allocated to 6 groups for the last 7 days: Sham (N = 11), sodium restricted diet (SRD-N = 11), sodium restricted diet + DDAVP (SRD+DDAVP, N = 12), and sodium restricted diet + DDAVP + AT1R antagonist (SRD+DDAVP+AT1R, N = 12). EF < 50% was the inclusion criteria for LAD ligated rats. DDAVP dose was 0.5 ng/kg/day for 7 days. The rats were sacrificed after 17 days, before cardiac remodeling was completed.

Results: Early standard sodium HF and LS-HF increased AQP4 but blunted increase in AQP2 and pSer256)-AQP2 in the presence of hyponatremia, hypoosmolality and decreased fractional excretion of sodium in spite of increased V2R abundance. LS-HF+D exhibited decreased creatinine clearance, severe HF (EF = 41 ± 2), severe hyponatremia, and hypoosmolality. IMAQP2, pSer256)-AQP2, AQP3, and AQP4 decreased vs. LS sham and LS-HF+D (P=0.03). In subgroup analysis, RRT increased patients’ survival rate in ESRD patients, however, it could not improve survival rate in non-ESRD patients. In non-ESRD patients, RRT group had significantly higher potassium levels and more comorbidities than medical treatment group. The average time from diagnosis to dialysis was 9.1 ± 9.6 hours. Those in the ED group had a mortality rate of ED group was significantly higher than that of late dialysis (LD) group (P=0.007). Potassium level of ED group was higher than that of LD group (ED vs. LD, 7.15 ± 0.74 vs. 6.86 ± 0.53 mEq/L, P = 0.037).

Conclusions: Renal replacement therapy with medical treatment improved clinical outcomes in patients with severe hyperkalemia. But, timing of dialysis treatment could not affect the patients’ survival.

PUB276
Young Soul with Old Bones

Payaswini Vasanth, Amsalu Erko. UT Southwestern Residency Program at Seton Family of Hospitals, Austin, TX.

Background: Acid-base balance plays an important role in calcium homeostasis and bone metabolism. We present a case of osteoporosis with an objective to discuss partial absence of renal acidification as a preventable cause of osteoporosis.

Methods: A 37 year-old male was evaluated for fatigue for 2 years, was diagnosed for depression and was treated with fluoxetine. While on this medication, he developed insomnia which led to sleep deprivation seizure, and he experienced acute back pain after falling. The physical exam was notable for kyphosis and lumbar spines. A lumbar x-ray revealed a T5-T6 compression fracture with diffuse osteopenia. A subsequent DEXA scan showed a T-score of -2.4 of lumbar spine. Urinary studies showed a pH of

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

935A
7, calcium of 637 mg/24h (normal range: 100-300 mg/24h), citric acid of 149 mg/24h (normal range: 320-1240 mg/24h), presence of ammonium and calcium phosphate crystals, and a positive urinary uric acid. Serum chemistries were normal, except for a potassium level of 3.3 mmol/L and a bicarbonate of 22 mmol/L. A diagnosis of incomplete distal tubular acidosis was made based on the persistently high urine pH even after a trial of diuretics, and the presence of hypercalcemia and hypoparathyroidism in the setting of mild non-gap acidosis. A workup for major causes of RTA and osteoporosis were negative. The patient received potassium citrate, calcium and vitamin D supplements. A DEKA scan after a year showed an increase of 3.8% in bone density of the lumbar spine.

**Conclusions:** Adults with incomplete distal RTA (IDRTA) have a partial defect in renal acidification. The relationship between IDRTA and bone mineral density has been proposed but not proven based on current data. Although IDRTA patients do not have persistent systemic acidosis, they may develop mild to moderate acidosis episodically due to high acid load (as in high protein diet), and their limited ability to excrete such excess acid may be due to the bone causing its resorption and denitrification. Treating these patients with alkaline therapy, like potassium citrate, has shown to prevent, delay or reverse metabolic bone disease. Incomplete IDRTA should be suspected in patients with unexplained osteoporosis or osteopenia.

**PUB277**

**Traumatic Encephalopathy Leading to Cerebral Salt Wasting and Hyponatremia with Permanent Brain Damage**

**Authors:** Allen L. Arieff, Medicine, University of California, Sausalito, CA.

**Background:** 1.5 to 2 million USA civilians per year suffer traumatic brain injury. 4.5% of these sustain a chronic and severe disabling condition. It has not been previously noted that cerebral salt wasting, which often complicates head trauma, could lead to hyponatremia, and severe brain damage.

**Methods:** 14 individuals who suffered acute traumatic encephalopathy (motor vehicle accident (10), falls (7)) were admitted and had neuroimaging showing closed head injury. These patients were all subdural hematomas (6), diffuse subdural edema (5), cerebral infarction (3). All received isotonic fluids and all developed hyponatremia after 57±32 hours. Plasma Na fell from 138±4 to 119±7 mmol/L. All were initially diagnosed as having SIADH (urine osmolality>40400 mos/kg). All were initially treated with fluid restriction. Over 24 Hr the mean BP declined from 135/63 mm Hg to 92/48 mm Hg. Urine Na (184±66 mmol/day) was significantly above control (113±65 mmol/day, p <0.01). The systolic BP was restored to above 100 mm Hg by IV infusion of 0.9% NaCl. Two patients suffered hypoxic brain damage and died while the other 12 recovered. The 12 surviving patients were eventually maintained on oral NaCl tablets (mean 2.5 gm/day).

**Conclusions:**

- **Model:** Closed head trauma can lead to hyponatremia secondary to a Na wasting syndrome; b) fluid restriction can lead to shock, worsening of hyponatremia and hypoxic brain damage; c) the Na wasting can eventually be controlled with oral NaCl tablets.

**PUB278**

**Downregulation of RAGE Suppresses Cyst Growth in an ADPKD Mouse Model**

**Authors:** Dong Hoon Park, Eun Young Park, Bo Hye Kim, Eun Sun Chang, Dept of Biological Science, Sooam Women’s Univ, Seoul, Korea.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder. Although a myriad of research groups have attempted that blocking RAGE function attenuates cyst growth to identify a new therapeutic target for ADPKD, no drug has worked well in clinical trials.

**Results:** We suggest that RAGE-related signaling may be closely associated with cyst growth in ADPKD. The Prevalence of Simple Renal Cyst in China and Its Correlative Factors

**Authors:** Hyun Suk Kim, 1 Miyeun Han, 1 Hyuk Huh, 1 Jong Cheol Jeong, 1 Kook-Hwan Oh, 1 Jaeckong Yang, 2 Tai Yeon Koo, 1 Young-Hwan Hwang, 1 Curie Ahn, 1 Dept of Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; 2 Transplantation Center, Seoul National Univ Hospital, Seoul, Korea; 1 Dept of Internal Medicine, Eulji General Hospital.

**Background:** We often experience blood pressure decrement after nephrectomy in asymptomatic polycystic kidney disease (ADPKD) patients. However, few studies have addressed the effect of native nephron on blood pressure and graft outcome after kidney transplantation in ADPKD patients.

**Results:** We conducted retrospective study in ADPKD patients who underwent kidney transplantation from 1999 to 2012. Cases with simultaneous native nephrectomy (n=26) were compared with non-nephrectomy (n=16). Primary outcome was graft function 1 year after kidney transplantation. The secondary outcomes were patient and graft survival, post-operative hypertensive events and changes in blood pressure.

**Conclusions:** Simultaneous native nephrectomy had no association with graft function at 3, 6, 12 months after kidney transplantation. There were more frequent hypertensive events in the simultaneous nephrectomy group than controls (64.7% in unilateral, 77.7% in bilateral nephrectomy group vs. 37.5 % in controls; p=0.045). Graft function at post-transplant 1 year was higher in patients with hypotensive events than those without events (67.2 vs. 57.3 mL/min/1.73 m²; p=0.02). The proportion of patients who had more than 3 anti-hypertensives was lower in patients with hypertensive events than those without events (5.5% vs.12.5% at 6 months; p=0.599).

**Conclusions:** Simultaneous native nephrectomy had no influence on graft outcome. Although hypertensive events occurred more frequently in the simultaneous nephrectomy group, patients with hypotensive events had better graft function than those without events. Better blood pressure control with fewer medication may explain the better graft function in patients with hypotensive events group.

**PUB281**

**The Prevalence of Simple Renal Cyst in China and Its Correlative Factors**

**Authors:** Jian Hui Yang, Renal Div, Zhejiang Provincial People’s Hospital.

**Background:** Present study was to understand the prevalence of simple renal cysts in Jinhua and to find the possible risk factors of them.

**Methods:** Abdominal sonography was performed in 10016 adults who received regular health check-up from February 2007 to May 2011. Their age, gender, blood pressure, BMI, values of serum cholesterol, glucose and creatinine, urine analysis, smoking habit and sonographic features were analyzed.

**Results:** The overall prevalence of simple renal cysts was 10.7%, ranging from 2.38% in the 2nd to 55.29% in the 7th or later decade of life. The incidence of simple renal cysts were associated with male gender, higher systolic blood pressure, older ages (p <0.001). The age of individuals with cysts was significantly older than those without cysts (57.65 ± 13.35 vs. 47.78 ± 12.40 years; p <0.001). Male-to-female ratio was 2.81 (15.14% vs. 5.38%; p<0.001). The majority of cysts were solitary (82.3%). The diameter of cysts ranged from 0.000 to 12.60 cm (2.16±2.60 cm). The mean size of cysts in every age group was not statistically different. Factors significantly associated with simple renal cysts were age (odds ratio [OR], 4.37; p=0.001), gender (OR, 0.32; p<0.001), serum creatinine (OR, 11.77; p=0.001), proteinuria (OR, 3.11; p =0.004), renal stone (OR, 2.47; p =0.006), and smoking (OR, 2.80; p<0.001). However, in multivariate analysis, except proteinuria, all of the above factors were significantly related to the occurrence of simple renal cysts.

**Conclusions:** The overall prevalence of simple renal cysts in China was 10.7%. Age, sex, renal stone, serum creatinine, and smoking were to be risk factors for the presence of simple renal cysts.
UBOM Polymorphism rs12917707 Is Not Associated with Severe or Stable IgA Nephropathy in a Large Caucasian Cohort  
Mirianna Dinic, Ingrid Masson, Nicolas Maillard.  
Nephrology-Renal Transplantation Dept, CHU St. Etienne, France.

**Background:** The progression of IgA nephropathy (IgAN) varies among individuals and leads to a 20% global risk of End Stage Renal Failure. Genetic factors are involved in the physiopathology of IgAN. Genome-wide studies have recently addressed the genetic variants underlying interindividual renal function and Chronic Kidney Disease (CKD) in the general population. Single Nucleotide Polymorphisms (SNPs) in UBOM gene were significantly associated with CKD and increased serum creatinine. The minor T allele of rs12917707 was linked with a 20% reduced risk of CKD. In this study, we tested the hypothesis that UBOM polymorphism rs12917707 is associated with severe outcome in IgAN.

**Methods:** We constituted two groups of Caucasian patients based on the disease phenotype. The first group was composed of IgAN cases with severe outcome as indicated by terminal renal failure requiring kidney transplantation. The second group was composed of stable cases of IgAN defined by a diagnostic made since at least 10 years and eGFR>60mL/min/1.73m². A third, control group, consisted of Caucasian healthy volunteers. We performed TaqMan SNP genotyping assays and compared allele frequencies and genotype distributions.

**Results:**

<table>
<thead>
<tr>
<th>Allele and genotype</th>
<th>severe cases (n,%)*</th>
<th>stable cases (n,%)*</th>
<th>controls (n,%)*</th>
<th>p***</th>
<th>p****</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>86 (60.7)</td>
<td>110 (55.8)</td>
<td>254 (57.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>54 (36.0)</td>
<td>145 (70.7)</td>
<td>132 (29.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>12 (8.3)</td>
<td>11 (5.7)</td>
<td>20 (4.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Allele frequencies and genotype distribution among severe cases of IgAN, stable cases of IgAN and healthy volunteers. P*: comparison between the 3 cohorts; P**: comparison between severe cases and controls; P***: comparison between stable cases and controls; P****: comparison between severe and stable cases.

**Conclusions:** No difference in allele frequencies of UBOM polymorphism rs12917707 was found between 2 groups of IgAN cases as to disease phenotype. This result tends to suggest that UBOM gene is not involved in IgAN progression.

**Funding:** Clinical Revenue Support

**PUB283**

Enoxaparin-Induced Fatal Spontaneous Hemorrhage: The Case for Revising Dosing Guidelines for the Elderly  
Tarek H. Naguib.  
Internal Medicine, Texas Tech Univ Health Sciences Center, Amarillo, TX.

**Background:** Enoxaparin-induced hemorrhage may prove fatal. The literature shows that elderly persons with kidney disease are especially at risk for this complication. They were previously recommended to receive individualized enoxaparin dosing. However, the dosing guidelines still recommend double dose for patients with eGFR of 30 compared to 29 mL/min, despite the lack of significant difference between the 2 values and the risk of bleeding from this arbitrary dosing.

This case report reflects the complex factors that build the case for specific safety recommendations in the geriatric population with kidney disease.

**Methods:** A 78-year-old woman, who was admitted with heart failure due to aortic valve incompetence, was placed on enoxaparin due to atrial fibrillation. While on spironolactone and olmesartan, serum creatinine increased from 1.1 to 1.77 mg/dL and eGFR declined from 46 to 29 mL/min (Cockcroft-Gault formula, weight is 69 Kg). Olmesartan was discontinued and the patient was discharged, on the same enoxaparin dose, to return in 1 week for valve replacement surgery. After 3 days, she was readmitted with severe retroperitoneal hemorrhage, confirmed by ultrasound. Despite fresh frozen plasma, 7 units of blood transfusion, intravenous fluids, and pressors, she expired within 24 hours.

**Conclusions:** This case highlights lack of safety of the current dosing guidelines for enoxaparin in elderly persons with chronic kidney disease. The following is recommended to decrease the risk of death in this population.

1. All persons aged 75 years or older shall be monitored with measuring anti-factor Xa levels. The same should be done for those aged 60 to 74, whenever the eGFR is at 35 mL/min (rather than below 30 mL/min, allowing for eGFR variability among different formulas). Clinicians are encouraged, but not required, to use anti factor Xa monitoring, whenever the eGFR declines to 35 mL/min, regardless of age.
2. Clinicians shall avoid the use of intravenous contrast media and renin-aldosterone system antagonists, as possible, whenever enoxaparin is prescribed.
3. Pharmacy services shall flag medical records to ensure appropriate dosing that is consistent with the above recommendations.

**Funding:** Private Foundation Support

**PUB286**

**Frail and Elderly Patient Outcomes on Dialysis (FEPOD): A 2-Part Study**

Edwina A. Brown, Lina Johansson.  
Imperial College Renal and Transplant Centre, London, United Kingdom.

**Background:** The majority of frail older patients with ESRD are on haemodialysis (HD). FEPOD includes assisted peritoneal dialysis (APD), with paid assistance or carers, is increasingly available for frail patients in their home. Little is known, though, about outcomes (mortality, morbidity and quality of life) of older people on APD compared to HD.

**Methods:** Eligible patients on APD (require assistance for PD and ≥60 years) are matched to HD patients by age ≥1 year, sex, diabetes status, daytime time on dialysis, ethnicity and Index of Deprivation. Study design: 2 Part study: Part 1 cross-sectional (15 UK centres, 50 APD, completion August 2013) and Part 2 longitudinal (18 UK centres, 100 APD). Both assess quality of life through questionnaires (including Hospital Anxiety and Depression Scale, SF-36, Patient Health Outcomes Scale (WHOQOL)), falls, social support, frailty and activities of daily living. Part 2 assesses healthcare use and survival over 2 years. Complete Part 1 data with multiple regression will be presented at meeting.

**Results:** Preliminary results for some measures from Part 1:

<table>
<thead>
<tr>
<th>Measure</th>
<th>APD</th>
<th>HD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>0.28</td>
<td>0.24</td>
<td>0.57</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.25</td>
<td>0.37</td>
<td>0.39</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>0.22</td>
<td>0.36</td>
<td>0.58</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.23</td>
<td>0.38</td>
<td>0.46</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.33</td>
<td>0.57</td>
<td>0.27</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.31</td>
<td>0.49</td>
<td>0.31</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.39</td>
<td>0.53</td>
<td>0.27</td>
</tr>
</tbody>
</table>

**Conclusions:** This is the first study to compare outcomes on APD and HD. Results will provide valuable data to the understanding of how older frail patients manage on different dialysis options. Comparison of healthcare use and survival will be determined over the next 2 years in Part 2.

**Funding:** Clinical Revenue Support

**PUB284**

**Hyponatremia: When the Kidneys Flunk the Polypharmacy Tolerance Test**

Jack Rubin  
Heena M. Contractor.  
Medicine, Los Alamitos Hospital, Los Alamitos, CA.

**Background:** Depression in the elderly is common ranging in incidence up to 10%. Many new medications are available to treat the depressed patient and they are often used in combination. The elderly are often on medications for hypertension, diabetes, arthritis and congestive heart failure. We describe a patient who illustrates how rapidly and with the best of intentions one can move from routine care into a serious medical mishap.

**Methods:** Ms XX, age 74, was admitted from the emergency room with a diagnosis of depression. Her hospital medications and pertinent studies are listed by days from admission. Her medications were given between day 1 and 2 are listed below. Leuprolide 1 and 2; Zoflox day 1 to 4; Bupropion day 1 to 4; Buspar day 1 to 4; Protonix day 1 to 4; Losartan day 1 to 4; Hydrochlorothiazide day 2 to 4; Amlodipine day 2 to 4; Dicyclomine day 2 to 4; Lasix and 3% saline were given day 6. Lab studies: Na mmol/L: day 2: 144; day 4: 127; day 5: 109; day 6: 128; day 7: 137; Hg g/ml: 1 day: 12.5; 4 day: 11.3; 5 day: 6.11.5.

**Results:** Treatment was initiated by withdrawing the offending medications, restricting fluids and initiating Lasix and hypertonic saline. After return of her serum Na to the normal range Effexor (Venlafaxine) was introduced day 9 and gabapentin day 20. The sodium remained stable throughout the remaining treatment. Although Lexapro, Zoloft, Protonix and Hydrochlorothiazide are known to associate with hyponatremia and are all potentially implicated drugs, the rapidity of change in the serum sodium was eye-opening. The mechanism of hyponatremia remains speculative but the hemoglobin dropped approximately 10% suggesting at least some element of hemodilution from acute fluid retention.

**Conclusions:** In summary we illustrate a case of a 74 year old female with psychiatric and medical co-morbidities whose treatment rapidly induced hyponatremia. Occasionally the kidneys fail the multiple medication test.

**Funding:** Clinical Revenue Support
Background: Elderly patients comprise the most rapidly growing group of end stage renal disease (ESRD) patients. Unexplained anemia of the elderly (UAE) is now recognized as a distinct clinical entity in this patient population. Decreased erythropoietin levels, impaired bone marrow activity, and increased inflammation have been implicated as possible causes.

Delimiting the cause(s) may lead to a change in treatment practices. Increased erythropoietin (EPO) dose requirement in elderly ESRD patients could occur if bone marrow erythropoietic activity decreases and/or inflammation increases with age. In light of EPO-associated toxicity, if these two pathophysiological changes occur, consideration of lowering hemoglobin (Hb) target may be warranted. We studied the effect of age on EPO dose requirement in a prevalent hemodialysis population.

Methods: Hematologic data on 179 hemodialysis (HD) patients was analyzed. Patients were 18 years or older and on HD for at least 3 months. Individual EPO dose was calculated as mean weekly dose over a 3-month period. Mann-Whitney was used to assess the relation between age (<65 vs >65 years old) and median EPO dose expressed as units/week (wk), units/wk/kg, or units/wk/Hb.

Results: No correlation existed between age and EPO dose expressed as units/wk (9.4±4.1 units/wk, 0.560, p value = 0.480), units/wk/kg (107.8±37.98, p = 0.22), or units/wk/Hb (827.6± vs 930.45, p = 0.57).

Conclusions: By excluding previous literature, age does not appear to affect EPO dose or EPO resistance in HD patients. If impaired bone marrow activity or inflammation were causative factors in UA, then age would have been expected to associate with these EPO parameters. Therefore, by exclusion, these results indicate that UAE may be due to decreased EPO levels. Hypoxia inducible factor levels have been shown to decrease with age and may account for the decrease in EPO levels and subsequent development of UAE in general. In HD patients, exogenous EPO may effectively treat UAE.

Funding: Private Foundation Support

PUB288

Masked Hypertension and White Coat Hypertension Are Common and Chronic Conditions in CKD Patients Receiving Antihypertensive Therapy: Implications for Hypertension Management if Hypertension Control Is Based Only on Clinic Blood Pressure

Christopher Valentinelli, Ravishe Shah, Daniel J. Birmingham, Lee A. Hebert.

Background: Masked hypertension (MH) is defined as normal blood pressure (BP) in the clinic but hypertension at home (e.g., assessed by home BP monitoring (HBPM)). White coat hypertension (WCH) is the opposite of MH. MH increases cardiovascular (CV) risk. The risk of WCH is less clear. However, there is recent evidence that treated WCH can increase risk because BP is overcontrolled.

Methods: We assessed MH and WCH in 33 pts followed in our Nephrology Clinical Trials Unit (NCTU) with a diagnosis of hypertension, receiving antihypertensive therapy, and performing HBPM morning and evening at least 10 times per mo, using calibrated equipment and proper technique. NCTU BP was measured each 2-3 mo by Omron. There were 103 to 767 home BP measurements per pt, median 301. Follow-up was 4 to 15 mo, median 10 mo.

Results:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>P</th>
<th>TH vs FR</th>
<th>OR vs PUB</th>
<th>PUB vs FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>58±8</td>
<td></td>
<td>0.05</td>
<td>0.64</td>
<td>0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.3±18</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>130±17</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>80±10</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>26±4</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hb (gm/dL)</td>
<td>13.6±2</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.5±1</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>192±35</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Starling Index</td>
<td>3.4±0.8</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>124±120</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

The table shows that MH and WCH are chronic and common in CKD and non-CKD pts receiving BP therapy. If hypertension control is based only on clinic BP, MH will go untreated and WCH may be over treated. The prevalence of MH and WCH and their

Conclusions: In our population, elderly NDB patients show the same clinical features as adult NDB patients. Both groups are patients with long-standing DM with nephrotic proteinuria, NS and/or AKI.

PUB289

Metabolic Safety Profile of Thiazides in Patients with Diabetes Mellitus Type 2


Background: Thiazides remain the mainstay of antihypertensive therapy in the general population. Traditional concerns for thiazide induced glucose intolerance and dyslipidemias may deter its routine use in patients with concurrent hypertension and diabetes mellitus type 2 (DM2). We analyze various metabolic indices among DM2 patients with and without chronic thiazide use.

Methods: In this retrospective study, electronic records from patients with both DM2 and hypertension who were evaluated for any reason at UCLA-Olive View Medical Center during the months of January 2011 – January 2012 were collected. Inclusion criteria: all patients with ICD-9 codes 250.00 to 250.93 for diabetes and 401.0 to 404.93 for hypertension, who had at least 3 documented blood pressure measurements, estimated glomerular filtration rates (eGFR) by the 4 variable-MDRD formula, lipid profiles, hemoglobin, and A1C over the span of the previous 6 months and as available up to 24 months.

Results: 769 patients were included: 389 received thiazide diuretics; Thiazide group had significantly higher systolic blood pressure: 137±14 vs 131±12 mm Hg, p=0.0001, lower initial estimated glomerular filtration rate (eGFR): 93.2±27 vs 100±26 mL/min/1.73m², and heavier weight: 87.4±21.2 vs 83.3±18.3 kg, p=0.004. Differences in other biochemical values are as shown.

Conclusions: There were no detectable adverse effects in terms of A1C change, lipid profile difference, hemoglobin, or decline in eGFR in diabetic patients treated with thiazides compared to those who did not receive the medication.
**PUB291**

Association between Renal Function (MDRD-4 versus CKD-EPI) and Cardiovascular Risk. Prospective Observational Study Francisco Javier Lavilla, Carmen Calderon Gonzalez, Nuria Garcia-Fernandez, Paloma L. Martin Moreno, Jose Maria Mora Gutierrez, Diana Lopez Espinosa, Pedro Errasti. *Nephrology, Univ Clinic of Navarra, Pamplona, Navarra, Spain.*

**Background:** To study the relationship between cardiovascular risk (CVR) and renal function in healthy people.

**Methods:** 237 patients were studied in prospective cardiovascular risk study (5 to 10 years). Mean age 48.39 years (SD 6.9). CVR (PROCAM-PR, FRAMINGHAM-PR, SCORE score-SC-and cardiovascular-event probability-SCER), renal function (CKD-EPI and MDRD-4),metabolism parameters (cholesterol, triglycerides, glucose, uric acid), cardiovascular risk markers (von Willebrand factor-antigen-VWF, fibrinogen -F, and C-reactive protein-CRP), albuminuria (albumin/creatinine CRP-LBR1000-CR LBR1400), carotid intima-thickness(IM) and E/A echocardiography index were evaluated. Statistical analysis with SPSS 15.0.

**Results:** Observed greater association between CKD-EPI and CVR scores (PR r = -0.281, FR r = 0.432, SC r = -0.322, SCE r = -0.261 (p<0.005). CKD-EPI was better associated with IM thickness (r = -0.359), E/A ratio (r = 0.401) and uric acid (r = -0.357), than MDRD-4 (PR r = -0.223, FR r = -0.551, SC r = -0.468) than with MDRD-4 (PR r = -0.281, FR r = 0.432, SC r = -0.322, SCE r = -0.261) (p<0.005). The association of both formulas is similar with IALBCR. The best FG stratified according CKD-EPI stratified better GFR with CVR, showing significant increase below 90 ml / min (p <0.001). This effect depends on the age, associated with GFR (p <0.001), showing significant drop in people older than 50 years.  

<table>
<thead>
<tr>
<th>CKD-EPI</th>
<th>100</th>
<th>60-90</th>
<th>60-80</th>
<th>70-79</th>
<th>80-89</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG</td>
<td>-0.6</td>
<td>-0.4</td>
<td>-0.3</td>
<td>-0.2</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

**Conclusions:** In healthy population there are association between CVR and renal function. GFR below 90 ml/min in aged over 50 years is associated with significant increase CVR. CKD-EPI allows better assessing the relationship between renal function and cardiovascular risk.

**PUB292**

The Decreased Expression of Nephrin and CD2-Associated Protein in Patients with Hypertensive Kidney Injury Zifan Li, Wei Wang, Juan Hou, Hua Zhou, Lining Wang. *1 Dept of Nephrology, First Affiliated Hospital of China Medical Univ, Shenyang, China; 2 Institute of Nephropathology, China Medical Univ, Shenyang, China; 3 NIDDK/NIH.*

**Background:** Given that nephrin and CD2-associated protein (CD2AP), podocyte associated proteins, play important roles in maintenance of glomerular structural integrity, the study focused on the expression changes of nephrin and CD2AP induced by hypertensive kidney injury in patients with proteinuria.

**Methods:** The involved patients were divided into two groups as following: Hypertensive group: patients with hypertension and proteinuria who were diagnosed as hypertensive kidney injury via kidney biopsy. Control group: kidney trauma patients without hypertension and proteinuria. Kidney biopsy section taken from hypertensive group and normal kidney tissues taken from control group via urologic surgical procedures were fixed with immersion-fixation method. Then immunohistochemistry stainings were performed with HE, DAB, immunofluorescence, uranyl acetate, and observed by light microscopy,confocal laser scanning microscopy and immunoelectron microscopy.

**Results:** In control group, the capillary loops were smooth and plump. Nephrin and CD2AP were observed staining along the glomerular capillary loops continuously and evenly. However, in hypertensive group the capillary loops became wizened, and the Bowman’s space and luminal spaces of the proximal or distal tubules became more widely opened in the renal cortices. Additionally, nephrin and CD2AP decreased and stained intermittently. Through the immunoelectron microscopy, different degrees of foot processes effacement were observed in hypertensive group, nephrin and CD2AP decreased and stained weakly along the podocyte basol membrane, while in control group, they distributed evenly in podocytes.

**Conclusions:** Desregulation of podocyte associated proteins induced by hypertension may be an important cause leading to development of proteinuria and decline of renal function in hypertensive kidney injury patients.

**PUB293**

Blood Pressure Control among Diabetic CKD Patient in a Developing World Sample Jafar Al-Said, Teerath Kumar, Soni Murdeshwar. *Bahrain Specialist Hospital.*

**Background:** Hypertension is the most common CV risk factor. The presence of Diabetes with Hypertension increases the risk further. Well control BP reduces the CV risk significantly. From this aim we studied to:
1. Identify the prevalence of Hypertension among CKD population.
2. Determine the percentage of successful BP control among diabetic and non-diabetic CKD patients and the factors correlated with uncontrolled BP.

**Methods:** In this retrospective study all CKD patient followed for 9.5 years in our Nephrology department were identified. Demographic factors were collected from their medical records. Matching diabetic and non-diabetic CKD samples for age, gender and BMI were selected. BP measurement on the last visit was recorded. Patients with BP more than 140/90 mmHg were considered uncontrolled. Independent variables correlated with uncontrolled BP were tested using SPSS 18. Multivariate regression equation was performed for these variables.

**Results:** Total CKD population was 245 patients. Mean follow up was 23.6 months (SE 1.6), mean age was 58.7 years (SE 0.9), mean BMI was 30.5kg/m2 (SE 0.5). Males constitute 61%. Mean eGFR was 45.4ml/min (SE 1.4) and 51% of the populations were CKD stage III. We matched 77 diabetic with non-diabetic patients. HTN was present in 48% of which 59% had controlled BP on the last visit. Uncontrolled BP was present in 47% of the diabetic as compared to 28% in non-diabetic (p =0.019). Factors related with uncontrolled BP are:

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
</tr>
<tr>
<td>BMI</td>
<td>0.2</td>
</tr>
<tr>
<td>Systolic BP on first visit</td>
<td>0.2</td>
</tr>
<tr>
<td>HBP</td>
<td>0.23</td>
</tr>
<tr>
<td>Total CV risk factors</td>
<td>0.2</td>
</tr>
<tr>
<td>Number of Anti HTN medications</td>
<td>0.23</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>0.23</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Systolic BP on presentation and Nitroglycerin, in multivariate regression model with R 0.27, were the only significant factors correlated with uncontrolled BP.

**Conclusions:** Hypertension was highly prevalent among diabetic CKD patients. It was less well controlled among this subgroup as compared to non-diabetic. Several factors were identified to correlate with uncontrolled BP.

**PUB294**

Usefulness of 24h-Ambulatory Blood Pressure Monitoring in Discharged Patients with Chronic Kidney Disease Patrick Sauldan, Belen Ponte, Sophie M. De Seigneur, Pierre-Yves F. Martin. *Nephrology Unit, Dept of Medical Specialties, Geneva Univ Hospitals, Geneva City, Geneva, Switzerland.*

**Background:** Optimal blood pressure (BP) control is mandatory in patients with chronic kidney disease (CKD). These patients are often discharged from hospital with controlled BP based on ward measurements. Whether this control is satisfactory within the outpatient setting remains unknown.

**Methods:** 82 patients enrolled in the Implicate Study (ClinicalTrials.gov: NCT00929760) and with ward SBP < 140 mm Hg at discharge had an 24h-ambulatory blood pressure monitoring measurement (ABPM) within the following 3 months. Target BP values at daytime and nighttime were < 135/85 and 120/70 mm Hg respectively. Dipping was a night to day ratio < 0.90.

**Results:** There were 69% males and 27% diabetics. Mean age was 69 (9) years, mean eGFR was 33 (9) ml/mn. Seventy-one % of the patients were treated with ACEIs/ ARBs and 62% with diuretics. Mean daytime ABP were 135(81)/18(12) mm Hg and mean nighttime ABP were 124(72)/8(13) mm Hg. Dipping was present in 45% of the patients. Target daytime and nighttime BP were met in 54% and 38% of the patients respectively. Only 28% could achieve both daytime and nighttime BP targets.

**Conclusions:** In stage IIIb-IV CKD patients, ward good BP control did not predict the achievement of BP targets measured by ABPM within the outpatient setting. 24h-ABPM should be routinely used in CKD patients recently discharged from hospital in order to achieve BP targets, especially during nighttime.

**PUB295**

Influence of Central Blood Pressure on Significant Proteinuria in Chronic Kidney Disease Vinaya R. Soundararajan, Ramesh Soundararajan. *Nephrology, Associates in Nephrology, Chicago, IL.*

**Background:** Central aortic blood pressures are thought to be more reflective of the actual pressures the vital organs including the kidney and heart are subjected to rather than the brachial blood pressures. There is limited data regarding the effect of central aortic blood pressure on proteinuria in patients with chronic kidney disease (CKD).

**Methods:** We decided to study a selected population of our CKD patients in an office setting by evaluating the central aortic pressures, including systolic, diastolic, pulse pressure, and augmentation index, and their correlation to significant proteinuria. For this study, we defined significant proteinuria as having greater than 1 Gm of protein per Gm of creatinine.

Central aortic blood pressure was measured using Sphygmocor XCEL PWA from ATCor Medical (Itasca, IL). The data set included 37 patients with CKD between the stages of II and IV; both diabetics and non-diabetics.

**Results:** The central diastolic pressure for patients without significant proteinuria was 68.9 mmHg, which was found to be significantly lower than that for patients with proteinuria > 1 gm/gm of creatinine 77.3 mmHg (p<0.039). However, the other central BP parameters did not display a significant correlation with significant proteinuria. We also studied the influence of antihypertensive medications (ace inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and non-dihydropyridine calcium channel blockers) on central systolic pressures and surprisingly found no significance between the type of medication and the resulting central pressure.

**Conclusions:** Unlike brachial pressures, where the control of systolic BP seems to correlate with proteinuria, this study determined that among the different central pressure parameters the central diastolic pressure is the best predictor of degree of significant
proteinuria in CKD patients. Further studies can be conducted with a greater sample size and for varying degrees of proteinuria to determine whether or not controlling central blood pressure can decrease the degree of proteinuria.

**PUB296**

Add-On Administration of HCTZ to the Preceding ARB Treatment Can Attain the Lower Sodium Balance Leading to the Successful Antihypertensive Effects for Daytime and Night-Time 1. Yuzo Fuku, 2 Michiko Fukuda, 1 Toshiyuki Miura, 1 Shuichi Watanabe, 3 Hiroyuki Togawa, 1 Yoshiki Ogiyama, 1 Yukako Isobe, 1 Hirokuni Kobori, 1 2 Cardio-Renal Medicine and Hypertension, Nagoya City Univ, Japan; 3 Tulean Univ Hypertension and Renal COE; 1 Dept of Pharmacology, Kagawa Univ, Japan.

**Background:** Previously, we have reported that the angiotensin receptor blockers (ARBs) or thiazide diuretics (HCTZ) can restore the circadian blood pressure (BP) rhythm. On this study, we investigated to demonstrate that an add-on administration of HCTZ to the preceding ARB treatment can further attenuate the lower sodium balance leading to the successful antihypertensive effects for daytime and night-time.

**Methods:** Major inclusion criteria were as follows: 1) chronic kidney disease (CKD, K/D0QI), 2) previous treatment with ARB (valsartan, 80 mg/day) for ≥2 days, and 3) office BP = 130/80 mmHg.

**Results:** At the interim analysis, two men and three women (69 ± 11 years old, GFR 65 ± 16 ml/min/1.73m²), were studied before and 8-wk add-on treatment of HCTZ (12.5 mg/day) to the ARB. Filtered sodium load (SNa x GFR, 16,590 ± 6,310 nmol/day, p = 0.01), tubular sodium reabsorption (tNa, 16,430 ± 6,330 nmol/day, p = 0.03), and fractional sodium reabsorption ([SNa x GFR, 98.9 ± 10.0% to 98.5 ± 1.1%, p = 0.009]) were shown to decrease. Urinary excretion of protein (2.1 ± 1.1 g/day, p = 0.03) was attenuated, but urinary excretion of angiotensinogen (UAGTV, 610 ± 940 ng/day, p = 0.03) was attenuated, but urinary excretion of angiotensinogen (UAGTV, 610 ± 940 ng/day, p = 0.03) was increased. BP were lowered for both daytime [131/78 (SBP, p = 0.02; DBP, p = 0.01) and nighttime [126/72 (SBP, p = 0.01; DBP, p = 0.01)]. Nocturnal BP dip was determined by the increase in daytime natriuresis.

**PUB297**

Increase in Daytime Natriuresis during the ARB Treatment Is Not Attributed to the BP Reduction of the Night before Toshiyuki Miura, 1 Daicike Fuwa, 1 Shuichi Watanabe, 1 Hiroyuki Togawa, 1 Yoshiki Ogiyama, 1 Yukako Isobe, 1 Tadashi Ichikawa, 1 Shirasawa Yuichi, 1 Yoshida Atsushi, 1 Michio Fukuda, 1 Genjiro Kimura, 1 Cardio-Renal Medicine and Hypertension, Nagoya City Univ, Japan; 2Ashai Rosai Hospital, Japan Labour Health and Welfare Organization.

**Background:** Previously, we have reported that the angiotensin receptor blocker (ARB), olmesartan can increase the natriuresis during the daytime to attain a lower sodium balance leading to the successful antihypertensive effects for daytime and night-time, accompanied by the increase in U_{\text{Na}}/V, which was the indicator of the intrarenal renin-angiotensin system status. Careful studies are needed to investigate whether the increase in U_{\text{Na}}/V is merely the result from lowering the sodium balance, or is it the risk for CKD progression.

**Methods:** We studied which comes first the increase in daytime natriuresis, or the decrease in night-time BP, in seven patients with CKD (five men, two women, 52 ± 19 year-old, GFR 60 ± 64 ml/min/1.73m²) before and within 2 days after commencing the ARB.

**Results:** Baseline, two out of the seven patients exhibited dipper circadian BP rhythm, whereas five had non-dipper BP rhythm. Although their BP rhythm had been dipper type before the treatment, the two patients exhibited the increase in daytime natriuresis on the first day after starting ARB. One of the five non-dippers demonstrated the increase in natriuresis first day of the treatment and on that day, the rhythm was restored into dipper pattern. Other four patients, who were non-dippers at baseline, remained as the non-dippers 2 days after the institution of treatment. However, all of these four patients demonstrated the increase in daytime natriuresis within 2 days after starting treatment (1 day for three patients; 2 days for one patient) even though circadian BP rhythm was not restored.

**Conclusions:** These findings suggest that the increase in daytime natriuresis during the ARB treatment is not attributed to the BP reduction of the night before.

**PUB298**

L-arginine Improves Endothelial Function, Independent of Arginine Transport System, in Chronic Renal Failure Female Rats 1 Idit F. Schwartz, 1 Doron Schwartz. 2 Nephrology, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel.

**Background:** Endothelial cell dysfunction (ECD) is a common feature of chronic renal failure (CRF). Defective nitric oxide (NO) generation due to decreased endothelial nitric oxide synthase (eNOS) activity is a crucial parameter characterizing ECD. Decreased activity of cationic amino acid transporter-1 (CAT-1), the selective arginine transporter of eNOS, has been shown to inhibit eNOS in uremia. Recently, we failed to demonstrate a decrease in glomerular arginine transport in uremic female rats. The current experiments were designed to determine whether the sexual dimorphism which characterizes the glomerular arginine transport system in uremia is a generalized phenomenon.

**Methods:** Contractile and vasodilatory responses, ultrastructural changes, and measures of the L-arginine NO system were performed in thoracic aortas of female rats subjected to 5/6 nephrectomy.

**Results:** Contractile response to KC1 was significantly reduced in CRF dames when compared to healthy rats while arginine administration abolished this decline. Aortic rings contraction by Phenylephrine was unchanged in all experimental groups. Acetyl Choline induced vasodilatation was significantly impaired in the aortas from CRF rats compared with controls. L-Arginine normalized the capacity of aortic vasodilation in CRF rats. The decrease in both cGMP generation, a measure of eNOS activity and abundance of aortic eNOS and phosphorylated ENOS observed in CRF rats were completely abolished by L-arginine while both arginine transport and CAT-1 protein abundance did not differ in all experimental groups.

**Conclusions:** Arginine administration has a profound beneficial effect on ECD independent of cellular arginine uptake, in CRF female rats. Funding: Government Support - Non-U.S.
Conclusions: PHF increased endothelin-1 binding to ET-A receptors in equilibrium binding assays. ANG II and PHF, share greater than 80% amino acid homology. ANG-II has been reported to enhance ET-1 binding to ET-A receptors and it appears that PHF, may mimic this effect.

Funding: NIDDK Support, Other U.S. Government Support

PUB301

Serum Asymmetric Dimethylarginine and Nitric Oxide Levels and Their Correlation with Kidney Functions in Turkish Patients with Acute Ischemic Stroke

Hakki Yilmaz, Huseyin tugrul Celik, Ali Akay, Nuket Babek, Ayse Mukadder Bilgic, Turgut Ozal Univ, School of Medicine, Ankara, Turkey.

Background: Nitric oxide synthase (NOS) is present in the brain and cerebral arteries and enables the synthesis of nitric oxide (NO), which plays a critical role in brain perfusion. Asymmetrical dimethyl arginine (ADMA) is an endogenous NOS inhibitor. The goal of this study was to examine ADMA as an indicator of endothelial dysfunction of renal functions in patients with acute ischemic stroke and determine if a correlation between ADMA and NO levels or L-arginine/ADMA ratios exists.

Methods: Fifty-two patients and 48 healthy controls were included in this study. ADMA and Arginine levels were measured with an Applied Biosystems MDS SCIEX API 3200 LC-MS/MS system device in the ESI mode and an Aglient Eclipse XDB-C18 column. NO was measured with a Nitrate/Nitrite colorimetric assay kit.

Results: The mean serum ADMA level was 0.46 ± 0.13 μM for the patients and 0.40 ± 0.11 μM for the controls. The NO levels were 2.78 ± 1.39 μM for the patients group and 4.34 ± 2.70 μM for the controls. The ADMA levels for the patient group were significantly higher than for the control group (p<0.01); the NO levels for the patients were significantly lower than for the controls (p<0.001). There was a negative correlation between the NO levels and age (r = -0.251), and a positive correlation between NO levels eGFR (r = 0.223). In addition, there was a positive correlation between ADMA and creatinine (r = 0.224) and a negative correlation between ADMA and eGFR (r = -0.216).

Conclusions: Increased plasma levels of the NOS inhibitor ADMA and decreased levels of NO were found to be independent risk factors for ischemic stroke. Decreased NO levels cause vasoconstriction and may be important in the pathogenesis of ischemic stroke.

PUB302

Regulation of Human Endothelial Cells by Vitamin D Metabolites

Jessica L. Sea, Tae Wuk Ko, Eileen W. Tsai, Isidro B. Salusky, Martin Turgut Ozal Univ, School of Medicine, Ankara, Turkey.

Background: Vitamin D-deficiency in humans has been linked to aberrant vascular function but the possible mechanisms for this remain unclear. In human umbilical vein endothelial cells (HUVEC) and primary cultures of HUVEC, HAEC and human monocytes were cultured in the presence of 25D, 1,25, as well as native vitamin D (VitD) and 24,25-dihydroxyvitamin D for 6, 12 or 24 hrs. Cells were then lysed to extract RNA and expression of various target genes assessed by qRT-PCR. Western blot analysis were carried out to assess changes in protein expression.

Results: HAEC showed induction of VEGF with the effect taking place at 6 hours in HAEC but not until after 12 hours in HUVEC. At 6 hours HAEC showed little response to vitamin D treatment with LPS led to a decrease in CYP27B1. Both HAEC and HUVEC treated with TNFa showed induction of VEGF with the effect taking place at 6 hours in HAEC but not until after 12 hours in HUVEC. At 6 hours HAEC showed little response to vitamin D metabolites but after 12 hours of culture HAEC treated with 25D, 1,25D and 24,25D showed decreased expression of VEGF. This was also seen in HUVEC with the effect being most pronounced after 24 hours.

Conclusions: These in vitro data suggest key differences between HAEC and HUVEC responses to LPS and suggest HAEC are more sensitive to vitamin D metabolites relative to HUVEC which exhibit more delayed responses to treatments of 25D, 1,25D and 24,25D.

Direct effects of vitamin D metabolites on VEGF in both HAEC and HUVEC suggest that vascular endothelial cells may be highly sensitive to changes in patient vitamin D status.

Funding: NIDDK Support, Other NIH Support - Ruth L. Kirschstein National Research Service Award T32HL69766

PUB303

Association between Renal Microangiopathy and Brachial Artery Flow-Mediated Vasodilation in Patients with Chronic Kidney Disease

Taisoviy Miyagi, Kentaro Kohagura, Yusuке Ohyama, Kenchito Ikemi, Dept of Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyus, Nishihara, Okinawa, Japan; 2 Dialysis Unit, Univ Hospital of the Ryukyus, Nishihara, Okinawa, Japan.

Background: Endothelial dysfunction is associated with progression of chronic kidney disease (CKD) and cardiovascular disease (CVD). However, underlying mechanism of this association is unknown. Pre-glomerular microvascular damage could be responsible for albuminuria and hypertension, both of which are risk factor for progression of CKD and CVD. We examined the cross-sectional association between renal microvascular damage and brachial artery endothelial function using renal biopsy specimen.

Methods: Small arterial intimal thickening and arteriolar hyalinosis were assessed by semi quantitative grading for small artery among 172 patients with CKD (55 men and 77 women), who underwent renal biopsy. Vascular endothelial cell function was assessed by flow mediated dilatation (FMD) of forearm.

Results: The mean of age, blood pressure (BP), estimated glomerular filtration rate (eGFR), urinary protein, %FM, and mean grade of arterial intimal thickening were 54.0 ± 15.7 years, 130.2 ± 18.9 mmHg, 71.4 ± 11.7 ml/min/1.73m², 17.5 ± gCr, 5.9%, and 2.3, respectively. %FMD was positively correlated with eGFR and negatively correlated with age, uric acid, HbA1C, and index of arterial intimal thickening. Multivariate regression analysis showed that %FMD was negatively correlated with max grade of arterial intimal thickening or arteriolar hyalinosis, respectively even after adjustment for age, sex, mean arterial BP, eGFR and Hba1C.

Conclusions: The results of present study suggested that renal microangiopathy might be associated with systemic endothelial dysfunction of macro- vessel, independent of classical CVD risk factors. This association might be involved in the link between endothelial dysfunction and progression of CKD and CVD.

PUB304

Dysfunctional Contractility and Endothelium Dependent Relaxation Mediated by Reactive Oxygen Species and Nitric Oxide Insufficiency in Microvessels from Renal Failure Mice

Dan Wang, Cheng Wang, Christopher S. Wilcox, Hyper tension, Kidney and Vascular Research Center, Georgetown Univ, Washington, DC; 2 Div of Nephrology, The Third Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.

Background: Cardiovascular disease (CVD) is major complication in chronic renal failure (CRF). Endothelial dysfunction is a starting point for vascular change. We hypothesized that reactive oxygen species (ROS) and insufficiency of nitric oxide (NO) mediated abnormal microvascular contraction and endothelial function in renal reduced mass (RRM) mice.

Methods: Mesenteric arteries (MA's) were isolated from C57BL/6 mice after sham-operation (SHAM) or RRM (56 nephrectomy) for 3 months (n=6/group), mounted on a wire myograph. Relaxations were tested to sodium nitroprusside (endothelium-independent relaxation, EIR) and acetylcholine (ACH) in preconstricted MA's for: endothelium-dependent relaxation (EDR); endothelium-derived relaxation factor (EDRF; NOS-dependent relaxation); endothelium-derived hyperpolarizing factor (EDHF; K channel dependent relaxation). Contractions were tested to endothelium-derived contracting factor (EDCF; ACh initiated contraction with blocked endothelial relaxation pathways); phenylephrine (PE); U-46,619 and endothelin-1 (ET-1). NO activity (DAF-FM fluorescence) and ROS generation (tempo-9-AC fluorescence) were measured by fluorescence microscope equipped with RatioMaster system. Data present as mean ±SEM.

Results: The MA's from RRM mice had diminished EDR (54.45 ± 7.7%; P<0.01), EDR (13.55 ± 27.4%; P<0.01) and NO activity (0.18 ± 0.03 vs. 0.36± 0.04 units; P<0.05), but not in EDFH and EIR, and developed an EDCF (14.1 ± 8.1%; P<0.05) and enhanced Ach-induced ROS (0.17±0.03 vs. 0.06±0.02 units; P<0.05). Contractions were enhanced to U-46, 619, endothelin-1 (ET-1). NO activity (DAF-FM fluorescence) and ROS generation (tempo-9-AC fluorescence) were measured by fluorescence microscope equipped with RatioMaster system. Data present as mean ±SEM.

Conclusions: These in vitro data suggest key differences between HAEC and HUVEC responses to LPS and suggest HAEC are more sensitive to vitamin D metabolites relative to HUVEC which exhibit more delayed responses to treatments of 25D, 1,25D and 24,25D.

Funding: NIDDK Support

PUB305

Arteriovenous Fistula Leads to Elevated Pulmonary Vascular Resistance in Hemodialysis Patients with Pulmonary Hypertension

Saranaya Buppanjanantham, Rapeepat Lekkham, Medicine, Albert Einstein Medical Center, Philadelphia, PA; 2Nephrology, Albert Einstein Medical Center, Philadelphia, PA.

Background: An incidence of pulmonary hypertension in ESRD is rising along with the increment of mortality rate. The mechanism of pulmonary hypertension in hemodialysis patients has been proposed as the effects of high cardiac output, which cause by arterio-

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

Underline represents presenting author.

941A
venous fistula (AVF) that functions as an artificial shunt. We hypothesized that after AVF created, changing of systemic hemodynamics and circulating vasoactive substances leads to increase pulmonary vascular resistance and pulmonary hypertension subsequently.

Methods: We conducted a retrospective study in hemodialysis patients, who had two right heart catheterization (RHC) from January 2002 through March 2013. After 71 charts reviewed, we recruited 19 patients with AVF and 13 patients with non-AVF as a dialysis access. The progression of hemodynamic parameters at two catheterizations was examined. Statistical analysis was done by paired two way t-test.

Results: In AVF group with mean pulmonary arterial pressure of second RHC more than 25 mmHg, pulmonary vascular resistance was increased (p=0.07), while mean arterial blood pressure and systemic vascular resistance were decreased (p=0.04 and 0.08 respectively). In both AVF and non-AVF groups, there was no difference in cardiac output or pulmonary capillary wedge pressure from two RHC. In non-AVF group, no difference between pulmonary vascular resistance from two RHC was observed.

Conclusions: Although we observed, pulmonary vascular resistance was elevated after AVF created. We proposed elevated pulmonary vascular resistance as a major mechanism of PH in hemodialysis patients with AVF and the increase of pulmonary vascular resistance is not affected by increased cardiac output.

PUB306

Gone but Not Forgotten

Hyuma V. Polimera,1 Sachinkumar B. Kanagali,2 Robert Pursell,1 David Leh1

1Internal Medicine, St. Luke’s Unv Health Network, Bethlehem, PA; 2Nephrology, St. Luke’s Unv Health Network, Bethlehem, PA.

Background: Fibromuscular dysplasia (FMD) is a non-inflammatory, nonatherosclerotic disease of medium size arteries of unknown etiology that can lead to arterial stenosis, aneurysm, and dissection.

Methods: A healthy 40 year old man was admitted with acute onset of severe, sharp, left flank pain. CT scan of the abdomen, with contrast, revealed acute, left renal infarct. There was also evidence of the right side in the infarct. A right digital subtraction angiogram showed duplication of the right renal artery and abnormal, beaded left renal arterial vasculature and multiple thrombi; findings consistent with FDM. Follow up abdominal aortogram showed an aneurysm and spontaneous dissection of the left renal artery. The aneurysm was successfully embolized using detachable coils. The patient was started on IV heparin and Coumadin, which was to be continued for 6 months, with close follow up of his kidney function. After an uneventful six year hiatus, the patient presented with severe, right flank pain. CT, with angiogram, of the abdomen revealed right, main renal artery dissection with infarction and abnormalities at the origin of the accessory right renal artery. A diffuse abnormality of the celiac artery, previously normal, was described. The patient was anticoagulated with IV heparin and Coumadin and conservatively managed for the arterial dissection. Follow up includes quarterly serum creatinine levels and annual renal duplex ultrasound.

Conclusions: Since first described in 1938, there has been little progress in understanding the pathogenesis and outcomes of FMD. The clinical course is highly variable, ranging from the asymptomatic to the symptomatic with hypertension or with grave complications like dissections, aneurysmal ruptures with organ infarctions or stroke depending on the severity and arterial segment involved. Though more common in young women, FMD should be considered in male patients presenting with flank pain and hypertension.

PUB307

Oral Administration of Calcium Carbonate Is a Risk for Coronary Artery Disease in Japanese Hemodialysis Patients in a Dose-Dependent Manner

Chisako Nakano, Yoko Shima, Naoko Morikage, Masafumi Yamato, Akira Wada, Takahito Is.

Div of Nephrology, Osaka National Hospital, Osaka, Japan.

Background: Coronary artery disease is the leading cause of hospital admission and death among patients with end-stage kidney disease. Several mechanisms are thought to contribute to vascular calcification and subsequent cardiovascular disease. It is known that calcium administration accelerates artery calcification and that cardiovascular events. In Japan, however, calcium carbonate is often prescribed as a phosphate binder to treat hypercalcemia. A variety of mechanisms may contribute to the reduction in magnesium reabsorption resulting from hypercalcemia. One well known mechanism is facilitated by the basolateral calcium-sensing receptor (CaSR) in the thick ascending limb. Also hypercalcemia may induce reduction in magnesium reabsorption from the proximal tubule, which can be stimulated by hormone causing calcium retention.

Methods: We studied the relationship between cardiovascular disease (CVD) and oral calcium supplementation in Japanese patients under maintenance hemodialysis. We performed a single-center case-control study using 90 individuals (68.6 ± 10.5 y, 67 males) who underwent maintenance hemodialysis while hospitalized in our hospital from December 1, 2011 to April 30, 2013. Blood analysis was done at the time of hospitalization or within one month prior to hospitalization. The case and control groups comprised 34 patients hospitalized for examination and/or treatment of coronary artery disease and 56 patients hospitalized for other medical issues, respectively. One with any previous history of CVD was excluded from the control group.

Results: More amount of calcium carbonate was administered in the case group than in the control at the time of hospitalization (2.25 ± 1.50 vs. 1.31 ± 1.19 g/day, P=0.0034), whereas there was no statistical difference regarding serum albumin, inorganic phosphate, albumin corrected calcium, calcium-phosphate product, intact PTH or C-reactive protein. Dialysis vintage was significantly longer in the case than in the control (64.2 [29.0 – 132.7] vs. 35.7 [15.8 – 69.7], P=0.0458). Male sex was a significant risk (P=0.0046) but diabetes was marginal (P=0.0612). Age was not significant. Odds ratio of calcium carbonate administration per 1 gram increment for CAD was 1.70 [95%CI: 1.22 – 2.45] (non-adjusted), and 1.65 [1.18 – 2.40] (adjusted by dialysis vintage and sex).

Conclusions: Calcium carbonate may be a risk factor of CVD-related hospitalization in a dose-dependent manner.

PUB308

Characteristics of Phosphate Binders Dissolution

Heather Busby, John Durham, 1Tarek M. Sobel, 1Abdullah Hamad.

1 Palmetto Nephrology, Orangeburg, SC; 2 Davita Dialysis, Orangeburg, SC.

Background: Controlling hyperphosphatemia continues to be a challenge in dialysis patients. We evaluated for qualitative differences in the in-vitro dissolution times and characteristics of several calcium and non-calcium based phosphate binders in the acidic medium of vinegar to determine if these changes might correlate with the clinical responses to these binders.

Methods: Commercial phosphate binders were placed in 3 ounces of distilled white vinegar and observed for 20 minutes in transparent containers. Time to dissolution and its qualitative characteristics were visually monitored by two observers.

Results: Results are summarized in the attached table.

PUB309

Hypomagnesemia Associated with Malignancy Induced Hypercalcaemia

Vasav Huramun, Aparna Rao.

Vanguard Internal Medicine, Macneal Hospital, Berwyn, IL.

Background: We report a case of a 81 y/o female patient who was admitted after a fall at home. Pt was found to have severe persistent hypomagnesemia despite attempts for repletion and hypercalcaemia on labs.

Methods: Patient’s detailed history was obtained a comprehensive physical exam was done. Patient’s chart and records reviewed from an OSH as well. Daily labs and imaging were reviewed along with speaking to the Endocrinologist and Nephrologist on the case.

Results: Significant labs show her calcium was elevated at 11.1 and her magnesium level was 1.2. Her intact PTH was less than 7 and a Vitamin 1.25 OH level was 114. Patient also had a CT abdomen which showed a 8 cm mass near the pancreas which was biopsied to show a diffuse large B-cell lymphoma.

Conclusions: Patient’s persistent hypomagnesemia was likely in renal etiology etiology. The utility of Fractional excretion of magnesium, which was calculated to be 3.7, helped differentiate renal from GI cause. The possible renal etiologies included: Loop diuretics, Bartter syndrome, Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), Autosomal Dominant hypocalciuria. Patient’s hypocalciuria likely secondary to the newly diagnosed lymphoma an interesting contributing factor. Hypercalcaemia may result in hypomagnesemia at least in part from the fact that calcium and magnesium functionally compete for transport in the thick ascending limb of the loop of Henle. A variety of mechanisms may contribute to the reduction in magnesium reabsorption resulting from hypercalcaemia. One well known mechanism is facilitated by the basolateral calcium-sensing receptor (CaSR) in the thick ascending limb: This leads to an inhibition of the apical ROMK channels. Also hypercalcaemia can decrease in serum magnesium by decreased paracellular transport of calcium.

PUB310

Amphotercin Induced Pseudohyperphosphatemia

Snezana H. Mijovic-Das,1 Darius Mason,2 Muhammad A. Ashraf,1 Wadad S. Mneimneh, 1 Nephrology, Albany Medical College, Albany, NY; 2Pharmacy, College of Pharmacy, Albany, NY;

Background: Previous studies have shown that liposomal Amphotericin-B (LAB) may interfere with inorganic phosphate (Pi) lab measurements, causing pseudohyperphosphatemia (PHP). LAB-associated PHP is not well recognized and may lead to unwarranted workup and therapy. We present a case of a previously healthy 47-year-old male patient with a baseline Scr of 0.9 mg/dl, who was diagnosed with cryptococcal meningitis. He was treated with LAB and subsequently developed PHP.

Methods: Pi measurements were obtained by endpoint assay (EPA) using two different instruments (Beckman Coulter Unicel DXC and Dimension Vista 500). Lipid ultracentrifugation (LUC) was applied on one of the samples. For further quality control we serially measured Pi levels with LAMB-spiked calibration solutions, using both EPA and kinetic assay (KA), and the intra- and inter-assay coefficients of variation were calculated. The assay for Pi was performed with the methods described in the literature.

Results: Table1 shows values of serum Pi, Scr and LAMB doses, throughout hospitalization.

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

Underline represents presenting author.

942A

Conclusions: Calcium carbonate may be a risk factor of CVD-related hospitalization in a dose-dependent manner.
The patient’s elevated Pi levels could not be explained by the degree of renal dysfunction reflected by Scr increase, whereas they directly correlated with LAMB doses, suggesting an interference effect. Previous studies had similarly shown erroneous linear elevation of Pi levels with increasing LAMB concentrations. The interference effect was supported by: Correction of PHP by either LUC or lipemic clearing agents (Microcron®, LipoClear®); Concurrent Pi measurement using EPA and KA; Ineffectiveness of PO4 binders to resolve PHP. Of note, LUC failed to correct Pi level in our case, but this single-sample result is inconclusive.

**Conclusions:** LAMB-associated PHP can lead to extensive and unwarranted workup. Awareness of this drug-assay interaction can prevent inappropriate therapy such as dietary restriction, phosphate binders, hemodialysis, or altering the choice of ideal antifungal regimen.

**PUB311**

**Ethanol Injections for Management of Severe Hyperparathyroidism: Case Reports**  
Ivan Lazich, Marc J. Alonzo, Carolyn Kirchgessner Donaldson, Stuart M. Sprague.  
NorthShore Univ Health System, Univ of Chicago, Evanston, IL.

**Background:** Uncontrolled hyperparathyroidism in the setting of CKD or primary hyperparathyroid adenoma remains a therapeutic challenge despite the developing pharmacotherapy. We evaluated the utility of percutaneous ethanol injection therapy (PEIT) for the management of severe hyperparathyroidism with hypercalcemia in patients with nodular parathyroid hyperplasia.

**Methods:** A total of nine patients with elevated PTH and calcium concentrations and discrete parathyroid nodules were evaluated. Parathyroid nodules were identified and localized via Doppler ultrasound (US) and 98% ethanol (<1 ml) was injected via US guidance. A successful procedure was defined as decrease in PTH > 50% over a mean interval of 6 months. To determine if response was a function of nodular size, mean nodule size was compared between responders and nonresponders (T-test).

**Results:** Five patients had uncontrolled tertiary hyperparathyroidism (either ESRD on HD or post renal transplant) and four had primary hyperparathyroidism. This population included seven Caucasians and seven females with mean age of 56 ± 4.4 years. PTH concentrations, prior the procedure, ranged between 88 - 2922 pg/ml and serum calcium ranged 10 - 12.7 mg/dl. Five of the nine patients were considered responders. Mean nodule size in responder group was 1.28 mm and in nonresponder group was 1.86 mm (NS). Of the patients who responded to treatment only two had normalization of PTH, whereas all of them had normalization of serum calcium concentrations.

**Conclusions:** This preliminary experience demonstrates that some patients with severe hyperparathyroidism with hypercalcemia could be controlled with PEIT. The procedure, however, is limited to selective group of patients who have readily identified US evidence of parathyroid adenomas. Our evaluation did not show impact of nodular size on outcome as reported previously, however, our sample was small. The risk is minimal but the potential downside is the need for repetitive interventions until desired results have been achieved. Further studies should be performed to evaluate this as a viable option to surgery or in those who are not a surgical candidate.

**Funding:** NIDDK Support

**PUB312**

**25-Hydroxy-Vitamin D3 Concentration Detection for Screening of Early Renal Damage in Diabetic Kidney Disease**  
Wenbo Zhao, Bo Huang, Cailian Cheng, Xun Liu, Zengchun Ye, Tan-qi Lou.  
Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; Nephrology, The Sichuan Academy of Medical Sciences &Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

**Background:** To detect the type of the 25-hydoryxoparathyroid neoplasms in early screening of diabetic kidney disease. We collected the clinical data and blood samples of hospitalized patients with type 2 diabetes. The material is assessed according to eGFR (k=0.125;30 min/1.73m², MDRD Formula) and proteinuria combined diagnostic criteria of DKD, 52 cases were acquired, consisting of 23 males and 29 females, divided into normal proteinuria group (31 cases) with average (56.29±13.84) years old, and microalbuminuria group (21 cases) with average (60.29±13.24) years old. The quantitative determination of serum 25(OH) VitD3 level in type 2 diabetic nephropathy patients’ 25-hydrox-vitamin D3 concentration, and analyze whether the concentration applies to screening of diabetic nephropathy early renal damage.

**Methods:** We collected the clinical data and blood samples of hospitalized patients with type 2 diabetes. The material is assessed according to eGFR (k=0.125;30 min/1.73m², MDRD Formula) and proteinuria combined diagnostic criteria of DKD. 52 cases were acquired, consisting of 23 males and 29 females, divided into normal proteinuria group (31 cases) with average (56.29±13.84) years old, and microalbuminuria group (21 cases) with average (60.29±13.24) years old. The quantitative determination of serum 25(OH) VitD3 level (IDS Corp., England) is further performed adopting ELISA. The 25(OH) VitD3 level of normal proteinuria group is (44.51±19.87)ng/ml, while that of (31.7±10.03) ng/ml for microalbuminuria group (P<0.05). SPSS 15.0 is used for statistical analysis. Multi-factors are brought into the variables, then applying the ROC curve method.

**Results:** Multi-factor analysis demonstrates that ALB, UA and 25(OH) VitD3 are the three main relevant factors. The areas under the curves of these three main relevant factors are 0.698, 0.770 and 0.707 respectively. The underlying area of ALB+UA+ 25(OH) VitD3 combined curve (ALB+UA+ 25 (OH) VitD3) is 0.909, which is the maximum, and also greater than the area of 0.814 combining (ALB+UA).

**Conclusions:** The concentration of 25(OH) VitD3 in microalbuminuria group is lower. The concentration of 25(OH) VitD3 in microalbuminuria group is lower. Further studies should be performed to evaluate this as a viable option to surgery or in those who are not a surgical candidate.

**Funding:** NIDDK Support

**PUB313**

**Dialysate-Magnesium Regulates Serum-Magnesium Regulates PTH**  
Bernd A. Winterberg.  
Dept of Nephrology, Marienhospital, Emsdetten, Germany.

**Background:** The magnesium balance is a function of absorption and excretion. The excretion of Mg is almost exclusively renal, is determined by the glomerular filtration rate and decreases with increasing renal impairment. In dialysis patients, magnesium is eliminated via the dialysate.

**Methods:** We measured PTH in dialysis patients typically have a mild hypermagnesemia (1.03 to 1.5 mmol/l, normal range 0.62 to 1.03 mmol/l). The serum magnesium in hemodialysis patients depends on the magnesium concentration in the dialysate. If you increase it, increases the serum magnesium. Hypermagnesemia below 1.5 mmol/l is usually asymptomatic, from 2.3 mmol/l connect symptoms such as lethargy and dizziness, at even higher values, loss of tendon reflexes, bradycardia, paralysis, acon and cardiac arrest.

**Results:** In these patients before HD the mean serum magnesium was 0.81 ± 0.22 mmol/l, n = 17 (1.3 ± 0.19 mmol/l, n = 7) and after HD the mean serum magnesium was 0.77 ± 0.14 mmol/l (or 1.37 ± 0.05 mmol/l).

**Conclusions:** Regeneration of serum magnesium by modification of dialysate lead to serum magnesium concentrations (low or high) in the safe range, offering the chance to regulate PTH levels, to reduce vascular calcification, left ventricular hypertrophy and cardiovascular mortality.
A Rare Cause of Tumor-Induced Osteomalacia: Metastatic Prostate Cancer
Abdul Mubeen Mohammed, 1 Faheemuddin A. Ahmed. 2 1Swedish Covenant Hospital, Chicago, IL; 2Medical College of Wisconsin, Milwaukee, WI.

Background: We present a rare case of severe asymptomatic hyperparathyroidism in a patient with metastatic prostate cancer. It was associated with significant renal phosphate wasting as a consequence of high levels of fibroblast growth factor (FGF-23). We hypothesize that the metastatic prostate cancer caused high levels of FGF-23, resulting in tumour-induced osteomalacia symptoms receiving dialysis.

Methods: A 63-year-old man with history of metastatic prostate cancer was evaluated for phosphorus level of less than 1 mg/dL for four months. He was asymptomatic. His past oncologic history was significant for Gleason 6 score prostate cancer diagnosed seven years ago. Patient subsequently underwent radical prostatectomy, adjuvant hormonal therapy and eventually radiation. PSA declined from a peak of 60 ng/mL to 0.08, but started increasing again. Adjuvant hormonal therapy was restarted with LHHRH and bicalutamide. Follow-up staging scans revealed progressive metastatic disease and he was started on Docetaxel, three months prior to admission. Physical examination was unremarkable. Laboratory evaluation showed a calcium level of 8.4 mg/dL; 1.25 Vitamin D level 55.5 mg/mL and intact PTH level 182 mg/mL. Urine studies revealed renal phosphate wasting with fractional excretion of phosphorus of 60%. Serum FGF-23 levels were significantly elevated at 505 RU/mL (normal range of less than 180 RU/mL). Bone survey showed abnormal diffuse axial and proximal appendicular skeletal metastatic disease. Further work-up with Octreotide scintigraphy scan to locate for neuroendocrine tumor activity was negative. Patient was continued on potassium phosphate supplements (10 tablets/day) with calcitriol. Subsequent phosphate levels were at lower end of normal range.

Conclusions: Tumor induced osteomalacia due to metastatic prostate cancer is rarely described in literature. FGF-23 released from the tumor cells impairs phosphate reabsorption and 1α-hydroxylation of 25-hydroxy vitamin D. This leads to hypophosphatemia and usually low levels of 1,25-dihydroxy vitamin D. As the particular lesion could not be located with the octreotide scan, medical management was offered which included phosphate supplements and active vitamin D.

Phosphate Binder Powder Formulations: Perspectives from the Renal Care Community
J. Brian Copley, 1 Elizabeth J. Lindley, 2 Maria Cruz Casal, 3 Susan Rogers, 4 Jitka Pancirova, 5 Jennifer Kerne, 1 Denis Fouque. 6
1Shire Pharmaceuticals, Wayne, PA; 2Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; 3Hospital 12 de Octubre, Madrid, Spain; 4Codia Waterland, Pampelune, Netherlands; 5EDTNA/ERAQ, Seaport, Prague, Czech Republic; 6Centre Hospitalier Lyon-Sud and CENS, Lyon, France.

Background: Phosphate binders are commonly used in tablet form to help patients with chronic kidney disease limit their absorption of dietary phosphorus. Alternative formulations, such as powders, provide choice and may facilitate medication adherence. A survey of renal nurses and dietitians (n = 83) in the Netherlands, Spain, Sweden and the UK were asked to complete a survey in September and October 2012.

Results: The most frequently reported (38/83 responders, 46%) perception of formulation was that they are likely to be beneficial because they are easier for the patient to take, followed by 15% who thought patients who chew or swallow tablets have better awareness of their medicine taking. This perception was reported by a similar proportion of nurses (14/35, 40%) and dietitians (22/48, 46%). When a powder formulation is administered with food, the associated reduced need for additional fluid intake was perceived as another benefit (7/83, 8%). The most frequently reported perceived drawbacks of powder formulations were poor palatability (16/84, 19%) and administration of inaccurate doses (15/83, 18%). A greater proportion had BMI 20-24, 7,011 (32%) had BMI 25-29, and 9,015 (41%) had BMI ≥30. There were 18,420 (82%) males and the mean age was 63.8 ± 13.5 years. The cause of this all-cause mortality. Due to the limited trials, there was not enough evidence to show the benefit of LC in lowering cardiovascular event or cardiovascular events, improving bone morphology or metabolism or improving bone turn over parameters. LC can significantly decrease serum phosphate level and Ca×P product, increase the control rate of serum phosphorus compared with placebo. Nevertheless, there was no difference in phosphate level, the control rate of serum phosphorus, iPTH and Ca×P product compared with calcium carbonate, but b i 17.7% patients respectively. Abnormal Ca × P was seen in 23% patients. Conclusions: The findings of our center have their values of calcium, phosphorus, alkaline phosphatase, PTH and Ca × P product out of the range recommended by K/DOQI guidelines. These results are similar to those achieved by the patients in developed countries.

Phosphate Binder Powder Formulations: Perspectives from the Renal Care Community
J. Brian Copley, 1 Elizabeth J. Lindley, 2 Maria Cruz Casal, 3 Susan Rogers, 4 Jitka Pancirova, 5 Jennifer Kerne, 1 Denis Fouque. 6
1Shire Pharmaceuticals, Wayne, PA; 2Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; 3Hospital 12 de Octubre, Madrid, Spain; 4Codia Waterland, Pampelune, Netherlands; 5EDTNA/ERAQ, Seaport, Prague, Czech Republic; 6Centre Hospitalier Lyon-Sud and CENS, Lyon, France.

Background: Phosphate binders are commonly used in tablet form to help patients with chronic kidney disease limit their absorption of dietary phosphorus. Alternative formulations, such as powders, provide choice and may facilitate medication adherence. A survey of renal nurses and dietitians (n = 83) in the Netherlands, Spain, Sweden and the UK were asked to complete a survey in September and October 2012.

Results: The most frequently reported (38/83 responders, 46%) perception of formulation was that they are likely to be beneficial because they are easier for the patient to take, followed by 15% who thought patients who chew or swallow tablets have better awareness of their medicine taking. This perception was reported by a similar proportion of nurses (14/35, 40%) and dietitians (22/48, 46%). When a powder formulation is administered with food, the associated reduced need for additional fluid intake was perceived as another benefit (7/83, 8%). The most frequently reported perceived drawbacks of powder formulations were poor palatability (16/84, 19%) and administration of inaccurate doses (15/83, 18%). A greater proportion had BMI 20-24, 7,011 (32%) had BMI 25-29, and 9,015 (41%) had BMI ≥30. There were 18,420 (82%) males and the mean age was 63.8 ± 13.5 years. The cause of this all-cause mortality. Due to the limited trials, there was not enough evidence to show the benefit of LC in lowering cardiovascular event or cardiovascular events, improving bone morphology or metabolism or improving bone turn over parameters. LC can significantly decrease serum phosphate level and Ca×P product, increase the control rate of serum phosphorus compared with placebo. Nevertheless, there was no difference in phosphate level, the control rate of serum phosphorus, iPTH and Ca×P product compared with calcium carbonate, but b i 17.7% patients respectively. Abnormal Ca × P was seen in 23% patients.
Lithogenic Risks in Calcium Oxalate Nephrolithiasis Family Members
Thasinas Dissayavutra, Jakkaphon Rattanaphan, Thania Chirargonkolisiri, Talergnak Kanjanabuch, Piyaratana Tosukhowong.

Biochemistry, Chulalongkorn Univ, Pathumwan, Bangkok, Thailand; Medicine, Chulalongkorn Univ, Pathumwan, Bangkok, Thailand.

Background: Many evidences suggested that nephrolithiasis familial members are at risk, although no pathologic gene has yet defined. This study aims to discover the epigenetic risk factors in calcium oxalate nephrolithiasis family.

Methods: 146 participants, including 28 stone-removed nephrolithiasis patients and 45 of their first-degree descendants, as well as 73 healthy volunteers were enrolled. Medical history about urologic disease, blood and 24-hour urine were collected. Urinary calcium, magnesium, potassium, and sodium were measured by inductively coupled plasma mass spectrometry (ICP), oxalate and citrate by capillary electrophoresis, and sulfated glycosaminoglycans (sGAGs) by dye binding assay. Statistical analyses were testing by SPSS (IBM, USA) version 16.0.

Results: Compared to healthy population, nephrolithiasis patients had elevated urinary protein (336.6 ± 30.4 mg/day, p=0.002), calcium (5.8 ± 3.1 mg/dL/day, p=0.005), oxalate (43.7 ± 12.7 mg/day, p=0.001) together with decreased urinary citrate (66.2 ± 185.9 mg/day, p=0.001) and sGAGs (5.3 ± 48.5 μg/mL, p=0.001). While the nephrolithiasis descendants had the following parameters being in-between of 2 groups: proteinuria (67.0 ± 7.0 mg/day, p=0.001), diminished urinary citrate (113.6 mg/day, p=0.001) and sGAGs (32.29 ± 39.3 μg/mL, p=0.001), all of which were more obviously changed by age. The descendant also had lower kalluria level (19.89 ± 26.49, p=0.001) compared to the controls. No other urinary indices or clinical characteristics showed any significant differences. Adjusted odd ratio of the nephrolithiasis for urinary protein, citrate, and sGAGs were 1.024 (1.012-1.036), 0.993 (0.989-0.997) and 0.936 (0.914-0.958), respectively.

Conclusions: Nephrolithiasis patients and their first-degree descendants, although no stone-forming, have elevated proteinuria as well as decreased urinary citrate and sGAGs compared to healthy controls. Stone imaging and primary prophylaxis should be warranted in the relatives with abnormalities of urinary protein, citrate, or sGAGs.

Funding: Government Support - Non-U.S.

Three Children Developing Enlarged and, Echogenic Kidneys while Receiving Circulatory Support from Pediatric Ventricular Assist Device
Abdallah Guerraoui, Richard E. Neiberger.

Dept of Pediatric Nephrology, Univ of Florida, Gainesville, FL; Dept of Pediatric Nephrology, Univ of Florida, Gainesville, FL.

Background: In last decade pediatric ventricular assist device (VAD) specially designed for small children have been increasing implanted in North America. Prospective trials have shown pediatric VAD decreases the mortality of patient on heart transplant list and improves to extracorporeal membrane oxygenation (ECMO). After Food and Drug Administration approval of pediatric VAD, Berlin Heart EXCOR in 2011, more use of this device is expected in future. We are presenting unexpected renal findings developing in three children receiving circulatory support using Pediatric VAD (Berlin Heart Excor).

Methods: The mechanisms of heart failure in these children included: 1) Hypoplastic left ventricle with aortic stenosis; 2) Anomalous coronary artery arising from the pulmonary artery and 3) Idiopathic progressive heart failure. During circulatory support with VAD each child had coagulation times maintained at 2-3 times normal. Each child had normal or mildly reduced renal function.Each of these children had imaging studies (Ultrasound or Computed tomography) while receiving VAD support which demonstrated enlarged echogenic kidneys. These children subsequently died and autopsy studies of two children showed multiple bilateral kidney infracts, parenchymal congestion and arterial thrombosis.

Conclusions: Our case series shows that thrombosisembolism of renal artery may be a cause of enlarged echogenic kidneys in patients on pediatric ventricular assist device.

A Case of Warfarin Related Nephropathy
Nicole Bautista, William Whittier.

Rush Univ Medical Center, Chicago, IL.

Background: Warfarin was approved in 1954 and currently is the most prescribed anticoagulant medication. Warfarin related nephropathy (WRN) is a recently described condition that involves acute kidney injury, supratherapeutic international normalized ratio (INR), and tubular obstruction with red blood cell (RBC) casts. WRN is associated with significant morbidity as many patients progress to end stage renal disease (ESRD) despite normalization of the INR. We report a case of WRN where the acute kidney injury improves after cessation of warfarin.

Methods: A 64-year old American African man presented with a two week history of gross hematuria. He had a history of chronic hepatitis C, CHF, well-controlled HIV, and an aortic arch aneurysm and was initiated on warfarin 8 months prior to presentation. He had a baseline creatinine of 0.9 mg/dl and a urinalysis with blood but protein. Serial INR levels were in the therapeutic range. On presentation, he was found to have an INR of 7.3, acute kidney injury with a creatinine of 4.2 mg/dl, and his urinalysis showed large blood, >200 RBCs, and no protein. A renal biopsy revealed acute tubular necrosis, widespread tubular RBC casts, and no tubulointerstitial nephritis. There was mild mesangial hypercellularity and the IF had trace deposits of C3 and IgG. The EM showed normal glomerular basement membrane thickness (470 nm) without electron dense deposits, and normal endothelial and podocyte structures. There were no electron dense deposits in the mesangium. There were no clinical or pathologic etiologies that could explain the presence of tubular RBC casts and he was diagnosed with WRN. Warfarin therapy was discontinued, aspirin started, and at one year follow-up his creatinine had improved to 2.3 mg/dl. His urinalysis revealed no protein, trace blood, and 4-10 RBCs.

Conclusions: The diagnostic criteria for WRN includes acute kidney injury, supratherapeutic INR, and the presence of tubular RBCs and RBC casts on kidney biopsy. Often renal function does not recover and progression to ESRD is common, even after cessation of warfarin. This report highlights that cessation of warfarin therapy can be associated with improvement or stabilization in renal function.

Taking Into Consideration Migrant Patients’ Cross-Cultural Features during Patient Educational Therapy for Patients
Abdallah Guerraoui, Guillaume Jean, Agnes Caillé-beauzion, Corinne Isnard-Bagnis.

Nephrologie Dialyse, Calydial, Vienne, France; Nephrologie Dialyse, Nephrocare, Lyon, France; Patient Education, Univ Pierre et Marie Curie, Paris, France.

Background: This work is based on the results of a qualitative research dealing with the educational nurse’s (EN) activity during a patient education session with migrant patients. More precisely, in this article we intend to report on the way the educational nurse takes into consideration all the cross-cultural factors and their repercussion/negative impact on the ENs’ practice.

Methods: This research is uses a method which stems from social sciences called “the simple auto confrontation. The process consists in filming the interaction between the EN and the patients during the educational diagnosis. This video-taped interaction is recorded and coded according to L Bardin’s method of content analysis. An auto confrontation between the EN and the researcher is carried out. This second interaction is also filmed, reviewed and coded according to the same method.

Results: We demonstrate how difficulties stemming from differences in presentations, beliefs and cultures between the EN and the migrant patient have a significant impact on the consultation. We will highlight the ability of both the EN and the migrant patient to adapt their interactions to new cross cultural realities. The EN adaptation is closely linked to the individual’s career path and their formation. Therefore, this work includes operationalizing the analysis in order to make the best use of educational therapy for patient (ETP) interviews.

Conclusions: When EN take into consideration each patient’s culture, their life path and their individual itinerary, this enhances the success of an ETP programme. Hence, this qualitative research on the cross cultural aspects of the ETP falls within a more global dimension which enables us to better analyze how the medical culture influences relationships with both migrant and non-migrant patients. The differences between these two cultures (the doctor or nurse and the patient’s cultures) lead to misunderstandings and divergences which complicate the health care provider the doctor-patient relationship.

Kidney Stone Formers
Serum 25-Hydroxyvitamin D Concentration and Survival among Incident Kidney Stone Formers
Talerngsak Kanjanabuch, Piyaratana Tosukhowong. 1 Nephrologie Dialyse, Calydial, Vienne, France; 2 Nephrologie Dialyse, Nephrocare, Lyon, France.

Heavy Chain Deposition Disease Sarah Margaret Moran, Maeve P. Crowley, Marek J. Mazur, Nephrology, Cork Univ Hospital, Ireland; Haematology, Cork Univ Hospital, Ireland.

Background: Heavy chain deposition disease (HCDD) is the least common of the plasma cell dyscrasias. 24 have been described in the literature to date. We report the presentation, diagnosis, treatment and complications of the 25th report patient. HCDD is an important but rare cause of renal impairment in association with plasma cell dyscrasia. Methods: A 56 year old male was referred to Nephrology OPD for evaluation of hypertension and elevated creatinine of 2.9mg/dL (eGFR 26ml/min/1.73m2). History revealed a nine month history of hypertension and dyslipidemia treated with rosuvastatin and perindopril. Examination revealed BP 177/105mmHg, nil else of note. Urinary protein excretion was 6.4 g/24 h, serum total protein 31 g/L. Thin-layer agarose electrophoresis revealed a monoclonal IgG kappa band, creatinine concentration 2.6mg/dL. Bone marrow aspiration showed 12% plasma cells, bone marrow biopsy 10-15% atypical plasma cell infiltrate. Renal biopsy revealed nodular glomerulosclerosis, PAS positive, Congo Red negative, electron microscopy reveals amorphous granular electron dense deposits. Treatment was initiated with bortezomib, cyclophosphamide and dexamethasone and subsequent stem cell harvest and transplantation. Stem cell harvest was complicated by AKI and ureaosipesis requiring renal replacement therapy. Repeat biopsy was morphologically similar to the initial biopsy, unfortunately baseline creatinine increased to 5.8mg/dL. Conclusions: HCDD is rare cause of renal dysfunction in plasma cell dyscrasia, which is caused by a deletion of the CH1 domain. Series to date have been limited by small numbers. Reported treatments include bortezomib, cyclophosphamide, dexamethasone, chlorambucil, melphalan and stem cell transplantation.

Invasive Pulmonary Aspergillosis in a Patient with Kidney Transplant Chudi Sifan, Elie El-Charabaty, Rabib Nasr, Chetana Rondla, Dinad D. Parekh, Suzanne E. El Sayegh. Medicine, Staten Island Univ Hospital.

Background: Invasive pulmonary aspergillosis is a serious medical condition with a high morbidity and mortality (40%). Risk factors include immunosuppressive therapy. While corticosteroid-dependant asthma, migrating pulmonary in plasma cell dyscrasias. 24 have been described in the literature to date. We report the CT chest showed a bilateral basilar consolidation and a right pneumothorax. bronchoalveolar exudate revealed 6.4 g/24 h and a monoclonal IgG kappa band. Creatinine concentration 2.6. Bone marrow aspiration showed 12% plasma cells, bone marrow biopsy 10-15% atypical plasma cell infiltrate. Renal biopsy revealed nodular glomerulosclerosis, PAS positive, Congo Red negative, electron microscopy reveals amorphous granular electron dense deposits. Treatment was initiated with bortezomib, cyclophosphamide and dexamethasone and subsequent stem cell harvest and transplantation. Stem cell harvest was complicated by AKI and ureaosipesis requiring renal replacement therapy. Repeat biopsy was morphologically similar to the initial biopsy, unfortunately baseline creatinine increased to 5.8mg/dL. Conclusions: HCDD is rare cause of renal dysfunction in plasma cell dyscrasia, which is caused by a deletion of the CH1 domain. Series to date have been limited by small numbers. Reported treatments include bortezomib, cyclophosphamide, dexamethasone, chlorambucil, melphalan and stem cell transplantation.

A Case of Minimal Change Disease in a Patient with Churg-Strauss Syndrome Philippe Lachance, David Philibert. Nephrology, CHUQ Quebec, Canada.

Background: Renal involvement in Churg-Strauss syndrome (CSS) ranges from 22 to 18%. Minimal change disease is highly rarely reported and no case of minimal change disease (MCD) has ever been reported. We herein present the case of a young man who presented with this entity. Methods: A 38 year-old male with a past medical history of CSS based on corticosteroid-dependent asthma, migrating pulmonary infiltrates, colitis, rash and peripheral eosinophilia presented to hospital on January 2012 with a two weeks history of leg edema. Laboratory studies revealed slight anemia, marked hypoalbuminemia, normal creatinine and a significant anti-PoL3 level of 13.1. The 24-hr urinary protein excretion was 13.4 g. The patient was started on prednisone, edaravone and edaravone. Recently he was readmitted and showed 9 g/h proteinuria. Results: Treatment was initiated with bortezomib, cyclophosphamide, dexamethasone, chlorambucil, melphalan and stem cell transplantation. Conclusions: The most common renal histological finding in CSS is necrotizing crescentic glomerulonephritis. Other forms of renal disease have also been reported including tubulointerstitial nephritis and IgA disease. Nephrotic range proteinuria in CSS is rare and the histopathologic lesion associated with this anomaly is focal and segmental glomerulosclerosis. To our knowledge it is the first case of MCD in the context of CSS reported in the literature. However, we cannot definitively exclude an unsampled FSGS. Regarding treatment, corticosteroids alone were first used as they are the mainstay of treatment in MCD. Because of established steroid dependance, cyclophosphamide and azathioprine were used in previous cases with relative success. Physicians should be aware of the possible complications due to ifosfamide.

Ibosfamide-Induced Nephrotoxicity: A Reversible Complication in Cancer Patients Chadi Safian, Rabih Nasr, Elie El-Charabaty, Dinad D. Parekh, Chetana Rondla, Suzanne E. El Sayegh. Medicine, Staten Island Univ Hospital.

Background: Ibosfamide is a synthetic analog of cyclophosphamide that is used in combination with other anti-neoplastic agents in the treatment of metastatic germ-cell tumors, testicular cancer and some sarcomas. Ibosfamide causes significant nephrotoxicity mainly due to direct tubular injury.

Methods: A 65 year old female with previous history of metastatic sarcomatous uterine cancer who was admitted to the hospital. She received ifosfamide chemotherapy 2 days prior. Her physical examination was benign. During the hospital stay she developed electrolyte abnormalities including hypokalemia, hypomagnesemia, and hypophosphatemia (see table) that required repletion. Urine analysis demonstrated increased 24 hours protein (1575mg/24h) and a magnesium value of (164.25mg/24h) excretion. Phosphorus was normalized by the time of outpatient follow-up (4.1 mg/dL), as well as the serum creatinine. Patient’s electrolyte abnormalities were thought to be due to proximal tubular dysfunction secondary to ifosfamide chemotherapy with associated acute kidney injury.

Ibosfamide-Induced Nephrotoxicity: A Reversible Complication in Cancer Patients Chadi Safian, Rabih Nasr, Elie El-Charabaty, Dinad D. Parekh, Chetana Rondla, Suzanne E. El Sayegh. Medicine, Staten Island Univ Hospital.

Methods: A 65 year old female with previous history of metastatic sarcomatous uterine cancer who was admitted to the hospital. She received ifosfamide chemotherapy 2 days prior. Her physical examination was benign. During the hospital stay she developed electrolyte abnormalities including hypokalemia, hypomagnesemia, and hypophosphatemia (see table) that required repletion. Urine analysis demonstrated increased 24 hours protein (1575mg/24h) and a magnesium value of (164.25mg/24h) excretion. Phosphorus was normalized by the time of outpatient follow-up (4.1 mg/dL), as well as the serum creatinine. Patient’s electrolyte abnormalities were thought to be due to proximal tubular dysfunction secondary to ifosfamide chemotherapy with associated acute kidney injury.

Conclusions: Nephrotoxicity caused by ifosfamide manifests by onset or one of more of the following tubular dysfunction sign including hypophosphatemia, glucosuria, aminoaciduria, hypokalemia and hypomagnesemia. Ibosfamide therapy can also cause a reduction in GFR which is usually mild unless given in conjunction with another nephrotoxin such as cisplatin. The risk factors for ifosfamide nephrotoxicity are cumulative dose, age under five to four years, and cisplatin therapy. MesiNA and N-acetylcysteine, have been evaluated but their efficacy is unknown. For patients receiving ifosfamide, we recommend telemetry monitoring and continuous intravenous hydration with electrolytes repletion to minimize the side effects. Physicians should be aware of the possible complications due to ifosfamide.

Invasive Pulmonary Aspergillosis in a Patient with Kidney Transplant Chudi Sifan, Elie El-Charabaty, Rabih Nasr, Chetana Rondla, Dinad D. Parekh, Suzanne E. El Sayegh. Medicine, Staten Island Univ Hospital.

Background: Invasive pulmonary aspergillosis is a serious medical condition with a high morbidity and mortality (40%). Risk factors include immunosuppressive therapy. While patients with solid organ transplants are at increased risk for such complication, it is thought to be lower in kidney transplant recipients.

Methods: A 56 year old female with history of deceased donor kidney transplant 3 months before presented complaining of low GI bleed. Patient’s hospital course after her kidney transplant was complicated by an IVC tear and a AA aneurysm s/p repair that led to her graft loss and she was back on hemodialysis. By the time she presented to the hospital, she was still on tacrolimus, mycophenolate mofetil, prednisone, bactrim, and valgancilovir. Her physical exam revealed a BP of 85/50, temp101, with decreased breath sounds. Labs revealed a WBC of 7.4, Cr 0.96, Hb 10.7, and a platelet count of 157,000. She was admitted to the ICU, was given blood transfusion, neupogen and was started on IV pressors. CT chest showed a bilateral basilar consolidation and a right pneumothorax. bronchoalveolar lavage grew fungal elements suggestive of aspergillus spp, and pseudomonas aeruginosa carbapenem sensitive. She was transferred to outside hospital and was treated with IV voriconazole, liposomal amphotericin B and wide spectrum antibiotics, but the patient subsequently expired after two weeks because of sepsisemia and respiratory failure.

Conclusions: Invasive aspergillosis appear to manifest in kidney transplant patients with pulmonary or CNS infection. A retrospective study by Abbott et Al in 2001 found that aspergillosis pneumonia is the second cause of fungal infections in 33,479 of kidney transplant patients after candida esophagitis. No randomized clinical trials have been done regarding the treatment of invasive aspergillosis, but voriconazole and amphotericin B have been used in previous cases with relative success. Physicians should be aware of the interactions of the antifungal therapies with calciumin inhibitors and should adjust the dose based on the creatinine clearance.
May be a therapeutic option: our patient affected by RF non responsive to steroids and was negative and ureteral stent was removed. Ureteral stent was changed every six months. In 01/2013 (with PET/CT positive) we treated 5 mg/day without response again. During this period creatinine was in normal range and since 10/2011 to 01/2013 treatment was shifted to tamoxifen 10 mg bid plus prednisone 06/2010 to 10/2011 we added full dose of methotexate (15 mg/week) without response. Around right ureter) at abdominal CT and positron emission tomography (PET/CT). Since 06/2008 to 06/2009 he was treated with prednisone alone (initially 5 mg/day). She was noted to have significant proteinuria and haptoglobin <15. Her initial hemoglobin was 11.8 g/dl, but was down trending, and the patient had edema. Laboratory results were significant for creatinine of 1.6 mg/dL, eGFR 57, urine sodium <20, albumin/creatinine 841 mg/g, and protein to creatinine ratio of 3.09 g/L. Urinalysis showed glucosuria with normal serum glucose of 102 and urine sediment demonstrating granular casts 4/lpf, tubular epithelial cells, oval fat bodies, and no dysmorphic RBCs. SLEP, UPEP, C3/C4, ANCA, RF, antiGBM Ab, ANA, antitDNA Ab, RPR, and hepatitis profile were negative. A high fractional excretion of phosphate and uric acid, hyperphosphatemia, hypouricemia, and aminociclohexamil were also demonstrated. He was subsequently scheduled for a renal biopsy, which demonstrated ATN possibly secondary to tenovifor exposure. After withdrawal of tenovifor, albumin/creatinine decreased to 126 mg/g and protein to creatinine ratio decreased to 0.5 g/L, serum creatinine was 0.8 mg/dL and eGFR >60.

Conclusions: This case provides organization of evidence of a rare case of tenovifor induced nephrotoxicity presenting with nephrotic-range proteinuria. In the light of this, it is important to consider this unique presentation.

PUB333

Warfarin-Induced Calciphylaxis Chadi Saifan, Elie El-Charabaty, Chetana Rondia, Ninad D. Parakh, Suzanne E. El Sayegh. Staten Island Univ Hospital.

Background: Calciphylaxis has been a challenging complication of ESRD with unknown underlying mechanism. Several risk factors were identified such as hyperphosphatemia, hypercalcemia, hyperparathyroidism, low serum albumin levels, history of warfarin therapy.

Methods: A 56 y/o female with DMII, morbid obesity (BMI =48kg/m²), DVT and PE on warfarin for 3 years, chronic kidney disease stage IV and peripheral vascular disease presented with s/p fall and worsening AKI (baseline creatinine 2.42). The patient had drop in hemoglobin, and warfarin was held for 4 days for suspicion of blood loss, and restarted on day 6 (INR=1.6) after placement of Ash Catheter and institution of dialysis. She developed a right foot blister on day 7 and bilateral thighs blisters on day 10.

Labs were Ca 7.4 mg/dL-Albumin 2.9 g/dL, TP 10.3 mg/dL, creatinine 7.68 mg/dL BUN 98 mg/dL. The skin became flaccid and the lesions had worsened progressively over 3 days to necrotic eschar. Extensive workup for vasculitis was negative. Patient had high renal extremity eschar of clavus with 75 x 20 cm, and a left lower extremity 75x20 cm and abdominal lesion of 10x5.5 cm. Patient was taken in charge by the burn specialist, underwent skin debridement and wound care but failed all resuscitation efforts on 42. Skin biopsy specimen showed a portion of skin and subcutaneous tissue with diffuse necrosis. Multiple small arteries showing calcification of the tunica media. This pattern is strongly suggestive of calciphylaxis.

Conclusions: We hypothesise that the reintroduction of warfarin in patients with ESRD induces an imbalance favoring calcification in the vessels in a previously sensitized conditions, which set our patient up for a catastrophic acceleration of vascular calcification. Understanding the pathophysiology of this process will certainly enhance our treatment approach and reduce the morbidity and mortality of this devastating condition.

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

947A
Medical Center - Wake

BUN 44, creatinine 2.8, calcium 8.8, albumin 1.7. Creatinine on 2/26/2012 was 0.9 and hemoglobin 10.6, platelets 298, chemistry shows sodium 142, k 4.8, Cl 111, bicarb 20, exam shows normal vital signs, short stature, hearing loss, left wrist swelling and tenderness is positive for same symptoms of arthritis and skin rash in a daughter and a son. Physical the histologic non-metabolizable macromolecules or substances. Histologic "look alikes" to osmotic changes, imparting "osmotic nephrosis". Cr plateaued to 11.2mg/dL, then started to improve only with gentle IV hydration to 1.7mg/dL on discharge.

Conclusions: Our patient developed oliguric AKI with histologic features of osmotic nephrosis just after being discharged from the hospital, without receiving any known non-metabolizable macromolecules or substances. Histologic “look alikes” to osmotic nephrosis have been described in calcineurin-inhibitor toxicity, foam cells in lipid storage, hypokalemia, ischemic tubular injury, or ethylene glycol intoxication. However the histometric findings of our patient conformed to the description of a classical osmotic nephrosis, but without an identifiable case.

Muckle-Wells Syndrome and Secondary Amyloidosis (AA) with Nephropathy

Jun Sohn,1 Ashok P. Chaudhari,2 Jinil Yoo.

Background: Incidence of AA amyloidosis in Muckle-Wells syndrome is 25 percent. Muckle-Wells syndrome consists of periodic fever, urticaria, arthralgia and deafness. Muckle-Wells syndrome is transmitted by an autosomal dominant trait. In clinical practice, renal failure due to amyloidosis and Muckle-Wells syndrome is rare and should be considered as differential diagnosis in difficult cases of renal failure.

Methods: A 77 year old male with PMH of Arthritis, Skin rash presented to ER with nausea, vomiting and abdominal pain for 3 weeks. Review of system is positive for joint pain, skin rash from childhood, and hearing loss for couple of years. Family history is positive for same symptoms of arthritis and skin rash in a daughter and a son. Physical exam shows normal vital signs, short stature, hearing loss, left wrist swelling and tenderness and diffuse skin rash. Initial laboratory work up shows CBC with white blood cells 10.18, hemoglobin 10.6, platelets 298, chemistry shows sodium 142, k 4.8, Cl 111, bicarb 20, BUN 44, creatinine 2.8, calcium 8.8, albumin 1.7. Creatinine on 2/26/2012 was 0.9 and on 7/26/12 was 2.9. Urine collection for 24 hours showed proteinuria with 6.3 gm per day. Renal ultrasound was unremarkable. Renal biopsy showed findings AA amyloidosis with mild chronicity. Rheumatological work up was negative. He was clinically diagnosed with Muckle-Wells syndrome because of episodic skin rash, arthralgias and generalized pain, fatigue, intermittent fever, late-onset sensorineural hearing loss. Genetics Consult was requested, they agreed with clinical diagnosis and they recommended NLRP3 gene testing. Renal function partially improved and patient was discharged.

Conclusions: Renal failure due to amyloidosis secondary to Muckle-Wells syndrome is rare and should be considered as differential diagnosis in difficult cases of renal failure.

Thyrotoxic Hypokalemic Periodic Paralysis

Jun Sohn,1 Ashok P. Chaudhari,2 Jinil Yoo.

Background: Thyrotoxic hypokalemic periodic paralysis (THPP) is a rare complication of thyrotoxicosis. Usually associated with Grave’s disease, it can also be seen in other forms of thyrotoxicosis like toxic nodular goiter, drug induced, use of thyroxine containing weight loss supplements and thyroiditis. Common in males (male to female ratio of 20:1), the typical presentation includes recurrent episodes of paresis, in the presence of low potassium levels usually precipitated by heavy meals, stress or strenuous exercise. Patients may also present with life threatening arrhythmias secondary to hypokalemia.

Methods: A 31 year old Hispanic male with no significant past medical history presented with acute onset bilateral lower extremity weakness. He was unable to get out of bed and had no sensation in his legs. Patient gave history of strenuous exercise and lower extremity cramps the day prior. In the emergency room, patient was anxious, tachycardic and exam was significant for 25 strength in both lower extremities proximally and 4/5 distally, 1+ reflexes and inability to walk. He was found to have potassium of 1.7mEq/L. EKG showed sinus tachycardia. He was given 80 meq’s of potassium with subsequent improvement of symptoms. Further work up showed TSH of 0.04Uu/ml, free T4 of 4.54pg/ml, creatinine 1.2mg/dL and Thyroglobulin antibody was negative. A thyroid uptake scan showed increased uptake of 54% and findings consistent with Grave’s disease. Patient was managed with propranolol and propylthiouracil and he returned to full strength in 48 hours. He subsequently underwent radioactive iodine ablation, following which he was discharged home with follow up.

Conclusions: THPP is an important differential of acute weakness and should be kept in mind for all patients presenting with a similar picture. Recognition of this is important since treatment is easy and provides quick and early relief of symptoms. Almost all patients show response to potassium replacement and management of thyrotoxicosis with non selective beta blockers like propranolol and anti thyroid agents. Definitive treatment in the form of radioactive iodine or thyroidectomy should be considered especially in cases refractory to medical management.

Successful Treatment of Telaprevir in Saudi Patient with Hepatitis C on Hemodialysis

Mamdouh Abdulghafour Nada.

Background: Telaprevir is a hepatitis C V interferon remains contraindicated post renal transplant; therefore, it is recommended to treat HCV infection in patients with concomitant kidney disease prior to kidney transplantation. A protease inhibitor that is both a substrate and an inhibitor of CYP3A. Methods: Our patient is a 44 year old male Saudi with ESRD Secondary to Chronic Pyelonephritis on Hemodialysis since 1990. Status post living non-related kidney transplant in India which survived for 4 years. Another attempt for a transplant was a cadaveric renal transplant which was removed 2 weeks after transplantation due to perihepatic hematomata and renal vein thrombosis. The patient had previously received treatment for the hepatitis by taking Peg-IFN as a single treatment, but failed to respond. Another attempt to cure him was done by administering a dual medication of Peg-IFN with Ribavirin. According to the kidney biopsy, the patient was considered to have grade 2 chronic hepatitis stage 2 associated with HCV. Abdominal ultrasound was unremarkable for the liver. Hepatitis C virus PCR (HCV viral load) was 197,731 IU/ml, genotype 1A. The patient had a
compensated liver function with normal liver enzymes. So the patient was considered to be a non-responder with a non-cirrhotic liver genotype 1. Therefore the team decided that this patient should start undergoing triple therapy to treat HCV, consisting of Peg-IFN alpha 120 mcg once weekly plus Ribavirin 200 mg three times per week. We then performed dual medication for 36 weeks as Peg-IFN alpha plus Ribavirin.

**Conclusion:** Renal involvement including dense infiltration of kidneys (often bilateral involving both cortex and medulla) is seen in up to 34% of patients diagnosed with AML, typically presenting with chronic mild alterations in glomeruli. A novel form of proliferative glomerulonephritis related to glomerular deposition of monoclonal IgM mimicking immune-complex glomerulonephritis, termed proliferative glomerulonephritis with monoclonal IgM deposits (PNCMID), is recently described.

**Methods:** The patient was a 60-year-old male with a medical history of alcoholic liver cirrhosis since he was 50 years old. He had an episode of hepatic encephalopathy 4 years before admission, when his serum creatinine (Cr) level was within normal range. He presented nephrotic syndrome with urinary protein excretion of 4.7g/day and serum albumin level of 2.3mg/dL, and the ultrasound revealed microscopic hematuria. Serum IgA level was 507mg/dL, and serum complement levels were normal. Serum anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies, cryoglobulins, and hepatitis B and C were all negative. C3 and C4 levels showed no evidence of systemic disease. Renal biopsy showed diffuse mesangial proliferation together with doubling of the glomerular basement membrane. Cellular crescents were also observed in about 20% of the glomeruli.

**Results:** Immunofluorescence (IF) showed granular deposition of IgA and C3 along the glomerular capillary walls. If findings of IgA subtypes and light chains showed only positive for IgA1 and IgA1κ. Granular electron dense deposits were observed in the subendothelial areas. These findings led us to the diagnosis of monoclonal IgA1κ deposition disease.

**Conclusion:** The clinicopathological features of our case are compatible with those of PNCMID with monoclonal IgM deposits, and our patient showed no evidence of systemic disease. Treatment regimen for acute glomerular lesions which is atypical in hepatic glomerulonephrosis. Lastly, our case suggests an importance of IF assays for immunglobulin subtypes and light chains in the differential diagnosis of glomerular immunoglobulin deposition diseases.
evaluation he had sub-nephrotic range proteinuria. Worsening of his renal function prompted kidney biopsy which showed granulomatous interstitial nephritis with focal acute tubular injury, classic noncaseating granulomas. Patient was started on pulse dose steroids with dramatic improvement in his renal function. ACE levels were normal, CT scan of chest did not reveal any hilar adenopathy. This case was a rare presentation of sarcoidosis manifestation as acute kidney injury in the absence of overt systemic sarcoidosis, normal levels of ACE and dramatic response to steroid therapy.

Conclusions:

PUB344

Emphysematous Pyelonephritis after Plasmapheresis in a Renal Transplant Patient

Rameenat Lekkham, Rasib Raja. Medicine, Albert Einstein Medical Center, Philadelphia, PA.

Background: Emphysematous pyelonephritis (EPN) is a rare but devastating complication after renal transplantation. It carries the risk of graft loss and is associated with a high mortality rate. The majority of cases reported thus far have undergone graft nephrectomy. Here we present a case of EPN in a renal allograft after plasmapheresis for recurrent FSGS that was successfully treated conservatively.

Methods: A 49-year-old woman received a second living-related renal allograft from her son in April 2009. Her first transplanted kidney from deceased donor in 2002 failed from acute rejection and required allograft nephrectomy. Her native kidney disease was FSGS. 3 weeks prior to the admission, she developed acute generalized edema with nephrotic range proteinuria with allograft dysfunction. Plasmapheresis was initiated after her allograft biopsy confirmed diagnosis of recurrent FSGS. After the 9th sessions, she developed fever, tachycardia, leukocytosis and thrombocytopenia. CT scan of the abdomen revealed focal medial enlargement of the transplant kidney, with a moderate sized area of gas-filled collection in the parenchymal with small subcapsular gas. The possible emergent need for transplant nephrectomy was discussed, but she decided to preserve the graft with medical management. Urgent intervention with percutaneous abscess drainage and empiric broad-spectrum antibiotic coverage with IV aztreonam and tobramycin (changed to ciprofloxacin later on) helped stabilize the patient’s condition. Mycoplasmatae moleitl and tacrolimus were held except for low dose prednisone. The urine culture, fluid from the drain and blood culture all grew Klebsiella pneumoniae. The drain was removed on day 23th, the antibiotic was continued for total of 14days. Repeat U/S 1 month later showed normal renal allograft parenchyma and collecting system, her allograft function was back to her baseline as well.

Conclusions: Plasmapheresis in renal transplant patient may increase risk of EPN. However, timely diagnosis and early conservative intervention with aggressive intravenous antibiotics and percutaneous drainage will help in preservation of renal allograft and may be able to avoid graft nephrectomy like in our patient.

PUB345

A Rare Case of Anti GBM Disease in Alpha 1 Antitrypsin Deficiency

Mandeep Singh,1 Roberto L. Collazo,2 Sreevalli Pariti.3 1Nephrology, Methodist Dallas Medical Center, Dallas, TX; 2Nephrology, Methodist Dallas Medical Center, Dallas, TX.

Background: We report a rare case of Anti GBM disease manifesting as acute kidney injury in a patient with history of liver cirrhosis secondary to alpha 1 antitrypsin deficiency.

Methods: A 61 y/o female with past medical history of liver cirrhosis due to alpha 1 antitrypsin deficiency admitted to the hospital for acute kidney injury with elevated BUN and creatinine. On admission, nephrotic syndrome was diagnosed and further investigation was initiated. The investigation came up positive only for the presence of anti-GBM antibodies and renal biopsy was compatible with membranous glomerulonephritis (MPGN). All patients underwent metilprednisolone pulse, followed by prednisone 1mg/kg and cyclophosphamide (CYC) pulse and plasmapheresis. Two patients underwent rituximab therapy, one due to lymphoma treatment and the other to CYC toxicity.

Conclusions: We described 3 cases of mixed cryoglobulinemia non-HCV related associated with NS. Prognosis was unfavorable and all patients required dialysis. According to literature, non-infectious cryoglobulinemia with renal involvement carries a poor prognosis despite treatment instituted as shown in this series of cases.

PUB346

Nephrptic Syndrome due to Mixed Cryoglobulinemia Non Hepatitis C-Related: Report of 3 Cases

Carla Queiroz Neves, Alline S. A. Oliveira, Camila Barbosa L. Oliveira, Luis H.B.C. Sette, Giusele Vaiigel Fernandes, Maria Alina G.M. Cavalcante, Lucila Maria Valente. Serviço de Nefrologia, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil.

Background: Mixed Cryoglobulinemia is a rare cause of glomerular disease and Membranoproliferative Glomerulonephritis (MPGN) is the most frequent histological finding. The association with hepatitis C (HCV) infection is approximately 90-100% of the patients.

Methods: We retrospectively analyzed 3 patients with Nephritic Syndrome (NS), positive serum cryoglobulins, negative serology and viral load by polymerase chain reaction (PCR) for HCV, between 2011 and 2013. Epidemiology, clinical manifestations and outcomes are described in table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>NS</th>
<th>Hep</th>
<th>Anti-GBM</th>
<th>Dialysis</th>
<th>Follow-up time</th>
<th>Plasmapheresis</th>
<th>Cyclophosphamide</th>
<th>Riruximab</th>
<th>Renal Biopsy</th>
<th>Membranoproliferative Glomerulonephritis (MPGN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>36y</td>
<td>Female</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>20</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>MPGN</td>
</tr>
<tr>
<td>Patient 2</td>
<td>64y</td>
<td>Male</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>17</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>MPGN</td>
</tr>
<tr>
<td>Patient 3</td>
<td>47y</td>
<td>Male</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>10</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>MPGN</td>
</tr>
</tbody>
</table>

All patients underwent metilprednisolone pulse, followed by prednisone 1mg/kg and cyclophosphamide (CYC) pulse and plasmapheresis.
imunosuppression, the initial diagnosis was challenged and laboratory and histological study was repeated: there was a re-potentiation of anti-GBM antibodies and crescentic glomerular findings in biopsy. The initial diagnosis was reaffirmed, plasmapheresis was resumed and Mofetil Mycophenolate (MMF) was replaced for CF, with good clinical and laboratory response. MMF was maintained for 2 years and then weaned. With 8 years of follow-up, the patient has remained asymptomatic, renal function and nephropathy syndrome fully recovered.

Conclusions: The case of GPS is atypical both for its nephrotic presentation and successful response to MMF, after relapse under CF. To the best of our knowledge, only two cases of successful therapy with MMF after failure of CF were reported. Based on our findings, GPS should be considered in the differential diagnosis of nephrotic syndrome with pulmonary involvement and additional study is needed to validate MMF as a therapeutic option.

**PUB348**

Delayed Intervention in Acute Renovascular Thromboembolic Disease Could Salvage Renal Function

Suyash Sharma, Hernani J. Mehta, Anup Chaudhari. Nephrology, Lilavati Hospital, Mumbai, Maharashtra, India.

Background: Acute renal arterial occlusion can happen due to in-situ thrombus or embolism. Unless immediately treated, it can lead to renal infarction. We are presenting a case where there was a delay in diagnosis, still renal function could be salvaged partially with prompt intervention.

Methods: 40/M, Non-smoker on routine health check up 7 years ago has BP of 130/94 mm Hg and S. Creatinine 1.3mg/dl. Presented to a gastroenterologist after 15 days with pain in right upper abdomen. S. Bilirubin: 1.8, direct 1.0mg/dl; all other laboratory investigations and USG abdomen were normal. Since the severe pain persisted after 1 week, CT abdomen with CT abdominal angiography was done, which showed right renal infarction and raised possibility of right renovascular cause. The patient was referred to our hospital. BP on admission 170/130 mm/Hg and except for mild tenderness over right lumbar area, no other clinical signs present. DSA showed right renal artery dissection, thrombus and right renal lower pole infarction.

The question was: Will an intervention be able to salvage the right renal function after 1 week? Right renal angioplasty with stenting was performed, the BP stabilized. One week later (and until now), right kidney GFR remains at 26ml/min on DTPA renogram and S. Creatinine value normal. BP is well controlled.

Conclusions: There is a dilemma about the outcome of interventions when the acute thromboembolic events of renal artery are diagnosed late. We have presented a case where, in spite of a delay of 1 week from the onset of symptoms to diagnosis and endovascular intervention, right kidney function could be salvaged partially. This case report should encourage clinicians to enforce immediate radiological intervention, especially in the patient at risk. Even if diagnostic procedures are delayed, radiological intervention should be taken into account.

**PUB349**

New Genetic Variant of ADPKD-2

Tetiana Litvinchuk, Tetyana L. Vasylyeva. Pediatrics, TTUHSC, Amarillo, TX.

Background: ADPKD is an autosomal dominant renal cyst disorder due to mutations in genes coding for polycystin-1 (PKD1), on ch 16p13.3) and polycystin-2 (PKD2, on ch 4q13-23), and PKD3 gene (gene unmapped). It is also associated with TSC2/PKD1 contiguous genes coding for polycystin1 (PKD1, on ch 16p13.3) and polycystin 2 (PKD2, on ch 4q13-23), and PKD3 gene syndrome. ADPKD is usually inherited but new mutations without a family history have been reported worldwide, and of those 3, only 2 reported in the U.S.

Methods: Two cases of B1bosom of myeloma were reported in the literature. We are presenting two cases of successful therapy with MMF after failure of CF were reported. Based on our findings, GPS should be considered in the differential diagnosis of nephrotic syndrome with pulmonary involvement and additional study is needed to validate MMF as a therapeutic option.

Conclusions: A smaller number of patients have a defect in the PKD2 locus on chromosome 4 (resulting in PKD2 disease) and a few families have an undefined defect. There are not known published cases on this genetic variant of ADPKD2 cystic kidney disease. In this case the disease is present unusually early in life.

**PUB350**

A Case of Cardiac Tamponade and Proteinuria: Is There an Etiological Relationship? Vasanth Balaraman, Shyam Ravisanankar, Robert D. Zenberg. Dept of Medicine, Saint Barnabas Medical Center, Livingston, NJ.

Background: Cardiac tamponade, as a cause of proteinuria has not been described in the literature. We demonstrate a temporal relationship between the onset of proteinuria with cardiac tamponade and its resolution subsequent to pericardial window on two occasions in the same patient.

Methods: A 75 year old lady with pancreatic adenocarcinoma was admitted for acute kidney injury and proteinuria. Physical examination was unremarkable. Laboratory data showed serum creatinine of 2.33 mg/dl (baseline creatinine 0.7-1.20 mg/dl) and proteinuria of 300 mg/dl on urinalysis. The spot urine protein to creatinine ratio was 3 gram/g creatinine. On day 3, she developed shortness of breath and palpitations. Echocardiogram showed a large pericardial effusion with early cardiac tamponade. Pericardial window was performed and 500cc of clear fluid was drained. Cytology revealed adenocarcinoma. Serum measurements of her spot urine protein to creatinine ratio decreased from 4.39 to 3.6 to 2.3 to 1.66 g/g creatinine subsequently. Four months after discharge, she was admitted with shortness of breath with albumin creatinine of 100 mg/dl on dipstick. Her proteinuria completely resolved after the pericardial window.

Conclusions: In acute febrile illnesses and subsequent to vigorous exercise, one can see proteinuria related to hemodynamic stress. In Orthostatic proteinuria, Cardiorenal syndrome and Notcracker phenomenon (left renal vein traverses under the superior mesenteric artery and becomes trapped between aorta and superior mesenteric artery), there is increased filip🎉glomerular vasoconstruction, increased glomerular back pressure with increased angiotensin II release and resultant proteinuria. Our case of cardiac tamponade can be categorized within a subset of “Type I” cardio-renal syndrome. Glomerular capillary hemodynamic changes due to renal venous back-pressure and elevated AT-II levels may influence glomerular perselectivity to macromolecules and can evoke proteinuria. The relationship between proteinuria and cardiac tamponade has not been specifically studied to our knowledge and warrants further research.

**PUB351**

Type B Lactic Acidosis in Multiple Myeloma

Luis Daniel Torres, Sreevalli Pariti. Nephrology Dept, Methodist Dallas Medical Center; Dallas, TX.

Background: Type B lactic acidosis is a rare manifestation related to underlying diseases, errors in metabolism, medications, intoxication and rarely in some hematologic malignancies and solid tumors. Only 3 cases of Type B lactic acidosis in multiple myeloma have been reported worldwide, and of those 3, only 2 reported in the U.S.

Methods: 62 year old female who was admitted due to back pain, weakness and difficulty breathing. Upon admission she was found to be volume depleted, with acute kidney injury and hypercalcemia and a type II hypercalciemia and a type II hypercalcemia was diagnosed. Treatment was initiated with aggressive volume expansion and broad spectrum antibiotic. Once her volume status improved and no evidence of infection, lactic acid levels remained high. Bone marrow biopsy showed atypical plasmacytosis consistent with multiple myeloma. During her stay her blood pressure remained normal and responded well to volume expansion with excellent urinary output. No evidence of tissue hypoperfusion was ever showed. She was treated aggressively for her hypercalcemia as well. Days later, once her serum creatinine improved to baseline, chemotherapy was started with bortezomib,dexamethasone and cyclophosphamide. On top of that, zoledronic acid and thiamine was added. It wasn’t until chemotherapy started that her lactic acid levels decreased slowly in the next 3 days from 12.4mmol/L to 4.2mmol/L.

Conclusions: This case illustrates how the high lactic acid levels were not associated with any episode of tissue hypoperfusion or hypotension, and it was more related to high lactic acidemia. Once the patient was ever showed.She was treated aggressively for her hypercalcemia as well. Days later, once her serum creatinine improved to baseline, chemotherapy was started with bortezomib,dexamethasone and cyclophosphamide. On top of that, zoledronic acid and thiamine was added. It wasn’t until chemotherapy started that her lactic acid levels decreased slowly in the next 3 days from 12.4mmol/L to 4.2mmol/L.

**PUB352**

Markedly Nephrotic Rapidly Progressive Glomerulonephritis

Lisa Aimee Hechanova. Nephrology, Loma Linda Univ Medical Center, Loma Linda, CA.

Background: Seronegative pusage-immune glomerulonephritis is much more common than traditionally thought, with an incidence of about 30%, instead of the previously thought 10-15%. Seronegative pusage-immune glomerulonephritis has much more aggressive presentation and worse prognosis than seropositive pusage-immune glomerulonephritis, and it is essential to diagnose and treat early. Herein is presented a severe case of seronegative pusage-immune glomerulonephritis.

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

951A
Methods: A 79-year-old black male with longstanding HTN, DM2, CKD stage 3 presented with several weeks fatigue, malaise, decreased appetite, unintentional 10lbs weight loss, new-onset SOB. On review of his prior labs, his creatinine worsened from his baseline of 2.0mg/dL to 4.2mg/dL over a ten month span, then rapidly progressed from 4.2mg/dL to 14.3mg/dL over a one month span. He was found to have iron deficiency anemia with hemoglobin 7.1. Spot urine protein/creatinine ratio 35.5g/g. SPEP negative, UPEP unable to be obtained due to progression to anuria, immunofluorescence microscopy was negative, skeletal survey with no focal lytic or blastic bony lesions. Anti-GBM negative, CANCA/pANCA negative, hepatitis panel negative, compliment normal. Renal ultrasound showed 11cm kidneys. Renal biopsy showed acute crescentic GN, moderate active chronic tubulointerstitial nephritis, mild to moderate interstitial fibrosis and tubular atrophy. Immunofluorescence was negative, and electron microscopy did not show any electron dense deposits.

Conclusions: Seronegative pauci-immune GN is much more common than thought, with an incidence of about 30%. Age of onset is generally younger: 39.7 ± 17yrs vs 57.6 ± 14yrs with seropositive pauci-immune GN. Only 20% will have constitutional symptoms vs 67% with seropositive pauci-immune GN. Renal failure is more dramatic, and patients generally have a worse renal survival rate. Proteinuria is also more severe with R. T24hr proteinuria >1g vs 2.2g/24hrs in seropositive pauci-immune GN. Thus it is imperative that one be aware of the high proportion of pauci-immune glomerulonephritis which can be seronegative, and be very aggressive about diagnosis and treatment.

PUB353

Hypotremia Associated with Unilateral Hand Weakness and Numbness

Fazeldin Dinyar, Buthayna Dinyar, Merugu Srinivas, Keyvan Ravakhab. Internal Medicine/Nephrology, St. Vincent Medical Center, Cleveland, OH.

Background: The key clinical feature in this case is making the diagnosis of apical lung cancer (Pancoast tumor) in a patient with brachial plexopathy and to recognize the association between SIADH as a paraneoplastic syndrome and non-small cell lung cancer (NSCLC).

Methods: A 62 year old mechanism male presented with 3 months h/o worsening right hand numbness and weakness with difficulty operating machinery at work. He reported anorexia, unintentional weight loss of about 20 lbs over 3 months and mild chronic cough with no fever, night sweats, hemoptysis or dyspnea. He denied neck pain, headaches or dizziness. His vitals were normal with BMI of 17. His grip strength in right hand was 4/5 on a scale of 0-5.

Results: Initial Labs included normal serum sodium of 121mmol/L. R. shoulder and chest x-ray showed R. apical pleural based density suggestive of a soft tissue mass lesion. CT scan and MRI of the chest showed large R. apical superior sulcus pulmonary mass (Pancoast tumor) with extensive spread to proximal R. first and second ribs. No R. parasternal or retrosternal mass. Histopathology revealed a poorly differentiatedImmDSCC. Tumor was staged IV (T3N2M1a). Workup for hyponatremia showed serum osmolality of 254 mOsmol/kg, urine osmolality of 451 mOsmol/kg, and urinary sodium of 69mEq/L. TSH, LFT and cosyntropin stimulation test were all normal. Results were consistent with SIADH. His initial treatment consisted of pain control and fluid restriction. At 4 months follow up, the hyponatremia resolved and reported partial improvement in his right hand weakness.

Conclusions: Tumor-associated SIADH in majority of the cases is caused by small cell lung cancer (NSCLC). NSCLC is shown to be a small proportion for a large proportion of cases reported in the literature. The optimal therapy for SIADH is to treat the underlying malignant disease which may improve this paraneoplastic condition. Although SIADH is rare in NSCLC, careful history and early workup for hyponatremia in patient with weight loss and brachial plexopthy helps early detection and prevent progression of cancer.

PUB354

Lithium Nephropathy Presenting in CKD, DI, and Bilateral Cystic Kidney Disease

Sami Safadi, Vicente E. Torres. Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Lithium is used for the treatment of bipolar disorder. A frequent side effect is renal toxicity. The major biochemical action of lithium is inhibition of glycerol synthase kinase-3, an enzyme that has an important role in the regulation of vasopressin action in the distal collecting ducts.

Lithium nephrotoxicity can be divided into three main categories: nephrogenic diabetes insipidus, acute intoxication, and CKD.

Methods: A 56 y/o male with a past medical history significant for bipolar disorder, hypertension, and obstructive sleep apnea presented to our clinic for a second opinion regarding chronic kidney disease, and bilateral cysts on his kidneys. He was diagnosed with CKD several years ago when a routine laboratory workup revealed a serum creatinine of 1.7 mg/dL. He also had a sub-nephrotic range proteinuria around 1.5 g/m/day. The patient had bipolar disorder and received lithium for 20 years. The dose was adjusted based on his blood levels. His lithium was stopped 16 ago. Exam: The patient was afibrile; his blood pressure was 133/85. He looked comfortable, and his examination was unremarkable. Laboratories: He had an elevated serum creatinine of 2.6 mg/dL with an estimated GFR of 26 mL/minute. His serum sodium was 146 mmol/L. His urine osmolality was low indicating the presence of diabetes insipidus. He has a nephrotic range proteinuria. Imaging: MRI done several years ago showed a diffusely abnormal appearance of the kidneys with numerous tiny cysts throughout both kidneys. The cysts were less than 5 mm in size and more pronounced in the periphery of the kidneys near the corticomedullary junctions.

Conclusions: Nephrogenic DI is the most common adverse effect of lithium. The common defect and non-papillary defect develop within weeks of lithium initiation. After years of lithium exposure, full-blown nephropathy can develop, characterized by decreased GFR and CKD.

PUB355

Familial Hyperkalemia


Background: We present a case of hyperkalemia of undiagnosed etiology requiring multiple unwarranted admissions prior to his presentation to our institution.

Methods: A 22 year old man was referred for an incident serum potassium (K) of 7.7 mmol/L. He denied musculoskeletal symptoms, palpitations, high K intake, medication use, strenuous activity, or constipation. Family history: hyperkalemia in maternal grandmother, great-aunt, and uncle. Evaluation: Serum Na 137 mmol/L, K 6.8 mmol/L (non-hemolyzed), Cl 110 mmol/L, bicarbonate 23 mg/dL, creatinine 0.93 mg/dL, glucose 108 mg/dL. EKG: no peaked T waves. Physical exam: fibribolic; blood pressure 124/66 mmHg, heart rate 80 bpm. Well-nourished and developed, comfortable, moist oral mucosa. Heart, lungs, abdomen, extremities were unremarkable. Familial hyperkalemia due to K leakage from red blood cells with cooling to or below room temperature was ruled out (serial K measurements with blood cooling). Subsequent evaluation: urine transtubular potassium gradient: 3.3, random urine K concentrations of 17.8 mmol/L and 5.5 mmol/L with corresponding serum K of 5.7 and 5.6 mmol/L respectively on 2 different days. Blood gas consistent with non-gap metabolic acidosis. Hyperkalemia was suspected to be due to reduced K excretion and possible causes: inhibition of the Na epithelial channel (ENaC), hypokalodosteronism or pseudohyopaldosteronism, reduced ROMK activity and/or expression, or urinary stasis. Investigation for medication induced inhibition of ENaC, aldosterone, and ROMK was negative. Kidney, bladder ultrasound: no obstruction or retention. Plasma renin activity: 0.35 ng/mL/hr (range 0.23-5.82), aldosterone: 7 ng/dL. Both were considered low in the presence of hyperkalemia. Relative hyperinon hypaldosteronism was entertained. Patient responded minimally to a trial of fluoridecontines and high salt intake (K 5.7-5.8 mmol/L), but markedly to hydrochlorothiazide (K 4.7-4.8 mmol/L).

Conclusions: Our evaluation suggested Gordon’s syndrome, likely due to WNK1 or WNK4 mutations. A systematic approach to the evaluation of hyperkalemia can lead to the correct diagnosis and treatment, hence avoidance of unnecessary hospitalizations.

PUB356

Spontaneous Clearance of Hepatitis B Surface Antigenemia in a Chronic Hemodialysis Patient

Chimmay P. Patel, Divya Monga, Mohini Alexander, John D. Wagner, Joseph Mattana.

Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY; Nephrology, Winthrop Univ Hospital, Mineola, NY.

Background: Hepatitis B virus (HBV) infection is a substantial global health problem. For a variety of reasons, patients with end stage renal disease (ESRD) on hemodialysis (HD) are at increased risk of acquiring HBV. Because of cellular immunity disturbances, clearance of HBsAg is an unusual event in a HD patient with chronic HBV infection. We report a patient who was HBsAg positive for 9 years and then spontaneously seroconverted and offer a hypothesis for its occurrence.

Methods: A 62-year-old woman with ESRD from diabetic nephropathy was started on HD and found to be HBsAg positive. Her anti-HBs was negative and liver enzymes were in the normal range. She underwent arterio-venous graft (AVG) placement and developed multiple episodes of thrombosis requiring revisions. Two years after starting dialysis she developed staphylococcal bacteria due to infection of the AVG site. She received antibiotic therapy and underwent partial excision of the AVG. Cultures from the excised AVG revealed Staphylococcus aureus and Pseudomonas aeruginosa. Patient subsequently developed multiple episodes of AVG infection requiring aggressive antibiotic therapy. After approximately 10 years of starting HD, her HBsAg testing came back negative for the first time. Her anti-HBc was positive, anti-HBs was negative, HBsAg was negative, anti-HBe was positive, HBV DNA PCR was <60 IU/mL and anti-HCV was negative. Two years later her anti-HBs titer became positive at >100 and after 4 years her HBsAg has continued to remain negative.

PUB357

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

952A
Transplant Artery Stenosis Causing Hypertension and Acute Renal Failure Without Biopsy Evidence of Acute Tubular Necrosis Talal K. Mahmod, Iasmina Craici, Kenneth E. Kokko, Steven Wagner. Internal Medicine Nephrology, Univer of Mississippi Medical Center, Jackson, MS.

Background: Transplant artery stenosis (TRAS) is a potentially treatable and reversible cause of post-transplant hypertension and allograft dysfunction. It generally occurs months to 2 years post-transplant, and its prevalence varies from 1-23% depending on the diagnostic criteria and technique used. Renal hyperperfusion & renin-angiotensin system activation lead to ischemia & fluid retention.

Methods: A 50-year-old African American male with ESRD secondary to hypertension and type II diabetes underwent deceased donor ECD kidney transplant. Post transplant, he was complicated by delayed graft function before achieving a nadir creatinine of 2.3. He was admitted 4 months post-transplant with hypertension, emergency volume overload & acute kidney injury (BUN 55, Creatinine 3.7). He was also noted to have pancytopenia (WBC 3.8, Hb 8.4, PLT 75). Transplant renal ultrasound showed turbulent flow at the anastomosis. Allograft biopsy showed evidence of atypical thrombotic microangiopathy, including amorphous material in the glomerular capillaries, without significant evidence of acute tubular necrosis. He failed therapy with plasma exchange and was noted to have continued decline in renal function with degenerative oliguria. Dialysis was initiated secondary to hyperkalemia & volume overload. Repeat allograft biopsy showed no significant abnormality, and previously noted amorphous material in the glomerular capillaries was no longer present. Repeat ultrasound again showed turbulent flow in the region of anastomosis concerning for kinking. He underwent renal artery angiogram, angioplasty, and stent placement. Urine output increased immediately after the procedure and renal function started to improve without the need for further dialysis. Nine months after transplant, his creatinine is 1.85 and hypertension is well controlled with clonidine, metoprolol, and nifedipine.

Conclusions: This case illustrates that TRAS can cause severe allograft dysfunction requiring dialysis without biopsy evidence of acute tubular necrosis, and that timely intervention can lead to complete recovery of renal function.

Renal Failure in an Adult Niemann-Pick Disease Type E Cailian Cheng, Zhenda Zheng, Chenggang Shi, Xun Liu, Wenbo Zhao, Tan-qi Lou. Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China.

Background: Niemann-Pick (NP) disease is an autosomal recessive lipid-storage disorder. At least five forms (types A to E) of NP disease have been identified. However, NP disease type E is uncommon and seldom reported.

Methods: A 43-year-old woman was admitted to our hospital complaining of abdominal distension, weakness, and anorexia with a weight loss of 5 kg in a month. Laboratory findings revealed hemoglobin was 9.5 g/dl. All autoimmunity markers were negative. HIV and hepatitis B and C serologies were negative. Alanine transaminase and aspartate aminotransferase were normal. Laboratory tests confirmed glomerulopathy with renal failure, with serum creatin 3.7 mg/dL, serum albumin 31 g/L, proteinuria 2.5 g/24 h, and hematuria 20000 RBC/µl. Abdominal ultrasonography showed parenchyma of the liver and renal cortex showed diffuse increased echogenicity with the paraumbilical vein open and large amounts of ascites. Microscopic study of a kidney biopsy identified widespread cytoplasmic vacuolation of endothelial and visceral epithelial cells in the glomeruli. Widespread vascular degeneration, focal dissolution and degeneration in the proximal convoluted tubule, protein casts, and interstitial diffused foam cells were observed, but chronic changes such as interstitial fibrosis or tubular atrophy were absent. Inflammatory cell infiltration was not seen. Electron microscopy showed massive lipidic deposits in endothelial cells and podocytes. Liver biopsy showed widespread foam cells. Bone marrow examination identified the presence of NP cells. Acid sphingomyelinase activity was normal in leukocytes and chitotriosidase activity was moderately elevated at 768.7 µmol/L/h. Albumin, erythropoietin, and vitamins were administered. Atheroembolic renal disease was suspected, and cerebral magnetic resonance imaging (MRI) was performed to rule out intracerebral hemorrhage. MRI was normal. Additional laboratory studies revealed serum osmolality 262mOsm/kg, serum creatinine 0.63mg/dL, urine sodium 127mEq/L and urine osmolality 459mOsm/kg. Serum thyroin-stimulating hormone and cortisol levels were normal. The findings were felt to be most consistent with SAAH. Intravenous sodium bicarbonate was discontinued. He was placed on a 1L fluid restriction and furosemide 20mg daily was started. Over the next 2 days the serum sodium improved to 124 mEq/L and nausea resolved. Two days later, serum sodium was 129mEq/L.

Conclusions: The time-related onset of SAAH following administration of IT MTX in this patient supports IT MTX as a possible cause of this syndrome. The diagnosis of lymphoma-related SAAH is less likely given the near resolution of CNS lesions on MRI, absence of hyponatremia on admission, and onset of hyponatremia following chemotherapy administration. Close monitoring of the serum sodium level in patients receiving IT MTX is therefore warranted, particularly when administered in conjunction with intravenous hydration.

Hypoaetremia due to the Syndrome of Inappropiatate Antidiuretic Hormone (SIADH) following Administration of Intrathecal Methotrexate (IT MTX) Fernanda Payaro Schobert, Gerald A. Hladik. Nephrology, Univ of North Carolina, Chapel Hill, NC.

Background: IT MTX has been routinely used in treatment of primary central nervous system (CNS) lymphoma, leptomeningeal metastatic disease, and CNS prophylaxis in patients with non-CNS lymphoma. This case illustrates a possible link between IT MTX and SIADH.

Methods: A 50 year old man with diffuse large B-Cell lymphoma with CNS involvement was treated with IT MTX and Rituximab. He completed 2 of 6 cycles without complications and MRI of the brain showed response to treatment with decreased size and near resolution of CNS lesions. During the third cycle of therapy he was noted to develop acute hyponatremia. Serum sodium was 135mEq/L on admission. IT MTX was administered on day 4, which was followed by a fall in serum sodium from 133 mEq/L on day 5 to 120mEq/L on day 6. Notably, he had been receiving intravenous sodium bicarbonate to decrease the risk of MTX nephrotoxicity. He endorsed nausea, but had no other complaints. On physical examination he was alert and oriented. Blood pressure was 126/74 with no postural changes. There was no edema. Urinalysis was normal. Additional laboratory studies revealed serum osmolality 262mOsm/kg, serum creatinine 0.63mg/dL, urine sodium 127mEq/L and urine osmolality 459mOsm/kg. Serum thyroin-stimulating hormone and cortisol levels were normal. The findings were felt to be most consistent with SAAH. Intravenous sodium bicarbonate was discontinued. He was placed on a 1L fluid restriction and furosemide 20mg daily was started. Over the next 2 days the serum sodium improved to 124 mEq/L and nausea resolved. Two days later, serum sodium was 129mEq/L.

Conclusions: The time-related onset of SAAH following administration of IT MTX in this patient supports IT MTX as a possible cause of this syndrome. The diagnosis of lymphoma-related SIADH is less likely given the near resolution of CNS lesions on MRI, absence of hyponatremia on admission, and onset of hyponatremia following chemotherapy administration. Close monitoring of the serum sodium level in patients receiving IT MTX is therefore warranted, particularly when administered in conjunction with intravenous hydration.
nephritis and atheroembolic renal disease. The patient’s renal function progressed to a creatinine of 5.3 mg/dl in which renal function stabilized to 2.0-2.7 mg/dl with eGFR ~35 ml/min. She was treated with SLR and two cycles of steroids before commencement with cyclophosphamide and rituximab. Her vital sign was stable at the time of visiting. Her hemoglobin level and platelet count declined from 11.6 to 7.5 g/dl and from 1.3 x 10^11/L to 1.6 x 10^11/L within 5 weeks. Her absolute neutrophil count decreased from 3.85 x 10^9 to 1.89 x 10^9/L after hospitalization. Bone marrow revealed less than 50% of the erythroid and granulocytic precursors and megakaryocytes are markedly decreased in number. She was diagnosed with severe AA. Her serum anti-DNA antibody level fell from ~50 at the diagnosis of SLE to 23.27 IU/mL. After diagnosis with AA, she had gotten treatment with 5 times of cyclophosphamide and 1 time of steroid pulse. During the course of treatment with maintenance low dose prednisolone, her white blood cell and platelet counts have been normal and hemoglobin level was maintained between 9.5 and 11.5 g/dl with erythropoiesis stimulating agent (ESA).

Conclusions: Although severe AA is rarely developed in patients with SLERD due to lupus nephritis whose lupus activity fell over 50%, the patient successfully treated with formal immunosuppressive therapy of AA with cyclophosphamide. We do not hesitate to evaluate bone marrow study if anemia is acutely aggravated or poorly responded to ESA with cyclophosphamide. The significant linear changes in ESRD patients due to lupus nephritis even though their lupus activity is low.

Methods: A 26-year-old woman who has maintained continuous ambulatory peritoneal dialysis since 2 years ago visited our outpatient clinic because of general weakness. She was diagnosed with SLE in 2010 and started with cyclophosphamide and rituximab. Her vital sign was stable at the time of visiting. Her hemoglobin level and platelet count declined from 11.6 to 7.5 g/dl and from 1.3 x 10^11/L to 1.6 x 10^11/L within 5 weeks. Her absolute neutrophil count decreased from 3.85 x 10^9 to 1.89 x 10^9/L after hospitalization. Bone marrow revealed less than 50% of the erythroid and granulocytic precursors and megakaryocytes are markedly decreased in number. She was diagnosed with severe AA. Her serum anti-DNA antibody level fell from ~50 at the diagnosis of SLE to 23.27 IU/mL. After diagnosis with AA, she had gotten treatment with 5 times of cyclophosphamide and 1 time of steroid pulse. During the course of treatment with maintenance low dose prednisolone, her white blood cell and platelet counts have been normal and hemoglobin level was maintained between 9.5 and 11.5 g/dl with erythropoiesis stimulating agent (ESA).

Conclusions: Although severe AA is rarely developed in patients with SLERD due to lupus nephritis whose lupus activity fell over 50%, the patient successfully treated with formal immunosuppressive therapy of AA with cyclophosphamide. We do not hesitate to evaluate bone marrow study if anemia is acutely aggravated or poorly responded to ESA with cyclophosphamide. The significant linear changes in ESRD patients due to lupus nephritis even though their lupus activity is low.

Methods: A 26-year-old woman who has maintained continuous ambulatory peritoneal dialysis since 2 years ago visited our outpatient clinic because of general weakness. She was diagnosed with SLE in 2010 and started with cyclophosphamide and rituximab. Her vital sign was stable at the time of visiting. Her hemoglobin level and platelet count declined from 11.6 to 7.5 g/dl and from 1.3 x 10^11/L to 1.6 x 10^11/L within 5 weeks. Her absolute neutrophil count decreased from 3.85 x 10^9 to 1.89 x 10^9/L after hospitalization. Bone marrow revealed less than 50% of the erythroid and granulocytic precursors and megakaryocytes are markedly decreased in number. She was diagnosed with severe AA. Her serum anti-DNA antibody level fell from ~50 at the diagnosis of SLE to 23.27 IU/mL. After diagnosis with AA, she had gotten treatment with 5 times of cyclophosphamide and 1 time of steroid pulse. During the course of treatment with maintenance low dose prednisolone, her white blood cell and platelet counts have been normal and hemoglobin level was maintained between 9.5 and 11.5 g/dl with erythropoiesis stimulating agent (ESA).

Conclusions: Although severe AA is rarely developed in patients with SLERD due to lupus nephritis whose lupus activity fell over 50%, the patient successfully treated with formal immunosuppressive therapy of AA with cyclophosphamide. We do not hesitate to evaluate bone marrow study if anemia is acutely aggravated or poorly responded to ESA with cyclophosphamide. The significant linear changes in ESRD patients due to lupus nephritis even though their lupus activity is low.

Methods: A 26-year-old woman who has maintained continuous ambulatory peritoneal dialysis since 2 years ago visited our outpatient clinic because of general weakness. She was diagnosed with SLE in 2010 and started with cyclophosphamide and rituximab. Her vital sign was stable at the time of visiting. Her hemoglobin level and platelet count declined from 11.6 to 7.5 g/dl and from 1.3 x 10^11/L to 1.6 x 10^11/L within 5 weeks. Her absolute neutrophil count decreased from 3.85 x 10^9 to 1.89 x 10^9/L after hospitalization. Bone marrow revealed less than 50% of the erythroid and granulocytic precursors and megakaryocytes are markedly decreased in number. She was diagnosed with severe AA. Her serum anti-DNA antibody level fell from ~50 at the diagnosis of SLE to 23.27 IU/mL. After diagnosis with AA, she had gotten treatment with 5 times of cyclophosphamide and 1 time of steroid pulse. During the course of treatment with maintenance low dose prednisolone, her white blood cell and platelet counts have been normal and hemoglobin level was maintained between 9.5 and 11.5 g/dl with erythropoiesis stimulating agent (ESA).

Conclusions: Although severe AA is rarely developed in patients with SLERD due to lupus nephritis whose lupus activity fell over 50%, the patient successfully treated with formal immunosuppressive therapy of AA with cyclophosphamide. We do not hesitate to evaluate bone marrow study if anemia is acutely aggravated or poorly responded to ESA with cyclophosphamide. The significant linear changes in ESRD patients due to lupus nephritis even though their lupus activity is low.
Long-Term Intravenous Vancomycin Hydrochloride Induced Erythema

Eleni Cheiloti,1 Maria Sotiraki,1 Alexia Papalexandrou,1 Evangelia Gikalitsiou,1 Evdokia Efthimiou,1 Kassiani Manoloudaki,1 Maria Tsilivigou.1 1Dept of Nephrology; General Hospital of Piraeus, Athens, Greece; 2Dept of Pathology, General Hospital of Piraeus, Athens, Greece.

Background: Erythema on face and on upper body (red neck or red man syndrome), with hyponatremia and flushing is reported as an adverse reaction on intravenous (iv) Vancomycin Hydrochloride (VAN-HCL). It is often associated with rapid infusion of the first dose and 94% of patients are undergoing treatment less than a month. We report a case of a generalized erythema due to iv VAN-HCL.

Methods: A 72-years-old man with a history of chronic kidney disease and long-term intravenous catheter due to prostatic hypertrophy presented in an urticlear state that necessitated urgent initiation of dialysis treatment. After few hemodialysis sessions, his renal function was improved. The patient experienced fever and presented recurrent urinary tract infections due to Escherichia coli. The patient was treated with cephalosporin parenteral antibiotics. On blood culture, Staphylococcus epidermidis, haemolyticus and capitus were treated by iv VAN-HCL.

Results: A clinical condition remained critical and in more than a month the symptoms were not improved. A serological test for Hepatitis B, Hepatitis C, was normal. Patient was started on oral prednisone for 6-8 weeks with further tapering. The patient sCr gradually improved with subsequently serum creatinine concentration levelled off at 1.2 mg/dl.

Conclusions: The pathogenesis of omeprazole-associated AIN is unclear and may be related to the involvement of both humoral and cellular immune mechanisms. Physicians should be aware of this disorder. Accurate and timely diagnosis and withdrawal of the offending drug can prevent potentially life-threatening renal failure.

Belatacept for Kidney Transplant Recipients with Baseline Low Blood Pressure: A New Indication?


Background: Calcineurin inhibitors (CNI) are the mainstay of immunosuppressive medications in transplantation. Unfortunately, acute tubular injury secondary to their vasocorticinhibitory properties is a common phenomenon. This may be particularly severe in kidney transplant recipients with low blood pressures, an identified risk factor for primary non-function (Webber et al. Transplantation 2005;93:54-60). Belatacept (CTLA-4-Ig fusion protein) is being evaluated as a CNI sparing agent in kidney transplant recipients. We report a case of a kidney transplant recipient with acute tubular injury attributed to tacrolimus therapy.

Methods: A 64yr old male with history of schizophrenia, non-compliant with antipsychotics, presented with altered mental status for 3 days. In addition to poor memory and inability to care for himself, he was also noted to be drinking large quantities of water. He was admitted 2 months prior for acute confusion with severe hyponatremia secondary to massive water ingestion. On initial evaluation, patient was awake but disoriented, dehydrated, and hemodynamically stable. Laboratory evaluation was significant for serum Na 120 meq/L, serum osmolality 250 mOsm/kg, BUN 11, and Cr 1.2. Thyroid and cortisol studies were unremarkable. Urine osm was found to be 157, with UNa of 18. Review of labs from prior admission revealed serum Na of 107meq/L with a corresponding Uosm of 229 mOsm/kg.

Results: Unfortunately, our patient became septicemic and died on month after onset.

Conclusions: The incidence of CNI-associated acute tubular injury is widely under-recognized. Belatacept conversion may be a novel approach for kidney transplant recipients with low mean arterial blood pressures and particularly sensitive to CNI-associated vasoconstriction and consequent renal injury.

Omeprazole-Induced Acute Tubulo-Interstitial Nephritis

Rakesh Malhotra,1 Srujana Polsani,1 Anjali Acharya,2 Zaher Hamadeh.1 1UMDNJ; 2Jacobi Medical Center.

Background: Proton pump inhibitors (PPIs) are widely prescribed to treat acid-related gastrointestinal disorders. We report a case of reversible acute renal failure due to acute tubulointerstitial nephritis (AIN), confirmed by histology of a renal biopsy, associated with taking omeprazole.

Methods: A 70-year-old female presented with complain of generalized weakness and fatigue for 2 months. She had a past medical history for HTN, diabetes, and CKD (baseline sCr 1.6 mg/dL). Physical examination revealed pale conjunctiva. There was no pedal edema, skin rash, petechiae or purpura. Labs revealed elevated BUN of 55 mg/dL and sCr of 2.4 mg/dL. Her Hb was 11g/dL. Urinalysis revealed proteinuria and eosinophilia. Complements were normal. Serological markers for Hep B, Hep C, and HIV were negative, and no cryoglobulins were detected. Renal ultrasonography was normal. Patient was started on IV fluids however her sCr kept worsening with peak sCr of 4.1 mg/dL. Nephrology consult was obtained and kidney biopsy performed. Biopsy showed interstitial inflammation with active tubulitis and acute tubular injury. Biopsy also showed chronic features including interstitial fibrosis and tubular atrophy. Overall, findings were consistent with severe interstitial nephritis. The patient had initiated treatment with omeprazole 3 months prior to admission. Omeprazole was discontinued in view of the diagnosis of AIN. Patient was started on oral prednisone for 6-8 weeks with further tapering. The patient sCr gradually improved with subsequently serum creatinine concentration levelled off at 1.2 mg/dL.

Conclusions: Reset osmostat is a variant of the SIADH marked by disordered ADH regulation. ADH levels can be maximally suppressed at a basal hyponatremic state, but rise quickly with serum sodium long before the hyponatremia is corrected. As shown in Figure 1, this patient demonstrated an ability to maximally dilute the urine when his serum sodium reaches a value of 107 meq/L, but ADH levels quickly rise as serum sodium levels approach 120 meq/L. The end result is a persistent hyponatremic state.
An Overlooked Entity: Warfarin Related Nephropathy – A Case Report

Manjunath Kottalgi, Pragnesh J. Patel, Amber S. Podoll, Kevin W. Finkel.

Crescentic IgAN is a devastating manifestation that can cause graft failure. Early recognition with cyclophosphamide appears to be effective with response similar to native IgAN. From our institution suggest steroid free regimen and sirolimus may increase risk. Treatment disease a 3rd biopsy was done and showed crescentic IgAN. Graft function returned to developing ESRD due to IgAN. Induction therapy included ATG, steroids (5 days) and al. The incidence, population at risk and outcomes has been described recently by Brodsky et al in a prospective study[3]. Warfarin-related nephropathy has been an overlooked entity; but it can have a significant impact on morbidity and mortality, more so in patients with chronic kidney disease[3].

Methods: A 68 year old female was recently started on warfarin anticoagulation for an acute pulmonary embolism one week prior to presentation. On readmission, she complained of fatigue, tremors of hands, decreasing urine output and dysuria. She denied any fever, chills, nausea, vomiting, abdominal pain, hematuria, prior history of renal disease or use of NSAIDS. She was initially hypoglycemic. She had an acute rise in her serum creatinine from 0.8 mg/dl to 8.0 mg/dl along with a correlated rise in INR from 1.11 to 5.67 over 9 days. She was oliguric at presentation with urine output of 20ml/hr. Urine analysis showed 6 rbcs/hpf, 42 wbcs/hpf, moderate blood, mild proteinuria. Urine culture was negative. Biopsy was deferred due to coagulopathy. Subsequently along with correction of INR with vitamin K, her renal functions improved over the course of 7 days to a creatinine of 1.7mg/dl and eGFR of 31ml/min/1.73m2 at discharge. She never required renal replacement therapy.

Results: Considering the large population on warfarin therapy clinicians should have a heightened awareness of this entity. This calls for a larger prospective study to identify at risk populations, guidelines to monitor renal functions while being treated with warfarin, precautions and therapies to minimize the risk of warfarin-related nephropathy.

Conclusions: We report a case of crescentic IgAN in a renal allograft successfully treated with oral cyclophosphamide. Crescentic IgAN in the renal allograft is rare. Reports from our institution suggest steroid free regimen and sirolimus may increase risk. Treatment with cyclophosphamide appears to be effective with response similar to native IgAN. Crescentic IgAN is a devastating manifestation that can cause graft failure. Early recognition and aggressive treatment provides the best chance for graft survival.

Crescentic IgA Nephropathy (IgAN) in the Renal Allograft: A Case Report

Shashikant Patel, Samir Parikh, Jon R. Von Visger. Dept of Nephrology, The Ohio State Univ Medical Center, Columbus, OH.

Background: Aggressive IgAN is rare in the renal allograft. We report a case of recurrent IgAN that manifested as a necrotizing and crescentic glomerulonephritis (GN).

Methods: 31 year old male received deceased donor renal transplant (Tx) after developing ESRD due to IgAN. Induction therapy included ATG, steroids (5 days) and sirolimus. Nine months after Tx he developed acute cellular and antibody mediated rejection with mild IgA staining which improved with steroids. Graft function again worsened and repeat biopsy showed crescentic GN but no IgA. Therapy was started but due to worsening disease a 3rd biopsy was done and showed crescentic IgAN. Graft function returned to baseline after treatment with oral cyclophosphamide and steroids.

Conclusions: We report a case of crescentic IgAN in a renal allograft successfully treated with oral cyclophosphamide. Crescentic IgAN in the renal allograft is rare. Reports from our institution suggest steroid free regimen and sirolimus may increase risk. Treatment with cyclophosphamide appears to be effective with response similar to native IgAN. Crescentic IgAN is a devastating manifestation that can cause graft failure. Early recognition and aggressive treatment provides the best chance for graft survival.

Multiple Brown Tumors as a Complication of Hyperparathyroidism in a Patient with Chronic Kidney Disease

Guilherme Fonseca Mendes, Talita Mourao Chaves Corrca, Talita Cardoso Proenca, Tatiana Santos, Maria izabel Neves de Holanda Barbosa, Luiz Fernando Christiansi. Nephrology, Hospital Federal de Bonsucorso, Rio de Janeiro, Brazil.

Background: Brown tumors are benign lesions with mass effect and intense osteoclastic activity caused by primary or secondary hyperparathyroidism. It is observed in 1.5-13% of secondary hyperparathyroidism. This should be managed with active Vitamin D and calcimimetics to avoid serious complications.

Methods: We report a case of a 42yo african-american female patient referred to our department for evaluation of hyperparathyroidism and chronic kidney disease managed by hemodialysis for 12 years. She was using calcitriol 3mcg 3x/week and Calcium 2g/day. Due to history of multiple kidney stones leading to left side nephrectomy, we considered the diagnosis of primary hyperparathyroidism. The physical exam was relevant for several deformities, especially left eye proptosis, chest enlargement and phalanx resorption. On chest x-ray was seen multiple masses close to chest wall; the skull, chest and spine CT performed showed multiple infiltrating lesions in ribs, severe spinal compression and orbital tumor.

The 99TC parathyroid scintigraphy evidence two hypercaptating areas, suggesting hyperplasia. Laboratory workup was relevant for: PTH: 1771 pg/ml; ALP: 1318 U/L; P: 4.6 mg/dl; Ca: 8.8 mg/dl. She underwent total parathyroidectomy with subcutaneous implant, improving significantly her quality of life and laboratory findings. The brown tumors still, but are being followed with CT and had no reduction in 4 months.

Conclusions: Several complications may be associated with hyperparathyroidism. In this patient, the lack of an early diagnosis and the development of chronic kidney disease contributed to this level of deformity. Thus, hyperparathyroidism, either primary or secondary, must be controlled aggressively to avoid this level of complication.

Posterior Reversible Encephalopathy Syndrome in an Adult Patient with Thrombotic Microangiopathy and Diffuse Alveolar Hemorrhage

Zhongguang Yang, John Doran, Titilayo O. Ilori. Nephrology, Emory Univ School of Medicine, Atlanta, GA.

Background: Posterior reversible encephalopathy syndrome (PRES) is a neurologic condition characterized by headache, altered consciousness, seizures, and cortical visual loss with typical MRI features. Its pathogenesis is unclear. Renal failure and hypertension
PUB376

Disseminated Primary Varicella Infection in Adult Renal Transplant Patient

Ramanandeep S. Bang, Maria Aurora C. Posadas, Dannah Wray, Tittu Srinivas. MUSC.

Background: Immunosuppressed patients are susceptible to disseminated varicella (VZV) due to impaired cell-mediated immunity. We present a case of primary varicella in an adult patient with kidney transplant.

Methods: A 37 year old African-American male who received a cadaveric renal transplant 3 years ago presented with rash. His maintenance immunosuppression included tacrolimus, mycophenolate mofetil (MMF), and prednisone. He denied any history of atypical HUS and thrombotic thrombocytopenic purpura. We believe our patient may have atypical HUS secondary to mutations in the complement pathway, genetic testing was not done. VZV, steroids and uncontrolled hypertension might also be causative factors for PRES. VZV may also cause water toxicity; corticosteroids may lead to hypertension and fluid overload. Early recognition and intervention with aggressive antihypertensive therapy and hemodialysis will improve outcome and avoid permanent brain injury and sequelae.

Conclusions: Since the introduction of Varicella vaccine in 1995, only approximately 2-4% of adult solid organ transplant (SOT) recipients are seronegative for VZV and therefore susceptible to primary varicella infection. Currently, there are no guidelines for using varicella vaccine in patients with end-stage renal disease. Early diagnosis and aggressive treatment with acyclovir effectively alters the clinical course and could save life. Varicella vaccination has been shown to reduce morbidity in VZV seronegative recipients and should be considered in ESRD patients anticipating kidney transplant. VZV seronegative transplant patients should also be counseled on precautions to take to reduce the risk of disease transmission from recently vaccinated or infected contacts.

PUB387

Subclinical Transient Immune-Complex Mediated Glomerulonephritis in Living Donor Kidney

Manpreet Singh, Jean M. Francis, Sandeep Ghai. Renal Section, Boston Univ School of Medicine, Boston, MA.

Background: Kidney transplantation is the best available therapy for patients with end-stage renal disease (ESRD) with live kidney donation having better long-term outcomes. Selection criteria for live donors should be very strict to prevent any long-term complications after kidney donation. We report a case of young living donor with transient immune complex (IC) mediated glomerulonephritis (GN) noted as an incidental finding on zero time allograft biopsy. We emphasize the importance of a systematic approach to donor evaluation.

Methods: A 31 year old female donated a kidney to her father who has ERSD from diabetic nephropathy. She has a history of well controlled skin psoriasis. She was deemed a good candidate by rheumatology with a negative workup. Her workup was completely normal, importantly she had two normal UA without proteinuria and hematuria and two 24-urine collections with normal creatinine clearance and normal proteinuria. Her physical Exam was unremarkable. A zero time biopsy was performed per our protocol which showed diffuse mild tubulointerstitial hyperplasia and proteinuria of 2+ and 3+ on protein stains. There were mild chronic changes and a focal finding of IC deposits predominantly distributed in the mesangium with immune-fluorescence positive for C3, IgM, trace IgA and IgG. A repeat biopsy 6 months after transplant, which showed persistence of the immune deposits. Both donor and recipient remain totally asymptomatic.

Conclusions: Despite the extensive workup performed in our patient to rule out the possibility of any potential kidney disease, her glomerular lesion remained silent and subclinical. Our patient likely had a transient IC mediated (GN) in the setting of a skin infection prior to kidney donation. Her skin infection was successfully treated, and she continues to do well without any serologic evidence of any disease process, and her kidney function remains normal without proteinuria and hematuria. This case underlines that a complete and thorough evaluation remains a difficult process. A systematic approach should be used on a case by case basis and follow up of all donors should be regimented.

PUB387

Overlapping Syndrome of ANCA Vasculitis and Lupus Nephritis

Noelle C. Juarez, Paramita Mukherjee. Div of Nephrology, Univ of Washington, Seattle, WA.

Background: ANCA associated vasculitis is rarely seen to occur simultaneously with lupus nephritis (LN). We present a case of an elderly man with no prior history of kidney disease, who presented with general malaise and acute kidney injury and was found to have lupus nephritis and ANCA related vasculitis concurrently.

Methods: 73 year old Caucasian man with known hypertension presented to his primary care doctor with anorexia, nausea and vomiting over 2 weeks and 30 pound weight loss over last 1 year. He had no prior history of kidney disease. Physical exam was remarkable only for a blood pressure of 143/83. Initial workup showed blood urea nitrogen of 118 mg/dL and creatinine of 10.9 mg/dL. His creatinine 1 year back was normal. Urinalysis was notable for 3+ blood and 3+ protein. Numerous monomorphic red blood cells (RBC) and few dysmorphic RBC were seen on urine sediment. Urine protein to creatinine ratio was 1.5 grams/gram, C3 was low at 75 mg/dL, C4 was normal, cryoglobulins, hepatitis and human immunodeficiency virus serologies were negative. Autoimmune workup revealed positive ANA, p-ANCA positive at 1:320 and myeloperoxidase autoantibodies at >100, and myeloperoxidase positive with fluorescence positive for C3, IgM, trace IgA and IgG. A repeat biopsy done on hospital day 6 showed findings consistent with concurrent LN and ANCA vasculitis. Subsequently, he was started on plasmapheresis, cyclophosphamide and pulse dose steroids. He had partial renal recovery and both plasmapheresis and dialysis were stopped after 2 weeks.

Conclusions: Although, cases of concurrent LN and ANCA related vasculitis reported in the literature is very low, their association occurs more frequently than just the coincidental occurrence of unrelated diseases. Both these diseases are mediated by a T helper 1 immune mechanism suggesting a possible pathogenic link. Therefore, it is important to consider both ANCA vasculitis and LN in patients with high suspicion of glomerulonephritis associated with renal failure.

PUB379

The Chronic Kidney Disease Water Intake Trial: Results from a Pilot Study


Background: Evidence from animal and human studies suggests a beneficial effect of increased water intake on kidney function. Prior to conducting a large trial on the effect of increased water intake on kidney function in chronic kidney disease (CKD) patients, we conducted a pilot trial to examine the safety and feasibility of increasing water intake in CKD patients.

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

Underline represents presenting author.

957A
Methods: In this randomized pilot trial, 29 adults with stage 3 CKD were randomly assigned, in a 2:1 ratio, to a hydration intervention (n=18) or control group (n=11). Participants in the hydration group were instructed to drink 1.0 to 1.5 L water per day for 6 weeks (in addition to usual fluid consumption), depending on sex and weight. Patients in the control group were instructed to maintain their current fluid intake. Participants collected 24-h urine samples at baseline, 2- and 6-weeks after randomization.

Results: Participants were an average of 61 years (SD 14), 63% male, and 81% Caucasian; 54% had diabetes and 86% had hypertension. Average eGFR at baseline was 40 mL/min/1.73m^2 (SD 11 mL/min/1.73m^2); the median albumin to creatinine ratio was 19 mg/mmol (IQR: 6-74 mg/mmol). Between baseline and 6-weeks, 24-hour urine volume increased by 0.7 L/d in the hydration group and decreased by 0.3 L/d in the control group (between-group difference in change 0.9 L/d; p = 0.002) (Figure 1). Average plasma sodium was 138 mmol/L in both groups at 6 weeks and remained above 130 mmol/L for all patients at all time points. No changes in electrolytes, osmolality, or eGFR were observed. Health-related quality of life remained similar between groups. No serious adverse events were reported nor observed.

Conclusions: Patients with stage 3 CKD can safely and successfully increase daily water intake up to 1.5 L/day in addition to usual daily fluid intake.

Funding: Pharmaceutical Company Support - Danone Research

PUB380

Uric Acid Lowering in Metabolic Syndrome Patients Utilizing a Phytochemical Approach

Günter Siegel,1 Janine Berkhof,1 Karl Winkler,1 Eugeny Ermliev,1 1CharitéCrossOver, Charité - Univ Clinic Berlin, Berlin, Germany; 2Biomedical Center, Univ of Uppsala, Uppsala, Sweden; 3Institute of Clinical Chemistry, Univ Clein Freiburg, Freiburg, Germany.

Background: As a rule, hyperuricaemia leaves to think of gout, renal insufficiency and/or especially metabolic syndrome (MetS). We sought to determine whether uric acid (URAC) could be lowered in MetS patients by a phytochemical approach. In a 2-month clinical pilot study with Ginkgo biloba (EGb761, 2×120 mg/d) on 11 MetS patients, a novel biomarker spectrum made point-of-care theranostics feasible.

Methods: Photometric methods, ELISAs, EIA, ellipsometry.

Results: The ratio oxLDL/LDL was reduced by 21.0% (p < 0.002), 8-iso-PGF_2α 39.8% (p < 0.002), MPO 29.6% (p = 0.0137), IL-6 12.9% (p = 0.0407), hsCRP 39.3% (p < 0.0049), Lp(a) 26.3% (p < 0.001), MMP-9 32.9% (p < 0.042), HOAIR 14.0% (p = 0.0244), nanoplaque formation 14.3% (p = 0.0077), nanoplaque size 23.4% (p < 0.0004), whereas SOD was augmented 17.7% (p < 0.0095), GPX 11.6% (p < 0.001), cAMP 43.5% (p < 0.001), and cGMP 32.9% (p < 0.001). Since none of the patients had a manifest kidney disease, we evaluated URAC. Fasting morning URAC was reduced by 10.6% (p < 0.0033) from 315.7 to 285.2 μmol/L.

Conclusions: Thus, changes in cytokine pattern and beneficial effects on oxidative stress parameters could unravel diminution of URAC.

Conclusions: Ginkgo had beneficial effects on a multitude of inflammatory, oxidative stress, diabetic and arteriosclerotic biomarkers. URAC reached reference values in all patients. Thus, ginkgo may be used as complementary drug in the treatment of MetS and gout patients.

PUB381

Supplemental Knowledge of an Elevated Creatinine

James Francis Dylewski,1 Christopher Neil Marshall,1 Robert Pursell,2 Internal Medicine, St. Luke’s Univ Hospital and Health Network, Bethlehem, PA; 2Nephrology, St. Luke’s Univ Hospital and Health Network, Bethlehem, PA.

Background: Serum creatinine (Cr) is conventionally used as a surrogate marker to estimate glomerular filtration rate and therefore kidney function. There are many causes for an elevated Cr, but the majority are due to decreased creatinine elimination resulting from kidney injury. However, this is not the only cause.

Methods: A 27-year-old Caucasian male presented for evaluation of flank pain of several days duration. It was found that his Cr was 5.4 mg/dl and BUN 34. The patient denied any urinary symptoms & denied taking any medications including NSAIDs or anabolic steroids. He did, however, relate he was taking arginine & creatine supplements for athletic enhancement. His urinalysis was bland in dip & microscopic examination. His CPK was 184 U/L & tests including CBC, ASO titer, C3, C4, CH50, ANA, HIV antibody, & hepatitis panel were all normal. Additionally, urine drug screen, eosinophils, & myoglobin were also normal. A retroperitoneal ultrasound showed normal sized kidneys without hydrenephrosis, calculi, or masses. CT of the abdomen did not demonstrate any abnormalities. The patient was given intravenous fluids & monitored closely. With discontinuation of the arginine & creatine supplements, his Cr fell significantly to 1.3 mg/dL, which was felt to be his baseline.

Conclusions: Creatine is an endogenous nitrogen based organic acid that is synthesized from arginine & serves as an energy source for skeletal muscles, particularly when phosphorylated. In muscle cells, creatine & creatine phosphate are converted to creatinine as part of degradation. Creatine monoborate is a common supplement used by athletes and is readily oxidized to creatine in the body. Consequently, with large exogenous intake of creatine & arginine, Cr could be elevated. This is a case of a patient who chronically ingested arginine & creatine that developed what appeared to be acute kidney injury from these substances. The supplements were stopped & his Cr improved accordingly. Review of the literature yielded a few cases of similar occurrences with the use of creatine supplements.

PUB382

L-Arginine or L-Citrulline Supplementation Does Not Protect Diabetic Renal Injury

Alan S. Awad,1 Hanning You,1 Ting Gao,1 Timothy K. Cooper,2 Sidney M. Morris.3 1Medicine, Penn State Univ College of Medicine, Hershey, PA; 2Comparative Medicine, Penn State Univ College of Medicine, Hershey, PA; 3Microbiology and Molecular Genetics, Univ of Pittsburgh, Pittsburgh, PA.

Background: Our recent publication showed that pharmacological blockade of arginases confers kidney protection in diabetic nephropathy via a nitric oxide synthase 3 (NOS3)-dependent mechanism. Arginases compete with NOS for the common substrate arginine, Cr could be elevated. This is a case of a patient who chronically ingested arginine & creatine that developed what appeared to be acute kidney injury from these substances. The supplements were stopped & his Cr improved accordingly. Review of the literature yielded a few cases of similar occurrences with the use of creatine supplements.

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

Underline represents presenting author.

958A
Effect of Intradialytic Parenteral Nutrition (IDPN) on Nutrition Status in Hemodialysis Patients
Zvi Barnea, Sara Blumberg Benyamini, Relu Cernes, Biro Alexander, Ze’ev Katzir. Nephrology, Wolfson Medical Center, Holon, Israel.

Background: Malnutrition is common in hemodialysis patients and is associated with an increase in morbidity and mortality. Intradialytic parenteral nutrition (IDPN) has been proposed to improve nutritional status and outcome in malnourished patients. The aim of this study was to evaluate the effect of IDPN in patients suffering from nutrition deterioration.

Methods: We have evaluated nutrition monthly score, based on six biochemical parameters (albumin, creatinine, urea, cholesterol, Kt/V, C-Reactive Protein) and weight change (paper in preparation) in 28 malnourished hemodialysis patients. We calculated the slope of three subsequent monthly scores prior to beginning of IDPN treatment and three months following beginning of treatment. We used paired t test to compare score, slope, and each of the score components before and after three months of IDPN treatment.

Results: In 28 HD patients, three months following beginning of treatment, IDPN treatment showed stopped nutritional deterioration. Average nutrition score was significantly improved. Slope values of three subsequent monthly scores turned positive compared to a negative slope before treatment. IDPN treatment induced a significant increase in albumin, urea and post dialytic weight. Creatinine, cholesterol, CRP, Kt/V were not significantly changed.

Conclusions: IDPN treatment improved nutrition parameters, score and slope of nutrition status, and stopped nutritional deterioration in HD patients.

IDPN385

Effect of an Increased Water Intake in DNA Adducts Formation and Urinary Mutagenicity in Smokers: A Randomised Controlled Trial
Joanigui Jimenez, 1 Inmaculada Buendia Jimenez, 1 Pascaline Richardot, 1 Marc Arnaud, 1 Marianna J. Zamlauski-Tuckier, 1 Pingwei Ye. Physiology & Health Science, Ball State Univ, Muncie, IN.

Background: A previous study reported that mitochondrial GSH levels in kidneys from young rats did not change with dietary supplementation. The present study investigated whether rat age influenced the effect of supplementation with NAC on mitochondrial and cytosolic GSH levels in the kidney.

Methods: Young Experimental (i.e., 3 months of age) and Old Experimental (i.e., 22 months of age) female Lewis rats were given NAC (200 mg/Kg body wt) via intraperitoneal injection for one week. Age-matched Control rats were not given any supplementation. At the end of the treatment period, the kidneys were harvested and separated into cortical and medullary sections. The sections were further separated into cytosolic and mitochondrial fractions by differential centrifugation. GSH levels in the fractions were measured using a spectrophotometric assay. There were 6 to 8 rats in each group and statistical comparisons between similar aged rats were done using a Student’s t-test.

Results: There were significant increases in mitochondrial and cytosolic GSH levels in kidney cortex and medulla from both Young and Old rats.

Conclusions: Rat age does not influence the increase in either mitochondrial or cytosolic GSH levels observed in rat kidneys following exogenous dietary supplementation with NAC.

PUB384

Effect of an Increased Water Intake in DNA Adducts Formation and Urinary Mutagenicity in Smokers: A Randomised Controlled Trial

Young Old

Cytosol

Young Control Experimental Control

Old Control Experimental

Albumin (mg/dL) 7.7 ± 2.0 9.6 ± 0.6 * 7.9 ± 0.5 11.4 ± 0.4 *

Glutathione Disulfide (GSSG) (umol/g kid wet wt) Cortex 5.5 ± 0.4 7.7 ± 0.6 * 5.6 ± 0.6 11.4 ± 0.4 *

Control

Young Control Experimental

Old Control Experimental

Albumin (mg/dL) 5.14 (0.3) 3.35 (0.34) 2.95 (0.8) 0.0001

Cholesterol (mg/dL) 135.9 (34.17) 138.2 (5.85) 0.247

Creatinine (mg/dL) 5.71 (1.29) 5.94 (1.24) 0.156

Urea (mg/dL) 91.24 (28.4) 106.0 (26.88) 0.0023

Albumin (mg/dL) 3.13 (0.49) 3.25 (0.4) 0.0454

Nutrition score 67 (7.77) 70 (8.37) 0.0426

Peripheral proteinuria 3.5 ± 0.2 3.6 ± 0.2 0.235

White blood cell count 5.2 ± 0.5 5.3 ± 0.5 0.64

Cytosol

Young Control Experimental

Old Control Experimental

Albumin (mg/dL) 6.6 ± 6.6 13.6 ± 6.6 26 ± 23 0.1 ± 0.3

Palaiseau, France; 2Dept of Environmental Health, Univ of Cincinnati, Cincinnati, OH; 3Laboratoire Mutagène Environnementale, Univ de la Méditerranée and IMBE, Marseille, France; 4Institute for European Expertise in Physiology, Paris, France.

Background: The association between fluid intake and bladder cancer risk remains controversial since epidemiological studies has produced mixed results. To date, very little is known about which extent the amount of water intake in bladders toxins upon the urinary system. We performed a proof of concept trial to investigate the effect of water intake on mutagenesis in smokers, a high risk population for bladder cancer.

Methods: Monocentric randomized controlled trial. Inclusion criteria: Male subjects aged 20-45 y/o, smokers (at least 15 cigarettes per day) and small drinkers (<1 L of fluid/day; <500 mL of water/day; urinary 24-hour urinal volume 700 mOsm/kg). Exclusion criteria: History of diseases which could affect the results of the study or under treatment during the study period. T-Test was used to assess association between laboratory values and HL.

Results: 65 subjects were randomized. Mean age was 30 y/o and mean cigarettes per day was 20. A slight decrease in adducts formation was observed between baseline and last visit but no statistically significant difference was demonstrated between the groups. Conversely, urinary mutagenicity significantly decreased.

Conclusions: Our study shows that increasing water intake decreases urinary mutagenicity. However, it is not confirmed by urinary adducts formation. Further research with a larger sample size or longer intervention period would be necessary to address the impact of water intake on this parameter.

Funding: Pharmaceutical Company Support - Danone Research

PUB386

Providing Snacks during Dialysis Treatment Contributes to an Adequate Protein-Energy Intake in Hemodialysis Patients
Geertreke J. Stuikj-wielenga, 1 Floor Neelmeaart, 1 Pieter Jm Weij, 1 Pieter M. Ter Wee, 2 Nutrition & Dietetics, Internal Medicine, VU Medisch Centrum, Amsterdam, Netherlands; 3Dept of Nephrology, VU Medisch Centrum, Amsterdam, Netherlands.

Background: Protein-energy wasting (PEW) is a strong predictor of mortality in hemodialysis patients. Although PEW is also caused by non nutritional conditions, nutritional support targeting adequate protein intake has been shown to improve PEW and...
patient outcome. Previously we found that our patients, consuming an in-center meal and snack during dialysis treatment were still short of 15 grams of protein and 240 kcal per day. Aim: to investigate a 6 week intervention of a snack with education focused on adequate protein-energy intake particularly on dialysis days.

Methods: Hemodialysis patients in a university hospital, dialysed three times per week, were offered a choice out of 7 different snacks (+15 g protein, 240 kcal). Indirect calorimetry and physical activity level were measured to provide daily energy needs. 24 hour dietary recall was completed for 2 dialysis days both at baseline (06) and after 6 weeks (06).

Results: 28 patients (15 men), age 57±12 year (mean ± SD), BMI 24±4 kg/m² were enrolled. At t0 protein intake was 78% of estimated requirements (65±25 g/d, p<0.01), and increased to 100% (85±29, p<0.002) at t6. At t0 energy intake was 84% of energy requirements (1693±535 kcal/d, p<0.007) and increased to 99% (1989±606, p<0.033) at t6. At t0 patients out of 25 (32%) achieved their protein goal, at t6 13 patients (57%) (p<0.003).

Conclusions: Protein and energy intake of hemodialysis patients on dialysis days is insufficient and can be improved by providing a snack (+15 g protein, 240 kcal) and education during dialysis treatment.

PUB388

Validation of Objective Malnutrition Inflammation Scores in Pediatric and Adolescent Cohort on Chronic Maintenance Dialysis

Fransa M. Iorember, Oluwatoyin F. Bamgbola.

Pediatric and Adolescent Cohort on Chronic Maintenance Dialysis Center, New Orleans, LA.

Background: Altered body composition and uremic milieu often confound accuracy of single-item diagnostic tools [including anthropometry]. In addition, shared pathophysiologic process makes it impractical to dissociate burden of nutritional deficiency and pro-inflammatory inflammatory process in dialysis patients. Hence, composite score of malnutrition-inflammation morbidity [MIM] has been validated in adult dialysis patients. However, despite greater burden of chronic uremia, similar tools are not widely available for pediatric use. Objective: To assess the validity of composite scoring of clinical indices of malnutrition-inflammation morbidity in pediatric chronic dialysis cohort.

Methods: We derived composite scores [OMI] from quantitative indices of renal pathology, nutrition, inflammation, energy adequacy, protein catabolism, and dialysis modality. We avoided items that required [cognitive] subjective responses in the questionnaire. We assessed reliability by a test-retest method and measured validity by examining predictive relationship of the indices with serum c-reactive protein [CRP] in a multiple regression analysis.

Results: Twenty patients on chronic dialysis with a mean age of 12.8 years were enrolled. Eight subjects with elevated CRP [> 0.3 mg/dl] had higher scores for MIM. Patients on hemodialysis [HD] had greater OMI score than those on peritoneal dialysis [PD]. Test-retest score showed high degree of reliability [typical error 0.07; r = 0.95]. Diagnostic indices of MIM were predictive of elevated serum CRP in a regression analysis [R² = 0.9, F = 4.3, p = 0.03]. Sensitivity of OMI score was 62.5%, specificity 83%, accuracy 75% and precision was 71%.

Conclusions: Anthropometric and laboratory indices of nutritional status are often confounded by proximate events [e.g. inflammation, fluid retention] in dialysis patients. Composite scoring system may be more accurate and cost effective. Unlike Subjective Global Assessment instrument in adults, we attempted to improve accuracy and enhance universal applicability by avoiding cognitive input [subjective responses] from patients. Large scale population studies are needed to optimize clinical effectiveness and refinement of the diagnostic tools.

PUB389

Effect of Appetite and Body Mass Index on Energy Intake in Chronic Kidney Disease Stages 3 and 4 Patients Anita Saxena,1 Amit Gupta,1 Raj K. Sharma,1 Reena Choudhary,1 1Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, UP, India; 2Nephrology, Madras Medical Mission, Chennai, TN, India; 3Inst#1; 4Inst#1.

Background: Assessment of nutritional status in chronic kidney disease requires multiple markers. Objective: To assess effect of appetite on nutritional status of predialysis patients on first visit to nephrology center.

Methods: Three day dietary intake of 141 stage 3 and 4 CKD patients was recorded. Appetite was classified as normal, average, poor and anorexic. Body mass index was classified as normal, underweight, severely, underweight and overweight.

Results: Serum albumin was 2.9± 0.9 g/dl; protein 5.7 ±1.40, and proteinuria 3.5 ±1.4g. Of 140 patients, 52.8% had normal BMI, 15% were underweight, 5.7% were severely underweight and 27.1% overweight. BMI correlated (r = 0.00) with energy, protein, carbohydrate, creatinine, serum protein, proteinuria and SGA scores. There was difference in energy intake in BMI groups in weight (p = .000), appetite (+0.004), energy (+0.004) and proteinuria (+0.003). Dietary intake was energy 18.8±8.9 kcal/g; protein 0.7±7.3 g/kg, fat 0.3±4.4g/kg and carbohydrate 3.0±1.4g/kg. Based on BMI classification, energy intake was: normal 18.8±9.0, overweight 19.3±10.0, severely overweight 16.3±11.1, overweight 19.0±7.8 kcal/kg. Protein intake was: normal 0.7±3.4; underweight 0.8±0.4, severely underweight 0.6±0.4; overweight 0.5±2.0 g/kg.

Appetite correlated (r = 0.00) with weight, BMI, dietary energy, protein, fat , serum albumin and creatinine. Based on appetite groups energy intake was: normal 29:9±4.6; average 20.4±5.4, poor 18.2±5.8 and anorexic 10.1±5.5 kcal/kg and protein intake was: normal 1.0±1.3; average 0.7±5.2; poor 0.6±1.2 and anorexic 0.4±3.2.

Conclusions: 47.2% patients were underweight. Energy intake was low. Protein intake was as required for predialysis patients. Serum albumin and serum protein were low. Loss of lean body mass and protein catabolism may have a synergistic effect and cause malnutrition in CKD stage 3 and 4 patients. Inadequate energy intake, poor appetite, body mass index and low serum albumin and protein are markers of malnutrition in predialysis population.

PUB390

Is Free Testosterone Concentration a Prognostic Factor of Survival in Chronic Renal Failure? Stanislaw Niemczyk,1 Katarzyna Szamatoluka,2 Longin Niemczyk,3 Malgorzata Gomolka.1 1Military Institute of Medicine; 2National Research Institute of Mother and Child, 3Medical Univ of Warsaw.

Background: Persons with chronic kidney disease (CKD) experience low quality of life and increased cardiovascular mortality. Understanding the reasons of poor outcomes in renal failure seems to be an important challenge.

Aims: 1) evaluation of total (T) and free testosterone (FT) concentrations in pre-dialysis patients and patients treated with different methods of dialysis 2) assessment of relationship of T and FT concentration with biochemical parameters, which are sensitive to renal failure 3) evaluation of prognostic importance of T and FT levels in predicting long-term survival of CKD patients.

Methods: Four groups of men were examined: 14 hemodialised (HD), 13 on peritoneal dialysis (PD), 9 pre-dialysis and 8 healthy aged 56±17, 53±15, 68±12, 43±10 years respectively. The concentrations of T, SHBG, TBG, prealbumin, CRP, Hb and gomometry were measured. FT was estimated from formula.

Results: T concentration [ng/ml] was 3.98±1.76 in HD, 5.46±1.95 in PD, 4.02±1.26 in pre-dialysis and 6.40±2.43 in healthy subjects (p<0.035) , FT [ng/ml] 0.065±0.025, 0.091±0.041, 0.060±0.14, 0.104±0.045, respectively (p<0.004). T and FT were negatively correlated with age in all studied groups. There was also observed a negative significant association between T concentration and body mass index (r =0.013), a negative marginally significant association between T concentration and HCO3 concentration (p =0.085), and a negative significant association between FT concentration and HCO3 concentration (p =0.006). Within six years from the baseline, there were 5 deaths in HD, in 1 PD and 3 in pre-dialysis. In univariate analysis, both age (p<0.002) and FT (p=0.001) were related to survival probability. However, when both variables were entered into the model only FT was marginally significant (p=0.094).

Conclusions: The concentration of free testosterone was lower in hemodialysis and pre-dialysis patients than in healthy subjects. Free testosterone is related to metabolic acidosis and in chronic renal failure may prognose long-term survival better than age.

PUB391


Background: Constipation is a common gastrointestinal symptom in patients with chronic kidney disease (CKD), especially those on hemodialysis (HD). Although effective and safe treatment for constipation has not been established, mineral oil is commonly used due to its laxative effect. Edible oils, such as olive oil, could also be an alternative for the management of constipation of these patients. Therefore we aimed to investigate the effect of olive oil in comparison to mineral oil on constipation of patients with CKD on HD.

Methods: This was a double-blind randomized controlled trial conducted for 4 weeks (wk4). Constipation was diagnosed by the Roma III criterion.Thirty-one patients (16M, 52.1±11.0 years) diagnosed as constipated were randomized to mineral oil (MG; n=16) or olive oil (OG; n=15) groups. The initial dose of each oil was 4ml/day and was adjusted as needed.

Results: There was no difference in total oil used between the groups during the follow-up (MG=143.5 ± 51.5 ml, OG=148.5 ± 42.7 ml, p=0.67). As shown in the table, the decrease in the frequency of the symptoms of constipation, evaluated by Roma III criterion, was similar between mineral oil and olive oil groups.

At the end of follow-up in 57% and 60% of the patients of mineral oil and olive oil, respectively, constipation was resolved (p<0.83).

Conclusions: Olive oil seems to be an effective and health alternative in the treatment of the constipation of HD patients.
Investigation of ANCA Induced Activation of Human Neutrophils Using High Content Analysis  
Alice M. Couplah,1 Vincent P. O’Reilly,1 Anthony Mitchell Davies,2 Julie M. Williams,3 Mark Alan Little.1  
1 Trinity Health Kidney Centre, Trinity College Dublin, Ireland; 2The Irish National Center for High Content Screening and Analysis, Trinity College Dublin, Ireland; 3School of Immunity and Infection, Univ of Birmingham, United Kingdom.

Background: ANCA vasculitis is associated with the presence of autoantibodies that are capable of stimulating neutrophils in vitro. There is marked variability in stimulatory capacity both between donors and IgG preparations. However, this phenomenon is difficult to study due to inter-assay variability.

Methods: To overcome this variability in ANCA induced neutrophil activation we used high content analysis (HCA) to screen IgG from vasculitis patients and controls for their ability to activate healthy donor neutrophils. Neutrophils from up to 8 donors were stimulated with a panel of protein-G purified IgG in 384 well plates. Activation was assessed by measuring actin rearrangement (phalloidin stain) and superoxide production (Dihydorhodamine 123) by automated fluorescence microscopy using an InCell Analyser 1000™.

Results: We were able to simultaneously assess the stimulatory potential of IgG from 22 patients or controls against neutrophils from 8 healthy donors. Neutrophil responses to ANCA varied greatly. Some donor neutrophils were poor responders to all ANCA preparations. Furthermore, ANCA preparations that did activate neutrophils, did so in a donor dependent manner. The HIR assay produced a more robust and reproducible signal than the phalloidin stain.

Conclusions: Using robotic fluid handlers and the InCell Analyser™ to miniaturise and automate ANCA neutrophil assays allowed us to overcome the inter-assay variability observed when neutrophil donors are assessed on different days and facilitated testing of a large number of IgG preparations simultaneously.

Funding: Government Support - Non-U.S.

Effect of IL-17 on the Proliferation and IgA1 Underglycosylation of B Cells  
Jimming Fan,1,2 Jiari Lin,3 Fugang Li,4 Li Liu.2  
1 Dept of Nephrology, West China Hospital of Sichuan Univ; 2Chengdu, Sichuan, China; 3Division of Nephrology, Dept of Internal Chinese Medicine, Luzhou Medical College, Luzhou, Sichuan, China.

Background: IL-17, a Th17 cell-derived proinflammatory molecule, has been found to play an important role in the pathogenesis of autoimmune diseases. IL-17 may be associated with IgA nephropathy (IgAN). Wherein it has been known whether IL-17 exerts a direct effect on B lymphocytes in IgA nephropathy. This study was to investigate the effect of IL-17 on the proliferation and underglycosylation of IgA1 in B lymphocytes.

Methods: DAKIKI, was cultured and stimulated by IL-17. For dose-dependent test, cell culture was conducted for 48h with different doses (5ng/ml, 10ng/ml, 20ng/ml, 40ng/ml, 80ng/ml, 160ng/ml, 320ng/ml) of IL-17. For time-dependent test, cell was cultured for 24, 48 and 72h. The cell proliferation was examined by CCK-8 assay. The IgA1 concentration and galactosylation in supernatant were measured by ELISA and HAA lectin binding assay.

Results: 1. The result of CCK-8 showed that the proliferation of DAKIKI cells in group with 10ng/ml, 20ng/ml, 40ng/ml concentration was statistical significance obviously increased (P<0.05) compared with medium group. 2. The ELISA showed that the DAKIKI cells secreted IgA1 more than control after induced by IL-17. The levels of IgA1 secreted by DAKIKI cells in IL-17 incubation were gradually increased with the dose- and time-dependent. 3. The HAA lectin showed that, the glycosylation of IgA1 were decreased with dose- and time-dependent manner after 48h incubation with IL-17.

Conclusions: IL-17 could induced the B cell proliferation, IgA1 secretion and IgA1 underglycosylation in DAKIKI cells with a dose-dependent and time-dependent manner. The results suggested that the possible mechanism IL-17 participation the pathogenesis of IgA1 nephropathy was associated with B lymphocytes secreting much IgA1 and underglycosylation of IgA1.

Funding: Government Support - Non-U.S.

Effect of AST-120 Treatment on Uremia-Induced Disruption of Colonic Epithelial Tight Junctions and the Associated Systemic Inflammation  
Hoang Anh Nguyen,1 Jun Yuan,2 Norsatola D. Vaziri.1  
1UCI Div of Nephrology & Hypertension.

Background: The primary functions of the intestinal mucosa are absorption of nutrients, secretion of waste products, and serving as a barrier to prevent absorption of waste products and entry of luminal microorganisms and their harmful by-products in the host’s internal milieu. Uremia results in depletion of the key protein constituents of the colonic epithelial tight junction and the associated systemic oxidative stress. ARF results in reduction of the key constituents of the tight junctional proteins using Western blot analysis and immunohistological staining.

Methods: Male Sprague-Dawley rats were randomized into control (CTL), experimental (CRF), and AST-120 treatment groups for two weeks. The CTL group consumed regular diet. Two CRF groups were rendered uremic by addition of 0.7% adenine to their food, and one of these CRF groups was exposed to AST-120 for two weeks. Then, they were euthanized and the colons were harvested and processed for the expression of the key constituents of the tight junctional proteins using Western blot analysis and immunohistological staining.

Results: The Western blot revealed that the CRF group showed a significantly marked reduction in protein expression of ZO1 (p < 0.01), occludin (p < 0.01), and claudin-1 (p < 0.01) compared to the CTL group. However, activated charcoal (CRF + AST) treatment group showed significant increase in protein expression only for ZO1 (p = 0.05). Immunohistological staining indicated that the colonic tissues have increased wall thickness and accumulation of mononuclear leukocytes in the lamina propria and microvilli in the CRF animals. With AST-120 treatment, the inflammatory markers in the colonic tissues decreased compared to the CRF group.

Conclusions: Uremia results in depletion of the key protein constituents of the tight junctional proteins leading to impairing intestinal barrier function and contributing to the systemic inflammation. Activated charcoal was effective in attenuating uremia-induced depletion of colonic epithelial tight junction and the associated systemic oxidative stress and inflammation.

The Involvement of Histone Acetylation in Kidney Injury of Dhal Salt-Sensitive Rats  
Kumiko Io,1 Tomoya Nishino,1 Shinichi Abe,1 Yoko Obata,2 Takehiko Koji,3 Shigeru Kohno.1 1Second Dept of Internal Medicine, Nagasaki Univ School of Medicine, Nagasaki City, Nagasaki Prefecture, Japan; 2Dept of Histology and Cell Biology, Nagasaki Univ School of Medicine, Nagasaki City, Nagasaki Prefecture, Japan.

Background: Renal sclerosis is caused by arteriosclerosis associated with long-term hypertension. Although epigenetics, which is an acquired regulation of gene expression, has recently been reported to be related to the progression of hypertension, it is unclear whether epigenetics is associated with the progression of renal sclerosis. Therefore, we investigated the relationship between epigenetics, especially histone acetylation, and renal sclerosis.

Methods: 6-week-old male Dahl salt-sensitive (DS) rats were used as models of renal sclerosis. Rats were divided into three groups: (i) rats fed normal salt diet defined as NS group, (ii) rats fed high salt diet defined as HS group, (iii) HS group administered curcumin, a histone acetyltransferase inhibitor, daily defined as HS+C group. After 6 week from the start of salt load, the kidneys of these rats were dissected out. Morphologic changes were assessed by Masson’s Trichrome staining. ED-1 which is a marker of macrophage, Monocyte Chemoattractant Protein-1 (MCP-1) and histone acetylation were assessed by immunohistochemistry or by Western blotting.

Results: Compared with NS group, HS and HS+C groups showed a significant increase of systolic blood pressure from the 2 weeks of salt load. Serum creatinine increased markedly in HS group at the 6 week, while the increase of serum creatinine was suppressed in HS+C group. In HS group, interstitial fibrosis and glomerular sclerosis were observed, and the numbers of ED-1 or MCP-1 positive cells were significantly increased more than those in NS group at the 6 week. On the other hand, HS+C group showed the inhibition of these inflammation and fibrosis. Histone acetylation was more increased in HS+C group than that in NS group, whereas the administration of curcumin decreased histone acetylation in the kidney.

Conclusions: Our results suggested that histone acetylation was involved in progression of hypertensive kidney injury in DS rats.
Mauro Giacomo D’Ambrosio. 1 Isao Shirato. 2
Early Glomerular Crescents Consist of the Accumulation of Podocytes That Undergo Detachment from the GBM Wilhelm Kriz. 1 Isao Shirato. 2
Early Glomerular Crescents Consist of the Accumulation of Podocytes That Undergo Detachment from the GBM Wilhelm Kriz. 1 Isao Shirato. 2
Mean ± SE, * p<0.05 vs. NxPre, Nx, and NxLH, respectively

FR - Friday
SA - Saturday
OR - Oral
PO - Poster
PUB - Publication Only
Unlikely represents presenting author.

PUB397
Isolation of MicroRNA from the Proximal Tubules of Archival Renal Biopsies Utilising Laser Capture Microdissection
Gerrant James Rees Dingley, 1 Juan Mason, 1 Sara Kathryn Campbell, 1, 2 Paul Steven Bass, 1 Jane Elizabeth Collins 1, 2

Funding: Private Foundation Support

PUB400
Hydrochlorothiazide Is Superior to Furosemide as a Renoprotective and Antiproliferative Add-On To Losartan in the Remnant Kidney Model
Simone C.A. Arias, Renata A. Souza, Claudia R. Sena, Camilla Fanelli, Denise M.A. Malheiro, Clarice K. Fujihara, Roberto Zatt. Univ. de Sao Paulo, Brazil.

Funding: Government Support - Non-U.S.

PUB398
Bone-Derived Mesenchymal Stromal Cells from HIV Transgenic Mice Exhibit Altered Proliferation, Differentiation Capacity and Paracrine Functions along with Impaired Therapeutic Potential in Kidney Injury

Funding: NIDDK Support

PUB399
Milkt Fat Globule-Epidermal Growth Factor-8 Modulates Tissue Fibrosis and Renal Damage in Ureteral Obstruction
Jean-Francois Cailhier, Marie-Joelle Brisette. Medicine, Institut du Cancer de Montreal, CRCHUM, Montreal, Canada.

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

PUB401
Early Glomerular Crescents Consist of the Accumulation of Podocytes That Undergo Detachment from the GBM
Wilhelm Kriz. 1

Funding: Private Foundation Support

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

692A
In addition, contacts to parietal cells were regularly seen. These manoeuvres prevented detached podocytes from being spoiled into the urine and led to their accumulation in Bowman's space.

Conclusions: Cellular crescents consist of detached and detached podocytes linked to each other as well as to the tuft and Bowman’s capsule.

Funding: Private Foundation Support

PUB402

Influence of Klotho in Cognitive Deficit Linked to Chronic Kidney Disease (CKD) on Animal Model of CKD (5/6 Nephrectomy) 
Sabrina Degaspardi, Carmen B. Tzanos-martins, Clarice K. Fujihara, Roberto Zarz, Tania Araujo Viel, Ana Elisa Bohmer, Cristoforo Scavone, Elisa M. Kawamoto. 1, 2Dept of Pharmacology, Univ of Sao Paulo - USP Brazil; 1CINE, Sao Paulo, Brazil; 2Faculdade de Medicina, USP Brazil; 3School of Arts, Sciences and Humanities, USP Brazil; 4Laboratory of Neurosciences, NIH.

Background: CKD is believed to have a negative impact on cognitive function. Recent studies have reported changes in serum klotho with aging, and levels of this protein are strongly influenced by renal function. Also, it may be involved in the cognitive impairment (CI) found in CKD. The aim of the present study is to evaluate the correlation between CI and levels of Klotho in serum and hippocampus and frontal cortex in 5/6 nephrectomized rats (Nx).

Methods: Forty Munich-Wistar rats underwent 5/6 nephrectomy (Sham rats were used as control groups). After 30 days of surgery, all animals were evaluated using different behavior tests (Fear Conditional Test and New Object Recognition Test) during five months. Nx animals which had only 25% or less of the markers of Sham group in the behavior tests were included in the CI group (Nx-CI). At the end of this period, blood and brain samples were collected. All samples were used to analyze Klotho levels by ELISA test.

Results: After Nx surgery, rats showed raised levels of creatinine (1.3±0.3 vs. 0.5±0.05, P<0.001) compared to Sham group (0.3±0.05, P<0.001), we found an increase of glomerulosclerosis in Nx group (9.9±1.9) from a level of 9.2±0.9, and an important intestinal expansion in Nx group (6.6±0.8) compared with Sham rats (0.0±0.1). Forty six percent of Nx rats (Nx-CI) showed impaired memory retention (novel object recognition test and contextual fear conditioning). After 4 months from Nx, we observed that serum Klotho was lower in Nx-CI than in Sham and Nx rats. Our data also show a decrease in frontal cortex Klotho in Nx-CI group comparing with Sham and Nx rats, however, hippocampus Klotho showed no difference between groups.

Conclusions: Together, the present data suggest that changes in Klotho signaling plays a role in the development of cognitive changes associated with chronic renal failure.

Funding: Government Support - Non-U.S.

PUB404

Iron Reduction Suppresses Renal Tubulointerstitial Fibrosis in Mice with Unilateral Ureteral Obstruction 
Iori Ozono, 1 Yasunaka Ikeda, 2 Shoji Kagami, 1 Toshiaki Tamaki. 1 Pharmacology, Institute of Health Biosciences, The Univ of Tokushima Graduate School, Tokushima, Japan; 2Student Laboratory, Tokushima Univ, Tokushima, Japan; 3Pediatrics, Institute of Health Biosciences, The Univ of Tokushima Graduate School, Tokushima.

Background: Renal fibrosis plays an important role in onset and progression of chronic renal diseases. We have clarified that iron is involved in the pathological conditions on obesity, atherosclerosis and diabetic nephropathy. Although several underlying mechanisms of renal fibrosis have been shown, the role of iron in the process of renal fibrosis remains unclear.

Methods: o A mouse model of unilateral ureteral obstruction (UUO) and mice with sham operation as control. Mice with UUO were divided into 2 groups, treatment with deferoxamine (DFO), an iron chelator, or vehicle.

Results: At 1 week after surgery, renal interstitial fibrosis, as same as increased mRNA expression of collagens, were increased in mice with UUO and these changes were suppressed by DFO treatment. UUO-induced macrophage infiltration was reduced in UUO mice with DFO. UUO-induced expression of inflammatory cytokines and extracellular matrices were ameliorated with iron reduction. Iron chelation inhibited the activated signaling of transforming growth factor-β1-Smad3 pathway in mice with UUO operation. UUO-induced renal superoxide production and p22(phox) expression was attenuated by DFO treatment. Additionally, renal expressions of interleukin-1β and NOD-like receptor, pyrin domain containing 3 were induced in mice with UUO, these changes were ameliorated by DFO treatment. In renal iron transporters, protein expressions of ferroportin and ferritins were upregulated, and transferrin receptor-1 and divalent metal transporter-1 were downregulated in mice with UUO compared to sham operated mice although no difference of renal iron content was seen between mice with sham and mice with UUO.

Conclusions: These results have suggested iron is involved in the progression of renal tubulointerstitial fibrosis through oxidative stress and inflammatory changes, therefore the iron reduction potentiates to be a new therapeutic approach for renal fibrosis.

Funding: Government Support - Non-U.S.

PUB405

Sphingosine-1-Phosphate Receptor 1 and 3 Are Pivotal Mediators of Renal Fibrosis 
Shanji Shiohira, Takumi Yoshida, Hidekazu Sugiyama, Miki Nishida, Kosaku Nitta, Ken Tsutchiya. Dept of Medicine Four, Tokyo Women’s Medical Univ, Shinjuku, Tokyo, Japan.

Background: Sphingosine-1-phosphate (SIP) has been suggested to be involved in the mechanism of renal fibrosis that functions through Sphingosine-1-phosphate receptor (SIPR) signaling pathways. Five subtypes of SIPRs have been identified. There have been few reports of the SIP and SIPR in each cell in each organ, and differences in effects of SIPRs have been reported in each organ. To get more insight into roles for SIP and receptor subtype effects in vitro, we performed siRNAs knockdown of receptor subtypes (1 and 3) and SIPR1 agonist and SIPR3 antagonist.

Methods: Normal rat kidney tubulointerstitial fibroblast (NRK-49F) cells were stimulated with exogenous SIP. Then the morphological changes of the NRK-49F cells after stimulation by SIP were examined. The growth and migration of cultured cells was quantified by using CL-Quant software to analyze time-lapse images in a Nikon BiosStation CT. The real-time images of cell migration were monitored for 2 days. And the expressions (mRNA/A/Western blotting) of a-SMA, E-cadherin, collagen type 1 (COL1), collagen type 4 (COL4), TIMP1 and PAI1 were examined. To specify the kidney specific signal pathway, siRNAs targeted to SIP receptor subtypes (1 and 3) were generated. And also NRK-49F cells were stimulated with SIP after the addition of SIPR1 agonist and SIPR3 antagonist were evaluated.

Results: SIP stimulated fibrosis of NRK-49F cells in a dose- and time-dependent manner as previously observed, and induced morphological changes of NRK-49F cells. Migration of NRK49F cells was accelerated and increased a-SMA, COL1, COL4, TIMP1, and PAI1 and decreased E-cadherin expression levels were observed in the SIP-stimulated cells. SIPR3 siRNA transfection to NRK-49F cells attenuated SIP-induced cell growth, cell migration, and the expression of fibrotic markers. And also in the presence of SIPR1 agonist and SIPR3 antagonist, fibrosis and migration induced by SIP were suppressed.

Conclusions: These results suggest that SIP signaling mediated by SIPR1 and SIPR3 results in renal fibrosis.

PUB406

Medullary Fibrosis Assessment in Human Renal Biopsies: Correlation with Cortical Fibrosis 
Alton Brad Farris, 1 Diane H. Lawson, 1 Cynthia Na Cohen, 1 Seymour Rosen. 2 Emory Univ; 3Harvard Univ/Beth Israel Deaconess Medical Center.

Background: Renal tubulointerstitial injury evaluation is important in both native and transplant kidneys; however, past studies have primarily focused on the renal cortex.

Methods: Native renal biopsies (n=77), included in the study if they contained medullary tissue, were scanned into digital whole slide images (WSIs); and IF was quantitated on trichrome stains and collagen III (CIII) immunohistochemistry using a positive pixel count algorithm. The algorithm was also used to quantify the 3% composed of BM material on a PAS stain. IF was also measured by subtracting the PAS-BM’s from the trichrome (Trichrome%−PAS%, referred to as T−P) in order to account for BM material also detected on trichrome staining. Pathologist visual assessment of %IDF was also obtained.

Results: IF showed a wide range by the different measurement modalities (e.g., 20-61% for the trichrome IFP%). Image analysis of trichrome staining ranged from 0 to 100% for all anatomic compartments (r=0.66–0.98, all p<0.0001). Visual images also showed a wide range, from 15-90% for all tissue and a significant correlation with all of the trichrome and T-P measures. CIII showed a range of 9.5-47% for all tissue and correlated between compartments (r=0.74, p<0.0001 for all tissue vs. cortex, r=0.89, p<0.0001 for all tissue vs. medulla, and r=0.71, P=0.0003 for cortex vs. medulla); however, CIII did not show a significant relationship with any of the other IF measures.

Conclusions: Trichrome and T-P WSIs analysis correlated between the cortex, medulla, and entire tissue, and with visual assessment. In this study, CIII deposition correlated strongly with most IF measures and medullary measurements could prove useful in drug studies, clinical trials, and evaluation of biopsies containing only medulla.

PUB407

Chronic Nicotine Attenuates Pro-Fibrotic Signal-Dependent Induction of HO-1: Its Role in Exacerbation of Renal Fibrosis 
Ivan Arany, Dustin Reed, Robert Kampen, Luis A. Juncos. Univ of Mississippi Medical Center.

Background: There is a strong epidemiological association between smoking and risk of development and accelerated progression of chronic kidney diseases (CKD). Since plasma levels of TGFβ1 − a known mediator of renal fibrosis − are elevated in smokers, smoking may contribute to progression of CKD by augmenting tubulointerstitial fibrosis. Smoking reduces the expression of HO-1 and mediators of fibrosis (TGFβ1, IL-6) in the obstructed kidneys of mice exposed or not
to Ch-NIC. Contralateral kidneys served as controls. In vitro, the impact of chronic NIC on TGFβ1-mediated activation of HO-1 and alpha-smooth muscle actin (αSMA: a marker of fibroblast activation) promoters were studied in renal interstitial fibroblasts (NRK-49F).

**Results:** UO significantly increased tubulointerstitial fibrosis (αSMA expression and Masson trichrome staining), expression of TGFβ1, IL-6 and HO-1 in the obstructed kidneys. Ch-NIC exposure augmented fibrosis and expression of IL-6 but not TGFβ1 while decreased HO-1. In vitro, chronic NIC or IL-6 augmented TGFβ1-mediated activation of the αSMA but attenuated the HO-1 promoter. Activation of endogenous HO-1 by cobalt protoporphyrin (CoPP) or exogenous overexpression of HO-1 greatly diminished promoter activity of αSMA.

**Conclusions:** Our results suggest that chronic NIC augments promoter activity of the αSMA gene through IL-6-dependent suppression of HO-1 induction. Further studies are on the way to determine whether this effect is associated with suppression of the antioxidant response element or other cis-acting element of the HO-1 promoter. Manipulation of those pathways may prove useful to ameliorate adverse effects of chronic NIC smoking on renal interstitial fibrosis.

**Funding:** NIDDK Support

**PB409**

Synergistic Interplay of the Canonical Wnt and TGFβ Pathways Induces Fibrosis

Omar H. Maarouf,1 Derek Paul DiRocco,2 Deepika Ranagarajan,2 Benjamin D. Humphreys.1 1Medicine/Renal, Brigham and Women’s Hospital, Boston, MA; 2Biotechnology, SRM Univ, Chennai, India.

**Background:** Fibrosis is the morphologic hallmark of CKD and is characterized by exaggerated accumulation of collagen and emergence of myofibroblasts. Both the TGFβ and canonical Wnt signaling pathways are activated during kidney fibrosis, but whether these pathways interact during myofibroblast activation is unknown. We hypothesize that these pathways synergize, through β-catenin activation, to drive fibrotic gene expression in myofibroblasts.

**Methods:** We used two cell culture myofibroblast models: immortalized NRK-49F cells and primary human dermal fibroblasts. The Wnt pathway was modulated pharmacologically, and the ability of TGFβ alone or with β-catenin stabilization to drive a luciferase-based β-catenin activity reporter (BAR) was assessed. Levels of activated myofibroblast transcripts, like fibronectin and αSMA, were also measured.

**Conclusions:** TGFβ1 independently induced β-catenin activation in both NRK-49F cells and primary human dermal fibroblasts. Blocking β-catenin activation with XAV939, a tankyrase inhibitor which induces β-catenin degradation, repressed TGFβ1-induced myofibroblast gene expression (fibronectin and αSMA). Stimulation of the Wnt pathway with the GSK3β inhibitor CHIR99021 induced fibroblast production. Combining TGFβ1 and CHIR99021 at sub-threshold doses led to an increase in the fibrotic phenotype by inducing fibronectin production and αSMA expression. Using the BAR system, sub-threshold doses of TGFβ1 and CHIR99021 were synergistic in inducing β-catenin pathway activation in a dose- and time-dependent fashion.

**Funding:** Other NIH Support - T32

**PB409**

Is Galectin-3 Responsible for Microvascular Dysfunction in Uremia?


**Background:** Microvascular dysfunction is universal in uremia and contributes to cardiovascular mortality. The aetiology of uremic microvascular dysfunction remains elusive. We investigated microvascular dysfunction in experimental chronic uremia by intravital microscopy (IVM) of leucocyte endothelial interactions in cremasteric venules. We aimed to establish if the pro-adherent leucocyte cell surface expression of E-selectin (a marker of endothelial cell activation) promoters were studied in renal interstitial fibroblasts (NRK-49F).

**Results:** UO significantly increased tubulointerstitial fibrosis (αSMA expression and Masson trichrome staining), expression of TGFβ1, IL-6 and HO-1 in the obstructed kidneys. Ch-NIC exposure augmented fibrosis and expression of IL-6 but not TGFβ1 while decreased HO-1. In vitro, chronic NIC or IL-6 augmented TGFβ1-mediated activation of the αSMA but attenuated the HO-1 promoter. Activation of endogenous HO-1 by cobalt protoporphyrin (CoPP) or exogenous overexpression of HO-1 greatly diminished promoter activity of αSMA.

**Conclusions:** Our results suggest that chronic NIC augments promoter activity of the αSMA gene through IL-6-dependent suppression of HO-1 induction. Further studies are on the way to determine whether this effect is associated with suppression of the antioxidant response element or other cis-acting element of the HO-1 promoter. Manipulation of those pathways may prove useful to ameliorate adverse effects of chronic NIC smoking on renal interstitial fibrosis.

**Funding:** NIDDK Support

**PB410**

Pressure Promotes Fibrotic Responses in Renal Tubular Cells through miR-328-Mediated CD44 Up-Regulation

Tso Hsiao Chen, Cheng-hsien Chen, Cheng-hsien Chen. Internal Medicine, Taipei Medical Univ-Wan Fang Medical Center, Taipei, Taiwan.

**Background:** Pressure force is an important mechanism contributing to the induction and progression of tubulointerstitial fibrogenesis in ureteric obstruction.

**Methods:** In this study, we set up an in vitro pressure culture system, and investigated microvascular protein expression alterations correlate with pressure treatment in rat renal tubular cells (NRK-52E). When NRK-52E cells were cultured in the pressure culture system, 60 mmHg of pressure induced the expression of connective tissue growth factor (CTGF), transforming growth factor (TGF)-β, and fibronectin.

**Results:** MicroRNA array assays showed that pressure reduced miR-328 at the initial stage of pressurization. The expression level of miR-328 in pressurized cells significantly decreased within 2 h, recovered at 4 h, and increased at 8 h. Potential target of miR-328 has been reported to be human CD44. We identified a potential target sequence of miR-328 in rat CD44 3’UTR as proven by 3’UTR analysis. Protein analysis demonstrated that expression of CD44 was up-regulated at the initial stage of pressurization. CD44 siRNA transfection significantly reduced pressure-induced fibronectin in NRK-52E cells. However, CTGF expression was not influenced by CD44 siRNA transfection. In normal cells, pressure reduced E-cadherin, an important EMT marker, at 4 and 8 h. CD44 siRNA transfection induced E-cadherin in pressurized cells at 4 and 8 h. In UUO animal model, we also found CD44 increased in renal tubular cells in slight dilated tubules.

**Conclusions:** Our results suggest that miR-328-mediated CD44 up-regulation play an important role in pressure-induced fibrotic responses in renal tubular cells.

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

**PB411**

Responses of Human Podocyte Grown on Different Cellular Matrices

Tarunkumar H. Madug, Myeore Keshavmurthy Phanish, Mark Edward Dockrell. SWT Institute for Renal Research, London, United Kingdom.

**Background:** Cell phenotype and survival is strongly regulated by interaction with the extracellular matrix proteins, particularly those of a basement membrane. The glomerular basement membrane (GBM) is dynamic structure made up of protein secreted by endothelial cells and podocytes. In renal disease there are changes to the quantity and quality of GBM proteins contributing to the progression of disease such as fibrosis. We previously described TGFβ1-induced EDA+Fn expression in human podocytes. In this study we investigate response of podocyte culture grown on GBM proteins such as collagen IV and cellular and plasma fibronectin.

We aim to investigate the role of different matrices on podocyte phenotype and responses to TGFβ1.

**Methods:** Human podocyte were grown dishes coated with different matrices; collagen IV, cellular fibronectin containing the EDA Exon (EDA+Fn), plasma fibronectin, which lacks the EDA Exon, (EDA–Fn). Expression of EDA+Fn, synaptopodin and alpha-SMA was assessed by RTFPCR and Q-PCR in the presence and absence of TGFβ1 (2.5ng/ml).

**Results:** Marked changes in podocyte morphology were observed by light microscopy in EDA+Fn grown on the different matrices. A decrease in EDA expression was observed in cells grown on collagen Fn. The expression alpha-SMA mRNA did not significantly change at this time point. Investigating the effects of different cellular matrix protein on TGFβ1-mediated responses demonstrated that the TGFβ1-mediated increase in and expression of EDA+Fn was completely abolished in cells grown on collagen IV. The effect of TGFβ3 on synaptopodin was also greatly affected by the growth surface, with opposite effects seen on collagen as compared to fibronectin. Activation of receptor Smads is unaffected by different matrices.

**Conclusions:** Alteration of the constituents of the GBM is likely to significantly alter podocyte phenotype and cellular responses to growth factors involved in podocytopathies, such as TGFβ.

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

**PB412**

Upregulation of Protein Phosphatase 2A Activity by Nitration in Endothelial Cells Is Associated with Renal Fibrosis

Min Han, Yuanjun Deng, Ping Liu, Gang Xu. Tongji Hospital, Tongji Medical College, Huazhong Univ of Science and Technology.

**Background:** Previous studies show that endothelial cells may acquire smooth muscle-like phenotype and contribute to extracellular matrix deposition in renal fibrosis. TGFβ1 induces fibrosis by activating mechanism, however, remains elusive. Here, we hypothesize that a protein post-transcriptional modification of P2PA may have profound effects on the process of extracellular matrix deposition resulted from endothelial cells.

**Methods:** The expression of VE-cadherin and α-SMA were detected by using western blot, immunofluorescence and flow cytometry 72h after human umbilical vein endothelial cell (HUVEC) were treated with TGF-β1. P2PA (P2PA catalytic subunit) nitration was determined by Immunoprecipitation (IP) after TGF-β1 stimulation. Further, we used tandem mass spectrometry to map the nitration sites of P2PA treated with Permoxinitrite (a nitration model) and superoxide- product in vitro. Site-specific liquid chromatography–mass spectrometry quantitative analyses were designed to specifically determine the order of the nitration sites.

**Funding:** Clinical Revenue Support

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

Underline represents presenting author.

964A
Results: After the stimulation of TGF-β1, certain subsets of endothelial cells lose endothelial characteristics and transformed into smooth muscle-like cells characterized by loss of endothelial marker VE-cadherin, and gain mesenchymal markers SMA. TGF-β1 stimulation upregulated PP2A activity combined with increased PP2Ac nitrination. Tandem mass spectrometry identified that of the fifteen tyrosine residues in PP2Ac, Tyr-284, Tyr-218, Tyr-265, and Tyr-267, Tyr-127 and Tyr-130 were nitrated. Site-specific liquid chromatography-mass spectrometry quantitative analyses demonstrated that the favored modification site following exposure to peroxynitrite is Tyr-284. And these profibrotic effects were significantly attenuated by adding okadaic acid and NADPH oxidase inhibitor apocynin.

Conclusions: Nitric oxide with superoxide pathway can regulate PP2A modification under oxidative stress conditions, which modulate TGF-β1 induced phenotype change mechanisms involved in profibrotic effects. This can augment extracellular matrix deposition and fibrosis linked to renal fibrosis.

PUB413
Effects of Membrane Cholesterol Content and the Anionic Amphipath Trinitrophenol on Mechanical Activation of TRPC6 Channels in Podocytes
Sneer S. Dryer,1 Cory Wilson,1 Marc Thomas Anderson,1 ’Biology and Biochemistry,’ Univ of Houston, Houston, TX; ‘Nephrology, Baylor College of Medicine, Houston, TX.

Background: We have previously shown that TRPC6 channels can be activated by mechanical stimuli in cultured podocytes and in podocytes in isolated glomerular preparations. Mechanical activation of TRPC6 in podocytes persists after inhibition of phospholipases or G proteins. Knockdown of the podocin increased TRPC6 activation by mechanical stimuli, but suppressed activation by diacylglycerol analogs.

Methods: Whole-cell recordings from mouse podocyte cell lines and filin staining of membrane cholesterol.

Results: Filin staining showed that cholesterol occurred in distinct patches, often arranged in an elliptical pattern on the surface of immortalized mouse podocytes. This spatial pattern of filin staining persisted in podocin knockdown cells. Filin staining was eliminated after 18-24 hr treatment with 10 nM methyl-j-cyclodextrin (MBCD). MBCD treatment caused a marked increase in hypoosmotic stretch-activation of TRPC6 in podocytes. Conversely, it is possible to increase membrane cholesterol content by pre-exposing MBDC with cholesterol in a 20:1 molar ratio. A 24-hr exposure to this reagent caused nearly complete inhibition of hypoosmotic stretch-activation of TRPC6. Exposure to 10 mM MBCD for just 20 min caused a marked increase in stretch-activation of TRPC6. It is possible that this brief treatment with MBCD selectively depletes cholesterol from the outer leaflet resulting in microfolding of the membrane. A similar effect was evoked by treating cells for 20 min with the anionic amphipath trinitrophenol (200 μM), which is known to cause crenelation of the plasma membrane.

Conclusions: These data suggest that cholesterol content regulates membrane mechanical properties in podocytes and the transmission of force to TRPC6 channel complexes. This is consistent with our observation that podocin interactions suppress mechanical activation of TRPC6 channels in podocytes.


PUB414
Mechanistic Studies of a Chinese Herbal Medicine Prescription for Treatment of IgA Nephropathy
Zhi Qian Huang,1 Yiping Chen,1 Nicolas Maillard,1 Stacy D. Hall,1 Bruce A. Julian,1 Jan Novak.1 ’Univ of Alabama at Birmingham, Birmingham, AL; 2Department of Pathology, UAB, Birmingham, AL; 3Nephrology, Univ of Michigan; 4Pathology, Univ of Michigan; 5Nephrology, Univ of Zurich.

Background: A 67-year old woman, baseline creatinine 1.0 mg/dL, developed a gallbladder-fossa infection after gallbladder resection for adenocarcinoma. Admission creatinine was 1.9 mg/dL with a bland urinary sediment. The infection cleared with antibiotics, and creatinine improved to 1.3 mg/dL at discharge. She was readmitted with acute renal failure, nephritic urinary sediment, 3.3 g/g proteinuria, leg edema, and hypertension. She had diarrhea later attributed to Clostridium difficile-induced colitis. Due to a rapidly rising creatinine, renal biopsy was performed. Light microscopy showed marked mesangial and endocapillary hypercellularity, immunofluorescence microscopy showed dominant IgG staining with less staining for IgA in the mesangium and capillary loops; electron microscopy showed large subendothelial and mesangial deposits consistent with immune deposits of a post-infectious glomerulonephritis (PGN). She became dialysis dependent. Because the pathogenesis of IgA-dominant PGN is unknown, we undertook additional laboratory studies.

Methods: Serum levels of IgA and galactose-deficient IgA1 were measured by ELISA. Western blot after SDS-PAGE separation of serum IgA under non-reducing conditions determined the ratio of monomeric and polymeric IgA. Serum (native or IgA- or IgG-depleted) was fractionated by size-exclusion chromatography, and fractions were added to cultures of human mesangial cells and proliferation assessed by thymidine incorporation. Fractions were assessed by ELISA for IgA and IgG profiles.

Results: Serum level of total IgA was markedly elevated, with normal polymeric-to-monomeric ratio of IgA. Total serum level of galactose-deficient IgA1 was elevated. Large-molecular-mass circulating immune complexes containing IgA and IgG stimulated proliferation of mesangial cells.

Conclusions: For this patient with IgA nephropathy associated with colitis due to Closytridium difficile, an increased serum level of galactose-deficient IgA1 likely led to formation of circulating nephritogenic IgA-IgG immune complexes.

Funding: NIDDK Support

IgA and Immune Complex Profile of an IgA-Dominant Post-Infectious Secondary Glomerulonephritis
Eric L. Wallace,1 Nicolas Maillard,1 Hiroyuki Ueda,1 Stacy D. Hall,1 Huma Fatima,1 Jan Novak,1 Bruce A. Julian,1 ’Div of Nephrology, UAB, Birmingham, AL; 2Dept of Pathology, UAB, Birmingham, AL; 3Dept of Microbiology, UAB, Birmingham, AL.

Background: A 67-year old woman, baseline creatinine 1.0 mg/dL, developed a gallbladder-fossa infection after gallbladder resection for adenocarcinoma. Admission creatinine was 1.9 mg/dL with a bland urinary sediment. The infection cleared with antibiotics, and creatinine improved to 1.3 mg/dL at discharge. She was readmitted with acute renal failure, nephritic urinary sediment, 3.3 g/g proteinuria, leg edema, and hypertension. She had diarrhea later attributed to Clostridium difficile-induced colitis. Due to a rapidly rising creatinine, renal biopsy was performed. Light microscopy showed marked mesangial and endocapillary hypercellularity, immunofluorescence microscopy showed dominant IgG staining with less staining for IgA in the mesangium and capillary loops; electron microscopy showed large subendothelial and mesangial deposits consistent with immune deposits of a post-infectious glomerulonephritis (PGN). She became dialysis dependent. Because the pathogenesis of IgA-dominant PGN is unknown, we undertook additional laboratory studies.

Methods: Serum levels of IgA and galactose-deficient IgA1 were measured by ELISA. Western blot after SDS-PAGE separation of serum IgA under non-reducing conditions determined the ratio of monomeric and polymeric IgA. Serum (native or IgA- or IgG-depleted) was fractionated by size-exclusion chromatography, and fractions were added to cultures of human mesangial cells and proliferation assessed by thymidine incorporation. Fractions were assessed by ELISA for IgA and IgG profiles.

Results: Serum level of total IgA was markedly elevated, with normal polymeric-to-monomeric ratio of IgA. Total serum level of galactose-deficient IgA1 was elevated. Large-molecular-mass circulating immune complexes containing IgA and IgG stimulated proliferation of mesangial cells.

Conclusions: For this patient with IgA nephropathy associated with colitis due to Closytridium difficile, an increased serum level of galactose-deficient IgA1 likely led to formation of circulating nephritogenic IgA-IgG immune complexes.

Funding: NIDDK Support

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

965A
PUB417


Background: Urine test is non-invasive and can reflect more general condition of the whole kidney than findings of renal biopsy.

Methods: We collected morning urine samples from 200 patients for kidney biopsy from 2008 to 2011. Logistic regression analysis was performed with the finding of renal biopsy as dependent variable (0 = normal; 1 = crescent existed) and with Claudin1 and CD68 positive cell count as predictor variables. And the relations of Claudin1 and CD68 positive cell count in urinary sediment with urinary protein or red blood cell were examined. Secondly, we evaluated phenotypes of the macrophage in urinary sediment. The relationship between relative levels of target mRNAs and the histological changes such as crescent formation (CF) (exist or none) or global sclerosis rate was evaluated.

Results: Logistic analysis of Claudin1 and CD68 positive cell count with the presence of CF revealed ROC curve with the area under the curve (AUC) of 0.60 and 0.70, respectively, both of which were statistically significant. There was significant positive trend between the Claudin1 positive cell count and the urinary protein, but no trend was found between the CD68 positive cell count and the urinary protein. Both Claudin1 and CD68 positive cell count showed significant positive correlation with the urinary red blood cell. The relative mRNA levels of the M2 markers (CD163, CD204, CD206, IL-10) were significantly higher in patients with than without CF. On the other hand, the relative mRNA levels of M1 markers (iNOS, IL-6) were similar in both patients with and without CF.

Conclusions: These data suggest that the Claudin1, CD68 positive cell count and quantification of the mRNA of the M2 markers of urinary sediment are useful for the evaluation of the state of the glomerular disease and that Claudin1 reflects parietal epithelial damage not only by glomerular inflammation but also by urinary protein.

PUB418

Pentraxin 3 Expression in Renal Tissue of HIV Positive and HIV Negative Patients with Glomerular Diseases Manuela Nebuloni, Angelita Ferri, Antonella Tosoni, Pietro Zerbi, Irina Edu, Giovanni Belgioioso, 1 Pathology Unit, DISBC, Univ Milan, Milan, Italy, 2 Path. Unit, L.Sacco Hospital.

Background: Pentraxin 3 (PTX3) is involved in the regulation of innate immunity. It has been detected in renal tissue of patients with glomerulonephritis (GNs), suggesting a possible role in glomerular and tubular injury. On the other side, HIV infection per se is a causative agent/eventual cofactor for GNs. The aim of the study is to evaluate the additional role of HIV infection in PTX3 expression as a modulatory factor in tissue injury in different GNs.

Methods: Renal biopsies from 35 HIV+ and 46 HIV- patients (pts) with various types of GNs were tested for PTX3 by immunohistochemistry. Immunoquantification and intensity were considered. Immune complex related GNs (IC) and non immune complex GNs (NIC), in HIV+ and HIV- groups were compared. The Mann Whitney U test was employed for statistical analysis of results.

Results: PTX3 immunostaining was localized in the interstitium and in the cytoplasm of some endothelial cells and macrophages. IC vs NIC GNs, irrespective of HIV infection: no statistical difference. IC GNs and NIC GNs, HIV-: pts: no statistical difference. IC vs NIC GNs, HIV+ pts: p=0.02. PTX3 expression in IC GNs higher than in NIC GNs. IC GNs, HIV+ vs, IC GNs, HIV-: pts: p=0.04. PTX3 expression in HIV+ pts higher than in HIV- pts. Results suggest that PTX3 can modulate tissue injury in glomerular diseases but its exact role is unclear.

PUB419

Clinicopathological Spectrum of Kidney Diseases in Patients Treated with Vascular Endothelial Growth Factor Inhibitor for Cancer Therapy Joichi Usui, I. Y. Gleznerman, Chandra B. Chandran, Steven Salvatore, Carlos D. Flombbaum, Surya V. Seshan. 1 Dept of Pathology, Weill Cornell Medical College, Cornell Univ, New York, NY, 2 Univ of Tsukuba, Japan; 3 Renal Service, Dept of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; 4 Nephrology Div, Dept of Medicine, St. Joseph’s Regional Medical Center, Paterson, NJ.

Background: Recently, cancer therapies have been supplemented by vascular endothelial growth factor (VEGF) inhibitors as anti-angiogenic agents. This report further discloses the spectrum of pathological features in VEGF inhibitor-associated kidney disease.

Methods: Clinicopathological findings of kidney disease were retroactively studied in 5 cancer patients treated with VEGF inhibitors.

Results: Four cases received bevacizumab (anti-VEGF-A) and one was given sorafenib (tyrosine kinase inhibitor affecting VEGFR2), with chemotherapeutic agents. All patients presented with acute kidney injury (serum Cr 1.6-6mg/dl), hypertension and/or proteinuria (none to 2.6g/day). All kidney biopsies showed endothelial injury of varying severity, including 2 with typical features of flash TMA (fTMA). Evidence of chronic endothelial injury and vascular sclerosis were also observed. Furthermore, acute tubular injury with focal necrosis was seen in all cases. While administration of VEGF inhibitor was discontinued in 4 cases, it was resumed for 5 more days. The patient, with the worst degree of baseline renal dysfunction, was successful in reverting anemia and led to improvement of hypertension and proteinuria in 4 of the 5 cases. One case with acute and severe TMA progressed to ESRD, but renal function of other 4 cases improved (final serum Cr 0.5-1.0mg/dl).

Conclusions: A range of renal pathologic lesions secondary to endothelial injury are noted often accompanied by acute tubular damage following anti-VEGF therapy, the most severe being TMA. While most of the clinical manifestations are reversible with discontinuation of therapy, the role of other nephrotoxic chemotherapeutic agents in enhancing renal injury and other host factors with possible poor outcome should be considered.

PUB420

Analysis of AKT/mTOR Signaling Pathway in the Renal Biopsy Tissue of Patients with Glomerulonephropathy by Luminesx xMAP Technology Hong Liu, Lujun Xu, Xiang Zhou, Fu-You Liu. Dept of Nephrology, The Second Xiangya Hospital of Central South Univ, Changsha, Hunan, China.

Background: To investigate role of AKT-mTOR signaling in the pathogenesis of glomerulonephropathy by the xMAP technology.

Methods: Kidney tissues were obtained from 25 patients who were diagnosed as IgA nephropathy, idiopathic membranous nephropathy, idiopathic FSGS or minor lesions nephropathy. The activation of AKT-mTOR signaling was determined by the xMAP technology. The correlation between AKT-mTOR and the clinical indicators was analyzed.

Results: 1. Compared with minor lesions nephropathy group, the level of hematuria of the IgAN group was higher (P=0.03). The level of pAKT, pGSK3β, pmTOR of the kidney tissue of the IgAN group was increased , and the level of pPTEN of the kidney tissue of the IgAN group was decreased than the minor lesions nephropathy group (P=0.03). Hematuria was positively correlated to pAKT, pGSK3β, pmtOR , and negatively correlated to pPTEN. 2. Compared with minor lesions nephropathy group, the level of cholestasis, triglycerides, proteinuria and hematuria of the idiopathic membranous nephropathy group was higher(P<0.04). The level of pAKT, pmtOR,pp70s6K of the kidney tissue of the idiopathic membranous nephropathy group was increased than the minor lesions nephropathy group( P=0.04). There was signifi
cant positive trend between the CD68 positive cell count and the urinary protein, but no trend was found between the CD68
cell count and the urinary protein.

Conclusions: Both entities are characterized by IgA deposits in glomeruli. However, a systemic approach to compare both diseases is lacking. The objective of this study was to assess the benefit of applying the newly described Oxford classification of IgA nephropathy, to distinguishing these two entities.

PUB421

Henoch-Schönlein Purpura Nephritis and IgA Nephropathy in Children: A Comparison Pathological Features Using “Oxford Classification of IgA Nephropathy” and Clinical Correlation Xu Zeng, 1 Murty Adabala, 2 David G. Bostwick, 1 Deloar Hossain, 1 Tej K. Mattoo. 1 Nephrocor, Bostwick Laboratories, Orlando, FL; 2 Pediatric Nephrology, Children Hospital of Michigan, Detroit, MI.

Background: Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) are common in children with overlapping clinical, genetic and immunological features. Both entities, however characterized by IgA deposits in glomeruli, have a systemic approach to compare both diseases is lacking. The objective of this study was to assess the benefit of applying the newly described Oxford classification of IgA nephropathy, to distinguishing these two entities.
Methods: Renal biopsies in Children's Hospital of Michigan during 2004-2010 with HSPN and IgAN were reviewed. The MEST scheme of "Oxford classification of IgA nephropathy" was applied to measure mesangial cellularity, endocapillary proliferation, segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis. Active glomerular lesions, i.e. the highest number of mesangial cells, percentage of glomeruli with endocapillary proliferation, cellular crescent and segmental necrosis were measured. Hypertension, protein/creatinine ratio, hematuria and estimate glomerular filtration rate were compared. Student t-test (P<0.05) is considered to be statistically significant.

Results: A total of 23 HSPN (F:M=12:11) and 26 IgAN (F:M=11:15) were included. The HSPN patients were younger than those with IgAN (7.8 ± 3.3 vs 12.4 ± 3.2, year-old, p<0.05). Patients with HSPN had more mesangial cells (11.3 ± 3.2 vs 8.3 ± 2.4), higher percentages of glomeruli with endocapillary proliferation (14.9 ± 2.2 vs 4.9 ± 8.2), cellular crescents (10.4 ± 1 vs 4.3 ± 2.8) and segmental necroses (6.6 ± 1.3 vs 0.7 ± 1.1, all P<0.05). There was no significant difference between HSPN and IgAN in MEST scheme (P<0.05). There is higher, but not significant difference in protein/creatinine ratio between HSPN and IgAN.

Conclusions: HSPN has more extensive mesangial/endocapillary proliferation and higher percentage of glomeruli with cellular crescents and segmental necrosis, thus more severe glomerular damage. These findings further characterize pediatric HSPN and will benefit to the clinical management.

PUB422
Histologic and Clinical Progression of ANCA Associated Glomerulonephritis

Background: Histologic correlates with outcomes in ANCA associated glomerulonephritis (ANCA-GN) based on IWGRP classification are limited findings on initial biopsy. Analysis of evolution of these changes over time would lead to better understanding of salvageable lesions.

Methods: Cases of ANCA-GN diagnosed from 1996 to 2009 with at least one follow up biopsy were identified. Clinical data at the time of initial (RB1) and follow up (RB2) biopsy were collected. Biopsies were categorized as Focal, Crescentic, Mixed, or Sclerotic (IWGRP classification for AA-GN) based on original pathology reports.

Results: Eighteen patients (mean age: 57 years, 50% males, 83% Caucasian, 50%p-ANCA, 33% c-ANCA) had RB2 at a mean of 47 months after RB1. RB2 was performed for suspected relapse (n=13), persistent hematuria (n=3) and CKD (n=2). Most cases were classified on RB1 as Focal (n=7) or Mixed (n=7), and showed mixed progression, with 3 Focal cases unchanged and 2 becoming Sclerotic; equal Mixed cases were classified as Focal or Sclerotic on RB2 (n=3 each). Among 7 patients who reached ESRD at a mean of 26 months post RB2, 5 patients progressed to Sclerotic and 2 were classified as Focal. Table 1. Although Crescentic cases demonstrated the lowest mean % global glomerulosclerosis (GS) at RB1, they showed greater progression to GS at RB2 when compared to Focal cases (Fig. 1).

Conclusions: All classes at initial biopsy showed progression to ESRD. The IWGRP class changes seen in follow up biopsy suggest that some active lesions revert to normal phenotype with therapy while others progress to a chronic pattern.

PUB423
The Anti-Aging Gene Klotho Represents a Potential Predictive Marker of Metastasis in Renal Cell Carcinoma (RCC). Margherita Gigante,1 Paola Pontrelli,1 Giuseppe Stefano Netti,2 C. Divella,1 Cesira Cafiero,1 Matteo Accetturo,1 Simona Simone,1 G. Grandaliano,2 Loreto Gesualdo,1 E. Ranieri,2 G. Stallone,2 "DETO, Univ. of Bari, Italy; Med and Surg Sciences Dept, Univ of Foggia, Italy.

Background: The identification of new therapeutic and prognostic biomarkers for clear cell renal cell carcinoma (ccRCC) is needed since most patients appear in advanced stages of disease at diagnosis. The nonprotective antiaging gene Klotho works as a tumor suppressor in different human cancers. Aim of our study was to evaluate Klotho expression in tissue and serum of RCC pts and correlate it with disease progression.

Methods: We used a genome wide screening of the human exons expressed in 11 ccRCCs paired adjacent non-tumoral tissue by microarray. Klotho expression in tumor tissue of primitive and metastatic RCC pts, was studied using quantitative RT-PCR and immunohistochemistry and the soluble serum levels were titrated in 35 primitive RCC, 25 metastatic RCC and 15 healthy donors, by sandwich ELISA. Comparisons of variables among different groups were performed by Student’s t-test and Mann-Whitney U-test.

Results: Frequencies were compared by chi-squared test. Kaplan-Meier estimates were used to generate overall patient survival curves and differences were assessed by log-rank test.

Results: Ingenuity pathway analysis revealed a set of genes modulated in ccRCC (FDR<5% and f.c.>2), associated with inflammatory response, cancer and renal disorders. Among them, Klotho was strongly down-regulated in all ccRCC (f.c.: -41.9, p=0.0007) respect to normal renal tissue (NT). Both at gene and protein level, Klotho significantly decreased in RCC vs NT and the down-regulation was more evident in metastatic RCC than primitive RCC. This trend was also observed in serum samples, where circulating Klotho significantly decreased in RCC when compared with healthy donors and it was dramatically decreased in metastatic RCC than primitive RCC sera (p<0.001). Lower serum levels of KLOTHO protein at RCC onset are related to worse clinical presentation and outcome.

Conclusions: The decrease of Klotho correlates with the progression of RCC and suggest a key role of Klotho in the onset of cancer metastasis.

PUB424
Proteomic Profile of Retained Proteins from Hemodialfiltration with On-Line Endogenous Reinfusion (HFR) Cartridge Mauro Atti,1 Marialuisa Caiazzo,2 Giuseppe Palladino,1 Aurora Cuoghi,1 Elisa Bellei,1 Emanuela Monari,3 Stefania Bergamini,1 Aldo Tomasi,1 Francesco Bruni,3 "Scientific Affairs, Bellico S.r.l., Mirandola, Modena, Italy; 2Nephrology and Dialysis, Civil Hospital of Modena, San Benedetto del Tronto, Ascoli Piceno, Italy; 3Dept of Diagnostic, Clinical and Public Health Medicine, Univ of Modena and Reggio Emilia, Modena, Italy.

Background: Hemodialfiltration with on-line endogenous reinfusion (HFR) is a dialytic method, which combines the processes of diffusion, convection and adsorption. The performance of this system is linked to the optimal combination of the membrane permeability and cartridge resin bed.

Lupus nephritis (LN) remains one of the most severe manifestation of systemic lupus erythematosus (LES), associated with considerable morbidity and mortality.

In this preliminary study, ESI-QTOF Mass Spectrometer was used for protein identification of ultraffrate (UF) and for the protein captured by resin bed, obtained from one dialysispatient with LN.

Methods: Plasma, UF (pre and post cartridge) of one patient with LN treated with HFR, were collected at the 15 min and at 235 min of the dialytic session. The cartridge utilized during treatment, containing styrenic resin, was opened and the proteins kept by the resin bed were eluted by incubation O/N with 60% ACN and 1%TFA. Samples was desalted and during treatment, containing styrenic resin, was opened and the proteins kept by the resin bed were eluted by incubation O/N with 60% ACN and 1%TFA. Samples was desalted and separated by SDS-page, interesting band was picked and "in gel" tricpic digested before ESI-QTOF analysis.

Results: ESI-QTOF analysis of eluted protein resulted in the identification of several biomarker of kidney injury in LN, such as Retinol binding protein 4, Neutrophil gelatinase-associated lipocain, and Cystatin-C (and TRFE, A1AG1, PTGDS, TTHY). Moreover we identify several fragment of Immunoglobulin, that are implicated in the etiopathogenesis of LES.

Conclusions: The results of this study demonstrate that, styrenic resin retain several proteins implicated in the Lupus nephritis pathogenesis the corresponding bands in the UF disappear confirming the remotion of this proteins from the cartridge.

PUB425

Background: ANCA-GN is the most common cause of rapidly progressive GN and diagnosis is made mainly by renal biopsy. The majority of cases of ANCA-GN occur in adult patients. The recent published “histopathologic classification of ANCA-GN” divides ANCA-GN into four categories, including focal, crescentic, mixed, and sclerotic, corresponding to the order of severity of renal impairment. Most of adult patients belong to the crescentic group, which has highly active renal disease and severely reduced renal function. Less is known about pediatric ANCA-GN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Renal biopsies with the diagnosis of ANCA-GN in children were reviewed. Based on the predominance of normal glomeruli, cellular crescents, and globally sclerotic glomeruli, each ANCA-GN case was categorized as mentioned above. The percentage of each group was recorded. In addition, the activity index, the percent of cellular crescent and segmental necrosis, as well as background renal function, global sclerotic glomeruli and tubular atrophy/interstitial fibrosis, were also recorded.

Results: A total of 10 ANCA-GNs (F/M=1:1) were diagnosed in children adolescents (age 12.8±3.0). The majority were female (6/10; 60%); four (30%) were crescentic, 1 was sclerotic (1/10, 10%) and none was mixed. The average percentage of crescents, necrosis, global sclerotic and tubular atrophy/interstitial fibrosis was 29.3%, 17.3%, 11.9% and 15, respectively.

Conclusions: Our findings indicate that pediatric ANCA-GN is predominately focal and has a relatively favorable outcome with mild activity including a small percentage of cellular crescents and segmental necrosis. Renal function at the time of biopsy was relatively good with a low number of globally sclerotic glomeruli and low tubular atrophy and interstitial fibrosis.

PUB426

Result of the Online Registry for Early Detection and Care of Lupus Nephritis and Other Glomerular Diseases in the Colombian Caribbean Region Gustavo Jose Aroca Martínez,1,2,3 Andres A. Cadena,1,2,4 Raul Garcia,1,5 Antonio Iglesias,5,6 Eder Augusto Hernandez Ruiz,7 Erick Estrada.7 1Nefrologia, Clinica de la Costa, Barranquilla, Atlantico, Colombia; 2Medicina, Universidad Simón Bolívar, Barranquilla, Atlantico, Colombia; 3Medicina Interna, Universidad del Norte, Barranquilla, Atlantico, Colombia; 4Nefrologia, Nefrologos del Caribe, Barranquilla, Atlantico, Colombia; 5Reumatologia, Universidad Nacional, Bogota, Cundinamarca, Colombia.

Background: The registry of the Latin American Society of Nephrology reports that 19,3% of cases of chronic kidney disease(CKD) in the region are due to Lupus Nephritis(LN) and Primary Glomerulonephritis(PGN). In the Colombian Caribbean region, there is a paucity of epidemiological data and many patients develop CKD secondary to delays in diagnosis and treatments. The purpose of this project is to create an online database that allows physicians to access in a opportune manner all the information of patients who are being actively worked up for LN and other PGN.

Methods: The NEFORED database (href="http://www.nefored.org") was created to access the information of patients being worked up for PGN and LN. The information include demographics, clinical, laboratory findings and renal pathology results.

Results: Currently the network covers 7 states in the northern side of Colombia. Collection of data started on January 2008 and continues to May 2013, 616 biopsies were included: 40.7 % of the biopsies were reported as LN and the 59.2% to PGN, 83% of the patients are mestizo and 81% are female. 65% of the biopsies with LN had an activity index between 1 and 8 and 33% between 9 and 17. In PGN the most common diagnosis were IgA GN(24.2%), Membranous GN(21.6%), Mesangial Proliferative GN(14.7%), Membranoproliferative GN(11.5%), Focal Segmental GN(9%), Minimal Change GN(4.3%) and Rapidly Progressive GN(4.3%).

Conclusions: The online Registry for Early detection and Care of LN and other GLD in the Colombian Caribbean Region improves communication between all the physicians treating patients with complex kidney diseases, the information stored in the database is an important tool to establish the prevalence, geographical distribution and to facilitate the management of patients with glomerular diseases.

Funding: Private Foundation Support

PUB427

Clinico-Pathological Features and Outcomes of Not Otherwise Specified (NOS) Variant in Focal Segmental Glomerulosclerosis (FSGS) Compared with NOS Variant in IgA Nephropathy (IgAN) Leticia Jorge, Lilian P.F. Carmon, Aline Lízara Resende, Eleson Costalonga, Leonardo Abreu Testagrossa, Denise M.A.C. Malheiros, Cristiane Bitencourt Dias, Rui Toledo Barros, Victoria Worumik. Nephrology, Univ of São Paulo, Brazil.

Background: Columbia Classification(CC) of FSGS discloses five variants with different progression rate to CKD and NOS variant is the most common form in primary FSGS. Columbia criteria can be applied to IgAAN although not usual. It is largely unknown if one histological phenotype (NOS)expressed in two different glomerular disorders(FSGS and IgAN) affects clinical disease expression and outcomes. The aim of our study was to compare clinical profile and outcomes of ours NOS FSGS patients with NOS IgAAN.

Methods: A retrospective analysis was carried out on all patients with biopsy-proven IgAN(n=165) or primary FSGS(n=80) between 1999-09. Biopsies were reviewed and classified according to CC. NOS subtypes was selected for analysis. Twenty-one patients with NOS FSGS and 25 patients with NOS IgA met inclusion criteria of age>18 years, biopsies containing at least 8 glomeruli and follow up longer than 1 year. The endpoint was defined as a variation of glomerular filtration rate(GFR) per year.(GFR/y), calculated as the difference between final and initial eGFR adjusted by follow-up time for each patient.

Results: The data are shown in Table 1.

PUB428

Clinical Course and Long-Term Follow-Up of 50 Patients with Idiopathic Membranous Nephropathy: Retrospective Cohort Camila Barbosa L. Oliveira, Alline S. A. Oliveira, Luis H.B.C. Sette, Carla Queiroz Neves, Clarissa Jacob Barros Carvalho, Gisèle Vajgel Fernandes, Maria Alina G.M. Cavalcante, Lucila Maria Valente. Nefrologia, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil.

Background: Natural course of idiopathic membranous nephropathy (IMN) is variable, and data related to prognosis were performed 2 or 3 decades ago, when antiproteinuric and immunosuppressive therapies were less well established and efficient than in present times. The aim of this study is to evaluate the clinical course and long-term prognosis of patients with IMN.

Methods: We conducted a retrospective cohort of adult patients with IMN and nephrotic syndrome between 1997 and 2012. Complete remission (CR) and partial remission (PR) were evaluated. Time to doubling creatinine (Cr), Cr clearance (Cl) < 30 ml/min/1,73m 2 and renal replacement therapy (RRT) were also analyzed. Patients were evaluated until RRT, last clinical visit or lost of follow up.

Results: Demographic data, clinical and prognostic characteristics are shown in Table 1.

PUB429


Background: Resistance to corticosteroids is difficult to overcome when treating idiopathic nephrotic syndrome (INS), namely minimal change disease (MCD) and focal and segmental glomerulosclerosis (FSGS). Rituximab and calcineurin-inhibitors are efficient drugs for the treatment of steroid-dependent or frequently relapsing INS. However, there
is a lack of data on the effect of these treatments on corticosteroid-resistant (CR)-INS. This pilot study was conducted in order to test the efficacy of the tacrolimus/rituximab combination in adults with CR-INS.

**Methods:** A total of 7 patients with CR INS (3 MCD, 4 FSGS) were enrolled in this study: 4 were corticosteroid-resistant from the beginning, 3 had developed resistance after an INS relapse. All patients had been unsuccessfully treated with 1mg/kg/day of corticoids for an average of 16 weeks prior to the introduction of the immunosuppressive regimen. Our protocol treatment combined tacrolimus (target levels 4 to 8 ng/ml) and 4 weekly injections of rituximab (375mg/m²/weekly). Complete remission (CR) was defined by an albuminemia above 30g/L and proteinuria below 0.05g/mmol of creatininuria. Patients were considered in partial remission (PR) if albuminemia was above 25g/L and proteinuria below 0.025g/mmol of creatininuria.

**Results:** After a mean follow up of 22 weeks, 4 patients showed CR and 3 were in PR, allowing a rapid tapering of corticosteroids. No significant side effects were observed, such as serious infections, gastrointestinal or acute deterioration of renal function. Only 1 relapse was noted and was concomitant with a rise in the CD19+ B-cell levels.

**Conclusions:** The Tacrolimus/Rituximab combination seems to be an efficient strategy for the treatment of patients with corticosteroid-resistant INS. Nevertheless, further controlled studies are necessary to confirm our preliminary data.

### PUB430

**Assessment of Predictive Factors for Resistance to Tonsillectomy and Steroid Pulse Therapy in Patients with IgA Nephropathy**

Hiroaki Kikuchi, Hiroyuki Tanaka, Teichi Tamura. Dept of Nephrology, Yokosuka Koyai Hospital, Kanagawa, Japan.

**Background:** Tonsillectomy plus steroid pulse (TSP) therapy has been proposed as an effective method for obtaining clinical remission (CR), defined as negative proteinuria, in IgA nephropathy (IgAN) patients. However, it remains a challenge to predict outcomes for IgAN patients receiving TSP therapy. The purpose of this study was to identify the clinical and histological factors which affect obtaining of CR in IgAN patients treated by TSP therapy.

**Methods:** We retrospectively investigated 48 IgAN patients who were followed up for more than 18 months after TSP therapy between 2005 and 2012. Patients were divided into two groups, based to whether CR was obtained (CR, n=28) or not (non-CR, n=20) 12 months after TSP therapy. The base line clinical characteristics and histological findings were compared between two groups.

**Results:** Univariate analysis revealed that there was a significant difference between non-CR and CR subgroups in terms of percentage of proteinuria (1.54±1.19 versus 0.94±0.89 g/day, p<0.04), male to female ratio (13/7 versus 8/20, p=0.01) and presence of chronic lesions including global sclerosis, segmental sclerosis and fibrous crescent (p<0.01). A multivariable logistic analysis demonstrated that resistance to TSP therapy depends on age at onset (p<0.03), presence of severe proteinuria (>0.5g/day) (p=0.01) and sex (p<0.01). Presence of chronic lesions was not significant in a multivariable analysis.

**Conclusions:** Older age, male and severe proteinuria were identified as predictive factors for resistance to TSP therapy in patient with IgAN. IgAN patients with these factors may require adjunctive therapy otherwise obtaining CR 12 months after TSP therapy.

### PUB431

**Successful Use of ACTHAR in Patient with Nephrotic Syndrome and Oral Steroid Refractory Disease**

Jong M. Kild, Patrick H. Nachman. University of North Carolina, Chapel Hill, NC.

**Background:** ACTHAR gel (repository corticotropin injection) has been reported to be effective at preventing death from pulmonary hemorrhage, but is insufficient in reversing 100% of crescents on renal biopsy became dialysis dependent. All patients survived to hospital discharge. 87% (20/23) had reached end stage kidney disease (on dialysis or had received transplant) at last follow up.

**Conclusions:** Patients with anti-GBM disease frequently present with very severe renal failure, either due to the fulminant nature of the disease, or to delay in diagnosis. Our retrospective study confirms the previously reported poor renal outcomes of patients with anti-GBM and severe renal failure (Cr > 5.7mg/dL; J1). Our current therapy appears effective at preventing death from pulmonary hemorrhage, but is insufficient in reversing 100% crescents on renal biopsy became dialysis dependent. All patients survived to hospital discharge. 87% (20/23) had reached end stage kidney disease (on dialysis or had received transplant) at last follow up.

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

Underline represents presenting author.

969A
according to the intensity of the treatment. In this retrospective study, we reviewed the clinical course, treatment and outcome of patients with ANCA-related glomerulonephritis.

**Methods:** We evaluated 28 patients with ANCA-related glomerulonephritis (mean age: 54.8±13.8 years, F:M: 9/19). Clinical characteristics and outcomes of patients were investigated.

**Results:** Wegener’s Granulomatosis in 14 patients, microscopic polyangiitis in 14 patients had been diagnosed. Baseline creatinine level was 3.8±3.5 mg/dl. 21 patients (75%) had active urinary sediment. 15 patients (53%) were needed hemodialysis at the beginning. Crescentic glomerulonephritis was found in 21 patients. All patients received steroid treatment. 23 patients were received intravenous cyclophosphamide. 13 patients also underwent plasmapheresis. The mean follow-up time was 40.7±44.8 months. End-stage renal disease (ESRD) developed in 6 (21%) patients. 5 patients (17%) died due to infectious complications (pneumonia in 4, cytomegalovirus disease in 1). ESRD and death were significantly higher in patient required hemodialysis compared to the patients did not required hemodialysis (6/15 vs. 0/13, p=0.013; 5/15 vs. 0/13, p=0.031). There was no need for hemodialysis after plasmapheresis in 9 of 15 patients required hemodialysis. After the treatment, mean creatinine level was stabilized at 2.4±2.2 mg/dl.

**Conclusions:** Initial hemodialysis requirement is the most important factor for ESRD development and death in ANCA-related glomerulonephritis. Plasmapheresis in addition to steroid and cyclophosphamide improves the renal outcome in these patients. However, infectious complications, especially in terms of pneumonia, should be closely followed.

**PUB435**

Clinical Factors Affecting Cardio-Ankle Vascular Index (CA VI) in Patients with IgA Nephropathy of Low CA VI Values

**Background:** Cardio-ankle vascular index (CAVI) is commonly used as a non-invasive indicator of arterial stiffness. In general, CAVI of 9 or more is considered significant for assessment of atherosclerosis. In our previous study concerning IgA nephropathy (IgAN), baseline change of different arterioles (HAA), which is one of the factors predicting adverse outcome, significantly correlated with CAVI, and the threshold of CAVI for diagnosis of the presence of HAA was 7.55 by receiver-operating characteristic analysis. Therefore, we examined the clinical parameters affecting CAVI in patients with IgAN of low CAVI values, i.e. those without marked atherosclerosis.

**Methods:** Thirty-three IgAN patients with CAVI of 8.5 or less at the time of renal biopsy were included. The relationship between CAVI and clinical findings including serum levels of inflammatory parameters were analyzed.

**Results:** CAVI significantly correlated with systolic blood pressure (BP) (r=0.407, p<0.05). Moreover, when patients were categorized into two groups by the CAVI=7.55, CAVI significantly correlated with lower estimated glomerular filtration rate (eGFR) (44 vs 67 ml/min/1.73m², p<0.05), higher uric acid (UA) (7.5 vs 6.2 mg/dl, p<0.05), and higher lipoprotein(a) (Lp(a)) (39 vs 14 mg/dl, p<0.05). However, CAVI did not correlate with proteinuria, Hba1c, LDL-C, non HDL-C, remnant-like particle cholesterol, high-sensitivity C-reactive protein, D-dimer, and thrombomodulin, while these parameters correlated with CAVI in previous studies including patients with higher CAVI values.

**Conclusions:** These results indicate that systolic BP, UA and Lp(a) correlate with CAVI in patients with IgAN of low CAVI values and, therefore, these clinical factors may be involved in formation of HAA in IgAN.

**PUB436**

Acute Kidney Injury and Diuretic-Resistant Anasarca in a Case of Idiopathic Membranous Glomerulonephritis

**Background:** Membranous glomerulonephritis (MGN) is the most common cause of nephrotic syndrome in adult patients. Acute kidney injury (AKI) in this setting is a rare complication. Although both primary and secondary FSGS are common, published data lacks comparative studies. In this study we compared degree of proteinuria, serum albumin, response to RAAS blockade therapy was initiated in 90% of secondary FSGS and in 76.19% of primary FSGS. Differences in the clinical features, laboratory parameters and outcomes are presented in Table 1.

**Results:** Average age at presentation was 50.33 ± 10.26 years and 54% were male. The follow up period was 2678.30 ± 1627.6 days. RAAS blockade therapy was initiated in 90% of secondary FSGS and in 76.19% of primary FSGS. Differences in the clinical features, laboratory parameters and outcomes are presented in Table 1.

**Conclusions:**

1. **Primary FSGS**

   - Baseline Creatinine (umol/L)
     - Baseline Proteinuria (grams/24hrs)
     - Albumin (g/L)
     - edal Oedema
     - Incidence of VTE
     - Progression to ESRD

   - Normal 0.1001 0.1001 0.1001 0.1001 0.1001 0.1001

2. **Secondary FSGS**

   - Baseline Creatinine (umol/L)
     - Baseline Proteinuria (grams/24hrs)
     - Albumin (g/L)
     - edal Oedema
     - Incidence of VTE
     - Progression to ESRD

   - Normal 0.1001 0.1001 0.1001 0.1001 0.1001 0.1001

**PUB438**

Proteinuria in Severe Lupus Nephritis Correlates with Diffuse Foot Process Effacement

**Background:** Among the lesions of lupus nephritis, membranous glomerulonephritis (GN), mesangial GN, and minimal change glomerulopathy have all been reported to occur in patients with nephrotic range proteinuria associated with diffuse foot process effacement (FPE). This podocytopathy has not been described in other forms of lupus nephritis. The purpose of this study was to determine if any histopathologic characteristics correlate with nephrotic range proteinuria in severe lupus nephritis.

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

**Underline** represents presenting author.
Methods: We conducted a retrospective clinicopathologic study of patients with lupus nephritis (N=265) at Rush University Medical Center. Mesangial and Membranous lupus GN were excluded. In patients with severe lupus nephritis (defined as ≥50% active segmental lesions, ISN/RPS Class III, IVs; and diffuse global lesions, ISN/RPS IVg) (N=63), demographic and clinical data were recorded and analyzed. Light, fluorescence (IF), and electron microscopy (EM) was used to detail the histologic characteristics and degree of FPE.

Results: Twenty-six patients (41%) had nephrotic range proteinuria (>3 grams proteinuria/gr creatinine [g/g]) and thirty-seven (59%) demonstrated subnephrotic range proteinuria (<3 g/g). Proteinuria was greater in the nephrotic patients (6.3±4.4 g/g compared to 1.3±0.9 g/g, p<0.001). There was a greater degree of FPE seen in the nephrotic compared to subnephrotic patients (foot process width [FPW], 1991±1655 nanometers (nm) compared to 939±467 nm, p<0.001). There was a positive correlation between FPE and proteinuria, r=0.694, p=0.0001. In ISN/RPS Lupus Class III and IVs, the proteinuria was less compared to Class IVg (2.5±3.0 g/g compared to 5.5±5.0 g/g, p=0.004). FPW in biopsies with Class III and IVs was also less (Class III, 1105±712 nm compared to Class IV, 1991±1840 nm, p=0.008).

Conclusions: In severe lupus nephritis, a distinguishing morphologic feature in pathologic renal biopsy is diffuse foot process effacement. Given a lack of difference in other histologic characteristics, nephrotic range proteinuria in severe lupus nephritis may be a manifestation of concomitant podocytopathy.

PUB439
Clinical Features and Outcome in Patients with ANCA-Associated Vasculitis (AAV) with Renal Involvement in Korea: An 12 Year Retrospective Single Center Study
Hyun Chul Chung, Jong Soo Lee, Jongha Park. Univ of Ulsan College of Medicine, Ulsan Univ Hospital, Ulsan, Korea.

Background: Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are major causes of rapid progressive glomerulonephritis. But they are not common in Korea, therefore little is known about their clinical features and outcome.

Methods: We respectively investigated 29 Korean patients with renal involvement in relation to AAV during 2001-2012.

Results: This study comprises 2 GPA, 22 MPA or 5 Renal limited vasculitides(RLY) patients (mean age 61.22±13.67 years), follow up for a median of 41 months (1.44). ANCA was detected by ELISA in 28 (96.6%) of patient, of whom 23 had MPO-ANCA, 3 had PR3-ANCA, 2 both, and one patient had negative. BVAS and lung involvement at diagnosis were 17.1±6.4 and 55.2%. Four patients (13.8%) were diagnosed after maintenance dialysis more than one month. Other twelve patients (41.4%) required dialysis at initial admission period, and 7 patients among them treated with immunosuppressive drug. 4 patients were able to be taken off dialysis during treatment. Twenty patients treated with prednisolone, cyclophosphamide and/or plasmapheresis, and nine patients received supportive care and/ or hemodialysis. During follow up period, 17 relapses in 11 patients were recorded. Eleven patients (37.9%) resulted in death and other ten patients (34.5%) developed end-stage renal disease during their disease course. Mortality was associated with presence of hemoptysis, and immunosuppressive treatment.

Conclusions: Immunosuppressive treatment decreased the risk of mortality (RR, 0.38, CI, 0.11 to 1.33) and hemoptysis increased the risk of mortality (RR, 6.05; CI, 1.06 to 34.42) in Korean AAV patients.

PUB440
High Prevalence of Thyroid Diseases in Patients with Glomerulonephritis Moltualizad, 1, Sedighe Jafarian, 1 Ali Zamani, 1 Joan Blondin, 2 Mohammad Mahdi Saghedi, 1 1Nephrology Research Center, Shiraz Univ of Medical Sciences, Shiraz, Islamic Republic of Iran; 2Dept of Medicine, LSUHSC, Shreveport, LA.

Background: There are few reports on the association of thyroid diseases with different types of glomerulonephritis (GN). However, this association has not been evaluated in a systematic study so far. The aim of this study was to evaluate the prevalence of thyroid diseases in patients with different types of GN.

Methods: We conducted an anonymous cross-sectional patient surveys from Nov 2011 to Dec 2012 during 3 phases of EHR implementation (pre, start and post-EHR). Surveys were done in the domains of satisfaction, care, distraction, waiting time and visit length. The primary objective was to assess patient’s satisfaction with physician’s visit with respect to EHR implementation.

Results: A total of 187 surveys were obtained. Visit satisfaction decreased (P=0.02), exam room wait time increased (P=0.009), and visit length increased (P=0.03) after EHR implementation along with a trend towards perception of improved care as shown in the table.

Conclusion: After implementation of EHR in our nephrology outpatient clinic, patient’s wait time in the exam room and length of visit increased significantly. We believe this could be related to the learning curve phenomenon regarding EHR use among staff. Overall patient satisfaction with the visit decreased as result. We plan to repeat the survey after EHR has been implemented for a year to get past the learning curve. Despite these observations, it is encouraging to note a trend towards improved patient perception regarding overall care.

PUB442
Utility of CD4+ T Lymphocyte Counts to Determine Need for PJP Prophylaxis in ANCA Vasculitis William Franklin Pendergraft, 1,2,3 Andrew P. Murphy, 1 Karen A. Laliberte, 1 John Niles. 1Joint Nephrology Fellowship Program, Massachusetts General Hospital (MGH) and Brigham and Women’s Hospital, Boston, MA; 1Div of Nephrology, MGH, Boston, MA; 1Vasculitis and Glomerulonephritis Clinic, MGH, Boston, MA.

Background: Our group currently manages over 400 patients with anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis, the majority of which were exposed prophylactically to numerous immunosuppressants and currently receiving trimethoprim every four to six months to maintain durable remission. Prophylactic antibiosis is employed universally in these patients to prevent Pneumocystis jirovecii pneumonia (PJP). It is unclear if PJP prophylaxis is needed once patients are transitioned to rituximab alone, and if CD4+ T cell counts can be used to guide use of prophylaxis. We sought to investigate the levels of CD4+ T cells in our cohort.

Methods: We reviewed absolute CD3+CD4+ T cell counts in patients with ANCA vasculitis in our cohort who were undergoing rituximab-induced continuous B cell depletion. Additional standard clinical and serologic parameters were measured and compared.

Results: 215 patients treated by our group from April 2006 through June 2013 underwent continuous CD20-positive B cell depletion with rituximab. None of these patients developed PJP. Furthermore, there has not been a case of PJP in an ANCA vasculitis patient in the past fifteen years in our center. CD3+CD4+ T cell counts were measured in 59 ANCA vasculitis patients (64% (n=38) MPO-ANCA, 56% (n=33) Women). Nine of these patients were euthyroid, 8 were hypothyroid and 4 had subclinical hypothyroidism. The prevalence of different types of GN and different types of thyroid diseases in cases are listed in the following table:

The total prevalence of thyroid diseases was significantly higher in patients with GN compared with controls (9% vs 12%, p<0.001). Moreover, thyroid diseases were more common in some types of GN like minimal change disease (60%), membranous GN (46%) and membranoproliferative GN (46%).

Comparison: Compared with general population, thyroid diseases are more common in patients with GN, particularly in some types like minimal change disease, membranous GN and membranoproliferative GN.

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

971A
were not receiving rituximab. B cells were undetectable in the rituximab group. Median absolute CD3+CD4+ count was 461 cells/mm³ (S.D. 284, normal range 348-1456 cells/mm³). Four patients had CD3+CD4−T cell counts < 200 cells/mm³.

Conclusions: CD3+CD4+ T cells were within normal limits in the majority of patients tested despite a history of prior cytotoxic therapy. These preliminary results suggest that cessation of PJP prophylaxis in patients receiving RTX monotherapy could be considered.

Funding: Clinical Revenue Support

PUB443
Pneumococcal Sepsis in Patients with Systemic Lupus Erythematosus

Tingting Li, Anitha Vijayan. Renal Div, Washington Univ, St. Louis, MO.

Background: Severe infections caused by Streptococcus pneumoniae are an important cause of morbidity and mortality in pts with systemic lupus erythematosus (SLE). Immunosuppressive therapy (IS), functional asplenia, hypocomplementemia, defective opsonization and phagocytosis, impaired humoral and cellular immunity, and nephritis may contribute to increased susceptibility and severity of pneumococcal infections in this pt population. We aim to describe pt characteristics, clinical presentation and outcome of SLE pts with pneumococcal sepsis (PS).

Methods: After retrospectively identifying all cases of PS in SLE pts over a 13-year period at a single center using ICD-9 codes, we conducted a thorough chart review.

Results: Thirty cases were identified in 11 pts between 2000 and 2013. One was male, 7 AA, 4 white, aged 19-60. Ten cases had active SLE, of which 7 had nephritis. Complement levels were low in 8 cases and not available in 3. IgG level was measured in 6 pts and was low in 1. Six pts were on steroids (10-60 mg/d) on presentation with 2 taking concurrent mycophenolate. One pt was on leflunomide. The rest were not on IS. Three cases had prior splenectomy. The rest had a normal-sized spleen on imaging. Blood cultures were positive in 2 pts with a history of positive cultures (12/13 in blood and 1/13 in pericardial fluid). Twelve required ICU stay and 9 had septic shock. Sources of PS included tubo-ovarian abscess (1), pneumonia/empyema (3), pericarditis (1), meningitis (2), endocarditis (2), cellulitis (2), septic arthritis (2). Infection source was not identified in 2 cases. Two pts had recurrent PS, 5 and 12 years after the initial episode. 10/11 pts survived.

Conclusions: Pts with SLE are susceptible to PS, even during periods of lupus inactivity or in the absence of IS therapy, implicating the role of immune dysfunction in SLE. Physicians should have heightened awareness for PS in this pt population. Pneumovax® should be recommended for all SLE pts and repeat vaccination should be given after 5 years. Per recent CDC recommendation, vaccination with Prevum 13® should also be a consideration.

PUB444
Analyses of Renal Dysfunction and Hyperuricemia in Patients with Chronic Hepatitis C Receiving Telaprevir-Based Triple Therapy

Satoshi Ooashin,1 Kenji Ito,1 Yasuhiro Abe,1 Mao Watanabe,1 Takao Saito,2 Hitoshi Nakashima,1 1Div of Nephrology and Rheumatology, Internal Medicine, Fukui University School of Medicine, Fukui, Japan; 2Medical General Research Center, Fukui University School of Medicine, Fukui, Japan.

Background: Telaprevir (TVR) are available in combination with peginterferon and ribavirin for the treatment of chronic hepatitis C. It was reported that TVR caused a limited case of transient and reversible increase in serum uric acid (UA) and decrease in eGFR in patients who were enrolled in phase 3 trial. Recently, reports of severe renal dysfunction and hyperuricemia were increasing in post-marketing surveillance. We evaluated the association between the background and adverse effects especially, renal dysfunction and hyperuricemia in patients treated by telaprevir-based triple therapy (TT).

Methods: Fifty seven patients were administered TVR. We measured the change of eGFR and serum UA, the percent of fractional excretion of UA (FEua), %recovery of eGFR and other laboratory findings.

Results: All patients decreased eGFR after TT including subclinical states. The decrease change rate of eGFR was divided into quartiles (Q): 70-48%, Q2: 47-39, Q3: 38-32, Q4: 31-12. There were no association between quartiles of the change of eGFR and background of patients on administration (age, sex, eGFR, hemoglobin, albumin, UA). Comparing with Q1, which had a 77% recovery of eGFR, there were lower in Q3 (91%, p<0.01) and Q4 (99%, p<0.01). Comparing with Q1, which had a 93% increased change of UA, there were higher in Q3 (60%, p=0.024) and Q4 (60%, p=0.027). A mean FEua was 3.95±1.55% after TT. There were no association between FEua and quartiles of change of eGFR. One case of patients had a renal hypouricemia (UA:0.4mg/dl), eGFR was decreased as well as other patients.

Conclusions: Renal dysfunction and hyperuricemia frequently occur after TT. The stronger a patient occurs renal dysfunction, the longer a patient has a time of renal recovery. Hyperuricemia appears to be the cause of lower UA excretion. Renal dysfunction is independent of hyperuricemia. It should be noted that eGFR is frequently measured after TT. We need to try uricosuric drug such as benzbromarone.

PUB445
Use of Monitoring Equipment and Fluoroscopy in the Insertion of Haemodialysis Permanent Catheter Essential or Ancillary – A Four Year Prospective Comparative Study

Ebadur Rahman, Naveed Aslam, Nader Mohamed Omran, Seddeq Younis, Ahmed Soliman, Raees Farhan Mushfaq, Dujanah Hassan Mousa. Nephrology, PSSMC.

Background: Monitoring equipments are used during the insertion of central lines and permanent catheters in hospital settings however, in proficient hands these equipments might not be essential. Hence a comparative study was done in Riyadh Military Hospital.

Methods: 388 consecutive patients were included in the study from June 2009 to June 2013. The Hemodialysis permanent catheter insertion was done by two groups: Nephrologists without monitoring equipment or fluoroscopy and vascular surgeons with monitoring equipment and fluoroscopy. Blood pressure, pulse and ECG were monitored by the monitoring equipment. The overall immediate complications and failure rates between the two groups were analyzed by SAS Software version 9.2. The unstable patients (with hypotension, with pacemaker or arrhythmia) were not included.

Results: The median age of the study group was 59 years and 52% patients were male. 51% of the cases were done by nephrologists. Overall complications and failure rates were less than 1% in both the groups. Minor complications like Hematoma exit site oozing were also less than 1% in both groups. There were no fatal complications in either of the groups. Each group had one major complication (pneumothorax) which did not require any intervention. Statistical analysis was not significant regarding complications and failure rates between the two groups.

Conclusions: Monitoring equipments are used universally for catheter insertion but did not show to improve procedure related morbidity in stable patients.

Funding: Government Support - Non-U.S.

PUB446
Successful Reduction in Interdialytic Weight Gain Using Decreased Sodium Dialysate Concentration

Madhavi Katikaneni, Carol J. Blanchard, Roger F. Carabajal Mendoza, Donald T. Baumstein, Ashok P. Chaudhari. Nephrology, Metropolitan Hospital, New York, NY.

Background: Excess Interdialytic weight gain (IDWG) is associated with increased morbidity and mortality in hemodialysis patients. As a quality improvement project in a outpatient hemodialysis unit we sought to reduce IDWG by lowering dialysate sodium after first trying patient counseling. Aim was to decrease the IDWG by 1lb in pts with IDWG>6lb in 3 months time.

Methods: 14 out of total 19 patients on the first 2 shifts of Monday Wednesday Friday group had greater than 6lb of IDWG on Monday after the 3 day interdialytic interval. Of those 14 patients 8 are male and 6 are female with age range 38 to 73 yrs and average dialysis vintage of 37yrs. 86% have diabetes, 100% have hypertension, and 78% have heart failure. 9 are Hispanic, 4 African American and 1 Korean. Average number of antihypertensive medications is 3. For 2 months patients were counseled by staff using various methods. 5 out of 14 (36%) patients achieved the goal of decreasing IDWG with counseling alone. Subsequently in 8 out of 14 patients dialysate sodium was reduced to 138 meq/L from 140meq/L. One patient was excluded due to hypotension at baseline.

Results: In 1st and 3rd week 5 out of 8 (62%) of them reached the target. In 2nd and 4th week 4 out of 8 (50%) of them reached the target. No hypotensive episodes were noted. Antihypertensives were unchanged. In 36% of patients goal of lower IDWG was achieved by counseling. In those who did not improve with counseling at least 50% of those patients achieved the goal by reducing dialysate sodium. Taken together in 9 out 14 (64%) achieved reduction in IDWG with our intervention.

Funding: Clinical Revenue Support

Table 1. Patients with excess IDWG

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Average IDWG(lbs) for 4 week</th>
<th>After counseling</th>
<th>After counseling plus sodium reduction</th>
<th>Dialysate sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.8</td>
<td>7.2</td>
<td>5</td>
<td>138 meq/L</td>
</tr>
<tr>
<td>2</td>
<td>6.4</td>
<td>8.0</td>
<td>5.4</td>
<td>138 meq/L</td>
</tr>
</tbody>
</table>

Conclusions: There is no established standard of acceptable IDWG but excess weight gain leads to fluid mobil removal increasing the complications. In our study we found that decreasing dialysate sodium increases goal of lesser IDWG beyond that obtained through patient education and staff support.

PUB447
Knot a Routine Central Line: Case Report of a Tangled Guidewire

Sunny Kar, Prat M. Kar. Prat M Kar MD PA, Orlando, FL.

Background: Central venous catheter placement is a common procedure. Complications resulting from line placement are not uncommon. This is a case report of a tangled guidewire.

Methods: The patient is a 74 year old male with a history of end status renal disease (ESRD) who presented to the ER with a clotted graft in his left arm. His lab work revealed a potassium level of 6.1 mEq/L, last hemodialysis was 48 hours prior. A decision to insert a catheter for emergency dialysis was made. Due to failed attempts to insert a catheter through this internal jugular, a subclavian catheter placement was planned. Complications including, but not limited to, bleeding, infection, pneumothorax, and death were explained to the patient and an informed consent was obtained. Using the Seldinger technique the subclavian vein was cannulated. The guidewire was inserted through the introducer and a slight resistance was felt after 13 cm of insertion. The introducer was then withdrawn and replaced with a dilator. Retraction of the guide was met with significant resistance. An X-ray revealed a tangled wire.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
972A
Biopt-Derived Immortalized Human Proximal Tubule Cells: A New Model to Study the Role of Pharmacogenetics in CNI-Associated Nephrotoxicity

Nool Koons,1,4 Dirk R. Kuypers,2 Rosaline Masereeuw,2 Elena N. Levchenko,1,3
1Pediatric Nephrology, UZ Leuven, Leuven, Belgium; 2Nephrology, UZ Leuven, Belgium; 3Pharmacology and Toxicology, Radboud Univ, Nijmegen, Netherlands; 4Laboratory for Pediatrics, Dept of Development & Regeneration, KU Leuven, Leuven, Belgium.

Background: Calcineurin inhibitors (CNI) constitute the basis of most immunosuppressive regimes in transplantation, but are associated with the development of histological lesions leading to kidney failure. CNI's are metabolized by CYP3A and excreted by Pgp (MDR1), primarily in the gut and liver but also in renal proximal tubule cells (PTC). Clinical studies demonstrated a relation between common variants of CYP3A45, MDR1 genes and CNI-associated nephrotoxicity (CNIT). The mechanism is unknown. Here we established a model of human PTC that can be used to study the pathogenesis of CNIT.

Methods: A method was developed to culture cells from a protocol biopsy in renal allograft recipients. Primary cells were transfected with the SV40 and hTERT virus for conditional immortalization and differentiation. Subclones were selected based upon specific PTC markers (AQP1 and CD13) using Western Blot (WB) and FACS. Light and scanning electron microscopy were performed to detect PTC morphology. PCR and sequencing was used to assess genotype, next to quantitative RT-PCR and WB. CYP3A45 activity was assessed by midazolam(MD) hydroxylation using LC-MS and Pgp activity by calcine accumulation.

Results: From 27 out of 38 biopsies cell lines were generated. Based upon genotype, 10 subclones with PTC biomarkers, cobblestone appearance and brush border micelles were selected. CYP3A45 and Pgp mRNA and protein expression was confirmed. CYP3A45*3carriers had increased 1H4H0MDZ formation (0.83 vs 0.41; p=0.05). Pgp activity was confirmed by 138% (95% CI: 113-163) calcine accumulation, but not related to MDR1 3435C>T genotype.

Conclusions: PTC cell lines can be generated from a kidney biopsy and demonstrate functional expression of genes involved in CNI metabolism after immortalization. Differences in protein function were detected for CYP3A45 but not MDR1 genotypes. This in vitro model can be used to study the role of pharmacogenetic variation in CNIT.

Funding: Pharmaceutical Company Support - Astellas

PUB451

Significance of Serum Cholesterol Concentration for the Cyclosporine Treatment of Idiopathic Membranous Nephropathy with Steroid Resistant Nephrotic Syndrome

Takao Saito,1 Yoshie Sasatomi,2 Satoru Ogahara,2 Maho Watanabe,2 Hitoshi Nakashima,21 General Medical Research Center, Fukuoka Univ School of Medicine, Fukuoka, Japan; 2Div of Nephrology and Rheumatology, Fukuoka Univ School of Medicine, Fukuoka, Japan.

Background: For the treatment of idiopathic membranous nephropathy (IMN) with steroid resistant nephrotic syndrome (SRNS), the combination of prednisolone (PSL) and cyclosporine (CYA) is one of the important tools, and therapeutic drug monitoring (TDM) of CYA is useful for predicting the effect. Based on data of receiver operating characteristic (ROC) curves, we proposed 600 ng/mL for the therapeutic target point of CYA (ASN 2009).

However, this proposal was criticized, because CYA may be influenced by various factors in the nephrotic condition. Now we compare CYA with several factors statistically and consider TDM of CYA again.

Methods: Thirty-seven IMN patients with SRNS were treated with PSL+CYA for 48 weeks. PSL was initially prescribed at 40mg/day and tapered. CYA was given at 3mg/kg BW/day. Biochemical data in serum and 24 hours urine protein (UP) were assayed repeatedly. The remission status of nephrotic syndrome were indicated by UP. CYA was monitored more than 4 times and the average was calculated. Significance of Serum Cholesterol Concentration for the Cyclosporine Treatment of Idiopathic Membranous Nephropathy with Steroid Resistant Nephrotic Syndrome

Results: Median off-dialysis clearance was 3.6 mL/min (IQR: 2.6-4.8 mL/min) and median on-dialysis clearance was 41.9 mL/min (IQR: 37.7-87.3 mL/min). Median off-dialysis half-life was 25.8 hours (IQR: 22.7-27.3 hr) as compared to 2.5 hours (IQR: 1.6-2.6 hours). The percent removal of cefazolin during dialysis varied between patients, ranging from 34.2 to 93.3 % with a median of 56.2% (IQR: 34.2-56.2%).

Conclusions: Estimated cefazolin dialysis clearance is higher than previous estimates with thrice weekly regimens. Current dosing recommendations appear to achieve serum drug concentrations that meet existing standards for microbiological eradication. Further study is warranted in a larger cohort of patients.
Uremic Serum Inhibits the Function of Multiple Human Drug Transporters

Catherine K. Yeung, 1,2 Danny D. Shen, 1,3 Kenneth E. Thummel, 1 Jane J. Huang, 4 Jonathan Himmelfarb, 2 (Dep of Pharmacy, Univ of Washington, Seattle, WA; 2Kidney Research Institute, Univ of Washington, Seattle, WA; 3Dept of Pharmaceutics, Univ of Washington, Seattle, WA; 4Optivia Biotechnology Inc., Menlo Park, CA)

Background: In vivo pharmacokinetic studies suggest that uremia alters drug transport and metabolism; however, the underlying molecular mechanisms remain poorly defined, especially in human subjects. The purpose of the study was to determine whether human uremic whole serum and serum ultrafiltrate inhibit the transport of substrate by P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1 or OATP1B3 transporter proteins.

Methods: For this study, MDCK-II cells expressing human solute carrier transporter carriers OCT1, OCT2, OCT3, OAT1, OATP1B1, OATP1B3, or ATP-Binding cassette transporter MDR1 and Caco-2 cells expressing the ATP-binding cassette transporter BCRP were utilized. Probe substrates for each transporter were OCT2: [14C]-metformin, OAT1: [3H]-p-aminohippurate, OAT3: [3H]-estrone-3-sulfate, OATP1B1: [3H]-estradiol-17ß-D-glucuronide, OATP1B3: [3H]-CCK-8, BCRP: [3H]-β-D-glucuronide, and P-gp: [3H]-digoxin. Appropriate positive controls for inhibition were included with each set of incubations. Pooled uremic whole serum and serum ultrafiltrate were evaluated at a concentration of 10% in standard incubation medium.

Results: Changes in transport of probe substrates were observed between control serum and uremic serum for OATP1B1, OAT1, and P-glycoprotein. This difference was attenuated by removal of protein bound uremic constituents. No change was observed between control serum and uremic serum (whole/ultrafiltrate) for transporters OAT1B3, OCT3, OCT2, or BCRP.

Conclusions: We have shown that uremic toxins can alter the in vitro activity of multiple specific drug transporters and that the changes in activity are due mostly to protein bound constituents. These alterations in transporter activity may explain some of the pharmacokinetic variability observed in subjects with CKD and uremia.

Funding: Other NIH Support - KL2 TR000421 (CKY) and UH2 TR000504

Conclusion of Uremic Serum in Human Drug Transporters: Uremic Serum Inhibits the Function of Multiple Human Drug Transporters

Levo

oxacin or gentamicin.

Menlo Park, CA.

Funding: Government Support - Non-U.S.

Racial Differences in the Risk of Tenofovir Related Nephrotoxicity

Srujana Polsani, 1 Sumit Mohan, 2 Jyotsana Thakkar, 3 Ali G. Ghavri, 2 Anjali Acharya. 1 2Nephrology, Jacobi Medical Center, Bronx, NY; 3Nephrology, Columbia Univ, New York, NY

Background: Tenofovir is an effective first line agent in the treatment of human immunodeficiency virus (HIV) infection. Although Tenofovir is thought to have a low overall toxicity profile, numerous case reports and studies in literature have shown that it can cause proximal tubular injury and Fanconi syndrome. There is limited information looking at its effect on phosphate wasting.

Methods: We reviewed charts for a 101 HIV patients (44% male, 45% Black, average age 46 with a deviation of 12 years) receiving care at the outpatient HIV clinic at Jacobi Medical Center. Our cohort includes 85 pts who received tenofovir for an average of 4.4±3 years.

Results: Exposure to tenofovir resulted in overt hypophosphatemia in only 4% of patients – all of them were females with somewhat longer exposure to tenofovir (5.8±3 vs 4.3±3.1 yrs, p=0.093) who were also receiving other HAART agents. Patients exposed to tenofovir had a small but significant drop in the serum phosphate (3.5±0.6 vs 3.3±0.5, p=0.01) which on subgroup analysis appeared to remain significant only among non-Black patients (3.4±0.6 vs 3.2±0.5, p=0.03) but not among Black pts (3.5±0.6 vs 3.3±0.6, p=0.23).

Conclusions: Our results suggest possible racial pharmacokinetic differences which may be protective. Blacks appear to be less prone to developing tenofovir related nephrotoxicity as evidenced by hypophosphatemia. Hypophosphatemia is likely related to increased urinary phosphate. This subtle change appears to be an early change that precedes the development of glycosuria. These findings are being confirmed in a larger cohort.

Conclusion of Racial Differences in the Risk of Tenofovir Related Nephrotoxicity: Racial Differences in the Risk of Tenofovir Related Nephrotoxicity

Dialysis Adequacy Measures and Dialytic Removal of Levofoxacin and Gentamicin

Brian S. Decker, 1 Mary Chambers, 1 Kevin M. Sowinski. 2

Menlo Park, CA.

Funding: Other NIH Support - KL2 TR000421 (CKY) and UH2 TR000504

Conclusion of Dialysis Adequacy Measures and Dialytic Removal of Levofoxacin and Gentamicin: Dialysis Adequacy Measures and Dialytic Removal of Levofoxacin and Gentamicin

Effect of Hemodialysis on Phenytoin

Robert Zoël Bell, 1 Sarah Bezzaoucha, 1 Jean-Philippe Lafrance, 1 Louis-Philippe Laurin, 2 Michel Vallee, 1 Vincent Pichette. 1 2Nephrology, Hôpital Maisonneuve-Rosemont, Montreal, Canada; 3UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.

Background: Phenytoin is one of the main drugs used in patients undergoing dialysis as treatment of various types of epileptic seizures. Several studies have revealed that the binding of phenytoin to albumin is dramatically decreased in patients with chronic kidney disease. This phenomenon could lead to increased free plasma levels and toxicity. However, no study has yet evaluated the effects of dialysis on phenytoin-protein binding and plasma concentrations.

Methods: The plasma protein binding of phenytoin was evaluated in 10 hemodialysis patients on phenytoin maintenance therapy. Total and free phenytoin serum concentrations were collected before and after hemodialysis sessions. All the patients were dialyzed 4 hours 3 times a week with high-flux polysulfon filters.

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

Conclusion of Effect of Hemodialysis on Phenytoin: Effect of Hemodialysis on Phenytoin

Therapeutic Effect and Safety of Ginseng in Chronic Cyclosporin Treatment

Kyoung Chan Doh, 1 Long Jin, 1 Shang Guo Piao, 1 Jian Jin, 1 Seong Beom Hyeo, 1 Sun Woo Lim, 1 Byung Ha Chung, 2,3 Chul Woo Yang, 1,2 CRCID & Transplant Research Center, The Catholic Univ of Korea, Republic of Korea; 2Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: Ginseng is a popular traditional herbal medicine and has been used since ancient times. However, the study associated with ginseng effect on CsA treatment has not yet been performed. Therefore, we investigated the following issues; First, whether ginseng treatment influence immune response. Second, whether ginseng protect CsA-induced renal and pancreatic injury. Third, whether ginseng leads to unwanted drugs interactions.

Methods: We evaluated population of Th1, Th2, Th17 and Treg in treatment of CsA and ginseng in mouse spleenocyte. Allogenic Tcell proliferation was also performed in standard incubation medium. We measured renal function, histopathology, IPGTT, serum insulin, islet size, oxidative stress marker(8-OHdG) in serum and urine. To confirm pharmacological interaction between CsA and ginseng, we measured CsA level using LC-MS/MS in whole blood, and tissues.

Results: Cotreatment of ginseng with CsA decreased the population of Th17 and Th1. But, the population of IL-4 and Treg was increased by addition of ginseng. MLR results showed ginseng treatment decreased T cell proliferation in dose dependent manner. Four weeks of CsA treatment caused renal dysfunction; typical interstitial fibrosis, high level of blood glucose level, low level of insulin,and reduction of islet size. However, addition of ginseng on CsA recovered above parameters compared with CsA alone. These changes were accompanied by decreased the level of 8-OHdG. There was no difference in the CsA level between CsA alone and treated group. In addition, blood and tissues levels of CsA and ginseng were measured by ultra high performance liquid chromatography coupled with tandem mass spectrometry.

Conclusions: Cotreatment of ginseng with CsA suppressed pathogenic Tcell proliferation and elicited immune tolerance. Chronically, addition of ginseng has protective effect in CsA-induced renal and pancreatic injury via decreasing oxidative stress without drug interactions. Our results provide good evidence that supplement of ginseng has significant effectiveness and safety in transplant patient receiving CsA.

Funding: Government Support - Non-U.S.
Effects of Omega-3 Polynsaturated Fatty Acid on Renal Function and Proteinuria in Kidney Transplant Recipients Tariq Shah,1,2,3 Don Vu,1,2 Robert Naraghi,1,2 Elizabeth Cadag,2 Caron Hutchinson,3 David I. Min,2 1Transplant Research Institute; 2Center for Health Outcomes and Prevention in eGFR and proteinuria from baseline, and a p-value <0.05 was of statistical significance. Progression of kidney disease and reduce proteinuria in kidney transplant recipients (KTR). (AGPN) remain unclear. Aim- To study the impact of graft pyelonephritis on graft outcome. However the risk factors and long-term outcome of acute graft pyelonephritis (AGPN) remain unclear. 11.8%, p=0.01) respectively. No differences were found for either graft or overall survival (HR, 27.61; p=0.001) compared to Caucasians, but no difference was found between Asian recipients. In this prospective study from 2002-2011, all transplant recipients were examined. Factors Associated with Preemptive Referral for Kidney Transplant Evaluation Mohua Basu, Brendan P. Lovasik, Justin D. Schrager, Nancy G. Kutner, Rachel E. Patzer, Emory Univ School of Medicine. Background: While kidney transplantation (KTx) prior to initiation of dialysis is the optimal treatment for end-stage renal disease (ESRD), racial and socioeconomic disparities exist in access to preemptive KTx. Little is known about factors associated with referral for KTx evaluation prior to initiation of dialysis, or preemptive referral. Methods: We examined factors associated with preemptive referral in patients with no previous transplant referred to a Southeastern KTx center for KTx evaluation from 2005-2010. KTx center referral data were linked to United States Renal Data System baseline and follow-up data through September 2011. Multivariable logistic regression was used to examine the association between patient factors and preemptive referral. Results: Of 4,914 referred patients, 934 (19%) were preemptively referred. In models adjusted for patient demographic, clinical, and socioeconomic factors, white (vs. Black) patients, patients who received pre-ESRD nephrology care, and patients with private (vs. public) insurance had a greater odds of preemptive referral (Table). Female sex, glomerulonephritis as cause of ESRD, erythropoiesis use, and higher albumin and hemoglobin levels were also significantly associated with access to preemptive referral (Table). Table: Factors Significantly Associated with Preemptive Referral (Adjusted Model) | OR (95% CI) | p-Value | Low Hemoglobin (<10 mg/dL) | 0.20 (1.0-1.4) | 0.0331 | Low Albumin (<3.5 mg/dL) | 1.01 (1.1-1.8) | 0.0490 | Female Sex | 1.00 (0.6-1.7) | 0.0001 | Pre-ESRD Nephrology Care | 1.00 (0.6-1.7) | 0.0001 | Patient Insurance Status | 1.00 (0.6-1.7) | 0.0001 | Race (White vs. Black) | 0.20 (1.0-1.4) | 0.0331 | Race (Native American vs. Caucasian) | 1.00 (0.6-1.7) | 0.0001 | Background: The Southeastern United States has the lowest kidney transplant (KTx) rates in the country. To most effectively promote more kidney transplant referrals among dialysis units in the area, the Southeastern KTx Coalition conducted an environmental scan to determine existing dialysis provider beliefs, attitudes and practices related to KTx in their unit. Methods: Every dialysis unit in GA, NC & SC (n=586) was invited to participate in a survey about facility practices in helping dialysis patients get a Ktx. 51% (n=297) of facility completed the survey. Data were analyzed with descriptive statistics and bivariate and multivariate analyses. Results: The majority of surveys were completed by nurse managers (48%) or social workers (22%). 90% of respondents reported that they were comfortable discussing KTx with their patients, and over 80% have a protocol in place for KTx education. Only 19% of respondents report that 50% or more of patients are interested in KTX as a treatment option, and 87% of respondents report that <50% of their patients have success in navigating the pathway to KTx. Respondents identified the following barriers to patients receiving a KTx: Lack of patient education materials (34%), unclear KTX center requirements (22%), insufficient patient social support (61%), patient transportation (74%) and patient financial status (89%). Conclusions: This is the first study in the Southeastern United States to survey dialysis units to determine the dialysis facility-level barriers and attitudes about KTX. Results suggest that dialysis professionals are equipped to explore KTx with patients (in that they feel comfortable doing so and have a process in place); however, patient and organizational-level barriers still exist that impede Ktx parity in this region. This study can help inform future research and program development to improve dialysis patient outcomes related to Ktx. Funding: NIDDK Support, Other NIH Support - NIMHID PUBL460 An Environmental Scan of Kidney Transplant Referral Practices in Georgia, North Carolina and South Carolina Dialysis Units. Teri Brown,1 M. Ahine Amamoo,2 Rachel E. Patzer,1 Leighann Sauls,2 Jenna Krischer,2 Stephen O. Pastan,3 1College of Social Work, Univ of South Carolina, Columbia, SC; 2Southeastern Kidney Council, Raleigh, NC; 3Emory Transplant Center, Emory Univ School of Medicine, Atlanta, GA. Background: The Southeastern United States has the lowest kidney transplant (KTx) rates in the country. To most effectively promote more kidney transplant referrals among dialysis units in the area, the Southeastern KTx Coalition conducted an environmental scan to determine existing dialysis provider beliefs, attitudes and practices related to KTx in their unit. Methods: Every dialysis unit in GA, NC & SC (n=586) was invited to participate in a survey about facility practices in helping dialysis patients get a Ktx. 51% (n=297) of facility completed the survey. Data were analyzed with descriptive statistics and bivariate and multivariate analyses. Results: The majority of surveys were completed by nurse managers (48%) or social workers (22%). 90% of respondents reported that they were comfortable discussing KTx with their patients, and over 80% have a protocol in place for KTx education. Only 19% of respondents report that 50% or more of patients are interested in KTX as a treatment option, and 87% of respondents report that <50% of their patients have success in navigating the pathway to KTx. Respondents identified the following barriers to patients receiving a KTx: Lack of patient education materials (34%), unclear KTX center requirements (22%), insufficient patient social support (61%), patient transportation (74%) and patient financial status (89%). Conclusions: This is the first study in the Southeastern United States to survey dialysis units to determine the dialysis facility-level barriers and attitudes about KTX. Results suggest that dialysis professionals are equipped to explore KTx with patients (in that they feel comfortable doing so and have a process in place); however, patient and organizational-level barriers still exist that impede Ktx parity in this region. This study can help inform future research and program development to improve dialysis patient outcomes related to Ktx. Funding: NIDDK Support, Other NIH Support - NIMHID PUBL460 An Environmental Scan of Kidney Transplant Referral Practices in Georgia, North Carolina and South Carolina Dialysis Units. Teri Brown,1 M. Ahine Amamoo,2 Rachel E. Patzer,1 Leighann Sauls,2 Jenna Krischer,2 Stephen O. Pastan,3 1College of Social Work, Univ of South Carolina, Columbia, SC; 2Southeastern Kidney Council, Raleigh, NC; 3Emory Transplant Center, Emory Univ School of Medicine, Atlanta, GA. Background: The Southeastern United States has the lowest kidney transplant (KTx) rates in the country. To most effectively promote more kidney transplant referrals among dialysis units in the area, the Southeastern KTx Coalition conducted an environmental scan to determine existing dialysis provider beliefs, attitudes and practices related to KTx in their unit. Methods: Every dialysis unit in GA, NC & SC (n=586) was invited to participate in a survey about facility practices in helping dialysis patients get a Ktx. 51% (n=297) of facility completed the survey. Data were analyzed with descriptive statistics and bivariate and multivariate analyses. Results: The majority of surveys were completed by nurse managers (48%) or social workers (22%). 90% of respondents reported that they were comfortable discussing KTx with their patients, and over 80% have a protocol in place for KTx education. Only 19% of respondents report that 50% or more of patients are interested in KTX as a treatment option, and 87% of respondents report that <50% of their patients have success in navigating the pathway to KTx. Respondents identified the following barriers to patients receiving a KTx: Lack of patient education materials (34%), unclear KTX center requirements (22%), insufficient patient social support (61%), patient transportation (74%) and patient financial status (89%). Conclusions: This is the first study in the Southeastern United States to survey dialysis units to determine the dialysis facility-level barriers and attitudes about KTX. Results suggest that dialysis professionals are equipped to explore KTx with patients (in that they feel comfortable doing so and have a process in place); however, patient and organizational-level barriers still exist that impede Ktx parity in this region. This study can help inform future research and program development to improve dialysis patient outcomes related to Ktx. Funding: NIDDK Support, Other NIH Support - NIMHID
Conclusions: Minority race, pre-ESRD nephrology care, private insurance, and other patient factors play a role in preemptive referral for KTx. Interventions to increase preemptive referral may reduce racial and socioeconomic disparities in KTx.

PUB464

Live Donor Evaluation, Why Do Potential Donors Not Proceed?

Mahajaran Raman, Rachel Middleton, Grahame N. Wood. Renal Medicine, Salford Royal Foundation NHS Trust, United Kingdom.

Background: Live donation represents 38% of Kidney transplants in the United Kingdom. Live donation has become a treatment of choice. Donor welfare is paramount. Vigilant donor care and management is essential to inspire public confidence. We evaluated the reasons for unsuitability and outcomes following live donor assessment.

Methods: Retrospectively analysis of 109 donors who were referred to the consultant led live donor clinic following initial assessment in the Nurse lead clinic between the year 2009 and 2011. 49 of these donors (45%) were found to be unsuitable for donation. Evaluated donor demographics, relationship to recipient, past medical history, reasons for unsuitability, recipient eGFR and change in modality during this period.

Results: The average donor age was observed to be 47 years and majority of them were Caucasians (91%). Hypertension (19%) was the commonest past medical history followed by mental health issues (11%) and high cholesterol (10%). 31% of the recipients were in the pre-dialysis group and 69% were on RRT. The average eGFR among the pre-dialysis group was observed to be 12ml/min. 6% changed modality form pre-dialysis to requiring RRT during the assessment period. The chart below shows the various reasons for unsuitability.

Conclusions: This study is the first of its kind to explore the barriers and facilitators of getting a kidney transplant in the area of the United States with the greatest kidney transplant disparity. The study findings provide the basis for the development of targeted interventions that can improve kidney transplant parity in a way that is patient-centered.

Funding: NIDDK Support, Other NIH Support - NIMHD

PUB465

Patient Navigation to Increase Kidney Transplant Evaluation Completion in High-Risk Patients


Background: Racial and socioeconomic disparities exist in the rate of kidney transplant (KTx) evaluation completion among referred patients. An ongoing pilot study will assess the effectiveness of a patient navigation (PN) intervention to increase the KTx evaluation completion rate and to decrease the time from KTx evaluation to candidacy decision in high-risk patients at a Southeastern KTx center.

Methods: We created a risk assessment tool that uses patient demographic and clinical factors to estimate probability of waitlisting for patients referred for KTx evaluation based on center-level and national surveillance follow-up data. Patients with <40% probability of waitlisting were classified as high-risk and randomly assigned to receive PN or standard of care during KTx evaluation. Kaplan-Meier methods and Cox models will be used to assess the KTx evaluation completion rate and time from evaluation to candidacy decision for patients receiving PN compared to standard of care.

Results: Since initiation of the study in January 2013, 213 (34%) patients referred for KTx evaluation were classified as high-risk. Currently 50 high-risk patients have been assigned to receive PN and 47 the standard of care. Characteristics of referred patients appear below (Table).

Conclusions: In our cohort of donors we found low isotopic GFR to be the commonest reason for unsuitability followed by high BMI and hypertension. Hence isotopic GFR can be used as an effective screening and a cost saving tool. Incidental findings discovered among the unsuitable donors during this assessment period were appropriately managed.
Conclusions: Preliminary data support the feasibility of identifying high-risk patients and intervening with PN. The effectiveness of PN to increase the KTx evaluation completion rate and decrease disparities in KTx access will be evaluated upon study completion. Results will inform decisions about the implementation of a long-term PN program in the KTx center.

Funding: Private Foundation Support

PUB466

Tacrolimus Dose and Trough Blood Levels in a U.S. Kidney Transplant Population

Brett Pinsky, Mary Helen Tran, Aylina Riedel, Ophnipschnitt, Eden Prairie, MN; Novartis Pharmaceuticals Corp, East Hanover, NJ.

Background: The goal of this study was to examine tacrolimus (TAC) dose over time and by TAC trough levels in kidney transplant (KTX) patients.

Methods: A retrospective analysis of transplanted kidney and a prescription claim for TAC (Tacrolimus) between 01Jan2004 and 31Aug2011 was conducted using a large US healthcare claims database. The date of the first TAC claim was defined as the index date.

All patients were required to have continuous enrollment for 1 year prior (pre-index) and a minimum of 6 months following (post-index). Evidence of KTX was defined in the pre-index period as at least one claim with a diagnosis or procedure code for KTX. Incident cases were defined as having evidence of transplant surgery during the pre-index period; all other cases were defined as prevalent. Patients had ≥1 lab result measuring TAC trough level in the post-index period. Average TAC trough levels were examined from index date in three month intervals through the first year. The average daily dose of TAC was examined during the same interval and in relation to trough level.

Results: Study sample included 531 incident and 336 prevalent KTX patients with a TAC trough result. Depending on time frame, 96% to 73% of patients had a TAC level in the same time period as an available TAC trough result. Over the first year the percentage of patients with TAC levels ≥7.5 mg/dL decreased from 46% to 41%. In the prevalent group, the percentage of patients with TAC levels ≥7.5 mg/dL is 40%. Table 1 examines the shift in the population’s TAC trough levels over time and the relationship between dose and TAC trough level.

Table 1: Tacrolimus Trough Level and Dose over Time

<table>
<thead>
<tr>
<th>Group</th>
<th>N (%)</th>
<th>TAC dose (mg/dL)</th>
<th>TAC trough level (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident</td>
<td>531 (100)</td>
<td>1.91 (1.0–2.91)</td>
<td>0.7–20.0 (1.0–16.0)</td>
</tr>
<tr>
<td>Prevalent</td>
<td>336 (100)</td>
<td>0.68 (0.0–1.91)</td>
<td>0.7–10.0 (0.0–12.0)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.0 ± 0.5</td>
<td>0.7 ± 0.2</td>
<td>9.1 ± 3.5</td>
</tr>
</tbody>
</table>

Conclusions: TAC dose and trough level appear to change over time as evidenced by decreasing dosage and levels. A significant number of patients remain at a TAC level ≥7.5 mg/dL or higher. This suggests that TAC management is not routinely occurring.

Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals Corporation

PUB467

Epidemiology of Infections Requiring Hospitalisation during Long Term Follow-Up in Kidney-Transplant Patients

Laurence Champion, Christel Renoux, Valérie Boutaud, Caroline Du Halgouet, Denis Glotz, François Vtokovnik, Eric Daugas, Nephrology, Bichat Hospital, Paris, France; McGill Univ, Montreal, Canada; Nephrology, Saint Louis Hospital, Paris, France.

Background: Are there more infections requiring hospitalisation (IRH) following renal transplantation nowadays than previously reported?

Methods: We performed a retrospective cohort study of 314 consecutive renal transplant recipients from 1999 to 2012. We stratified the cohort further by date of the renal transplantation: P1: 1999-2003; n=61; P2: 2004-2009; n=39; P3: 2008-2012; n=164. Data regarding the IRH, including bacterial, viral, parasitic and fungal infections, were collected. The main objectives of the study were to estimate the incidence rate of IRH (events/100 patients/year), the median time to the first IRH in the 3 time periods (P1 being the reference period) and the risk factors of IRH following survival analysis.

Results: The patients who underwent a transplant during P3 were older, had more cardiovascular risks factors, higher titre of pre-transplant antibiotics, and received an RATG induction therapy more often. At 3 and 5 years, the graft and patient survival rates were 95%-95% and 95%-95% respectively, with a growing incidence of acute rejection from P1 to P3 (1.09: 5.62: 8.83). Overall, 172 (54.8%) patients developed at least one IRH in a total of 381 during a median follow-up of 4.18 years. The median time for the occurrence of the first IRH was shorter for most recent transplant recipients: P1: 9.53 years (IQR:95%) : 3.40 to non estimable); P2: 2.83 years (1.30-4.55); P3: 1.74 years (0.95-3.18) (p<0.05).

Incidence rate of IRH adjusted for sex and age (3.38; 9.1; 14.03), opportunist infection (0.90; 5.04; 8.48), late infection (8.3; 22.16; 36.05) and death rate increased over time (p<0.001 for all). In a multivariate Cox regression analysis, the potential risk factors for IRH were age, time under dialysis before transplant, induction by RATG, corticoid use, and a transplant after 2004.

Conclusions: The incidence rate of IRH increases over time. This higher incidence might be related to different patient profiles and immunosuppressive protocols including RATG.

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

Underline represents presenting author.

977A
Lower Incidence of Post-Transplant Diabetes Mellitus after Kidney Transplantation with Reduced Tacrolimus Levels and Angiotensin Receptor Blockers

Medina Boran,1 Mertya Boran,1 Ertay Boran,1 Faruk Gonenc. 1Dept of Nephrology, Hemo dialysis and Transplantation, Turkiye Higher Education Hospital, Ankara, Turkey; 2Dept of Urology, Spectrum and experience high morbidity and mortality. Better allograft prognostic tools may allow recipients maintained on reduced tacrolimus (TAC) based immunosuppressive regimen that were associated with the development of this complication in kidney transplant that compared clinical outcomes of 137 kidney allograft recipients transplanted in a single center from 2004 to 2011 receiving reduced TAC, mycophenolate mofetil (MMF) and minimal prednisone and ARB. In an attempt to detect risk factors predisposing to PTDM, data were compared between 12 recipients with PTDM and 125 recipients without PTDM.

Results: In this study, we selected consecutive 137 kidney transplant recipients receiving TAC, MMF and steroid. PTDM occurred in 12 of the recipients (9.6%) 30 days after transplantation. A multivariate analysis including variables which have significant effect on PTDM risk in univariate analysis revealed that recipients who were overweight (>65kg) (p=0.004) and have target TAC trough levels (p=0.005) have significant risk of PTDM.

Conclusions: In our study, kidney transplant recipients with reduced dose of TAC and steroid and additional ARB therapy showed low incidence of PTDM. The incidence of PTDM was associated with the doses of immunosuppression and overweight of the kidney transplant recipients. These findings demonstrated that PTDM is more consistent with an insulin resistance than with an insulin deficient state. PTDM was not representing a risk for poor graft and recipient outcomes.

Interstitial Fibrosis and Tubular Atrophy as a Predictor of Median Renal Allograft Survival

Ana Paula Rossi,1 Maxwell Yisheng Li,2 Mahendra Mangray,1 Douglas M. Dressel,1 John P. Vella. 1Div of Nephrology and Transplantation, Maine Medical Center, Portland; 2Dept of Medicine, Medstar Georgetown Univ Hospital, Washington, DC; 3Dept of Pathology, Spectrum Medical Group, ME.

Background: Many patients with failing grafts start dialysis without adequate access and experience high morbidity and mortality. Better allograft prognostic tools may allow improved preparation for ESRD.

Methods: Retrospective review of 175 kidney transplant recipients undergoing for cause graft biopsies. IFTA was graded according to the Banff criteria. IFTA was graded according to the Banff criteria. Main outcome was graft loss. Kaplan Meier curves and Cox proportional hazards model were used for analyzing graft survival.

Results: Mean follow up time was 16 ±13 months. Thirty patients (17%) lost their grafts. Mean graft age was 47 ±51 vs 25 ±48 months for lost vs functioning grafts (p=0.02). Subjects with graft loss were younger (41 ±16 vs 48 ±14 years, p=0.03), had a higher creatinine (Cr) 3.3 ±2.1 vs 2.3 ±1.3 mg/dl, (p=0.002) and IFTA grade (p<0.001), and were more likely to have antibody mediated rejection (34.8 ±15.4% vs 15.4%, p<0.05). Independent predictors of DGF were AKI defined by AKIN criteria(OR 4.94, p<0.05) and non-AKI groups.

Working up for AKI donors (Ongoing / Ongoing – previous medical history / no medical history) 33 (18/18) 85% (17/21/17/17) 100% (11/4/5/11)

Conclusions: Median graft survival from biopsy is significantly shorter for grafts with IFTA grade II or higher compared to lower degrees of fibrosis.

What Factors Influence Renal Transplant Wait List Status

Mary McCarthy, Sarah Margaret Moran, William D. Plant. Nephrology, Cork Univ Hospital, Ireland.

Background: Renal transplantation (RTX) is the optimum form of renal replacement therapy (RRT) for End Stage Kidney Disease (ESKD) patients. Not all patients are suitable for listing; a variety of processes are necessary for patients to transition onto the wait-list; the reasons why a patient is not listed at a particular time point may vary; standardisation of processes may streamline future wait-listing strategies.

Methods: A cross-sectional single-centre study was performed. Departmental ESKD Registry identified all patients treated by any form of long-term dialysis on 31/12/12. Low clearance patients and patients with failing RTX were not included. Transplant wait-list status, transplant history, age, gender, ESKD vintage, modality of RRT, and reasons for current status were established by electronic and paper record review, supplemented by supervising Consultant interviews.

Results: 167 patients were identified. Mean age was 61 (range 26-90, median 62) years. Mean ESKD duration was 58 (range 0–368, median 36) months. 22 (13%) had had previous transplants. 134(80%) were undergoing centre haemodialysis, 6(4%) home haemodialysis, and 27(16%) home peritoneal dialysis.

Clinical Usefulness of AKI Criteria in Deceased Donor Kidney Transplantation

Myung Hyun Lee, Jong Hoon Lee, Keun Suk Yang, Yul Hee Cho, Ji Hyun Yu, Seun Deuk Hwang, Cheol Whee Park, Yong-Soo Kim, Chul Woo Yang. Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary's Hospital, Seoul, Republic of Korea.

Background: In this study, we analyzed the renal graft function and graft survival after kidney transplantation (KT) from deceased donors with acute kidney injury (AKI) defined using AKIN (Acute Kidney Injury Network) criteria.

Methods: We analyzed 157 deceased donor kidney grafts transplanted at our institution between September 1996 and December 2012. Donors were divided into non-AKI (n=112) and AKI groups(n=45) according to the AKIN classification. Out of 45 AKI donors, 35 donors(22%) were included in stage 1, (96%) in stage 2 and (0.6%) in stage 3 categories. We compared the incidence of delayed graft function(DGF), the change of allograft function assessed by MDRD-eGFR until 1 year from KT and graft failure between AKI and non-AKI groups.

Results: The proportion of deceased donors with diabetes, hypertension and old age (>50 years) did not differ between AKI and non-AKI groups. The development of DGF was significantly higher in the AKI group than in the non-AKI group recipients (12.3% vs 8.3%, p<0.05). Independent predictors of DGF were AKI defined by AKIN criteria (OR 4.94, p<0.001) and PRa(panel reactive antibody) percentage (OR 1.01, p<0.009) in multivariate
analysis. Allograft function until 6 months from KT showed significantly deteriorated pattern in AKI group compared to non-AKI group as well (9.12±5.69 vs 19.37±15.61, 43.74±24.83 vs 58.65±26.73, 53.29±32.3 vs 61.34±20.81, 54.97±18.72 vs 61.26±18.05, 56.39±19.09 vs 62.09±18.18, p<0.05; MDRD-eGFR on 3 day, 2week, 1month, 3months and 6months in AKI and non-AKI group, respectively). However, allograft function at 12 months from KT did not differ between two groups (58.92±20.63 vs 63.07±23.57, p=0.05; MDRD-eGFR in AKI and non-AKI group, respectively). Graft failure also did not differ between two groups (2% vs 7.4%, p>0.05, AKI and non-AKI group, respectively).

Conclusions: In conclusion, definition of AKI according to AKIN criteria in deceased donor is useful to depict the development of DGF and the change of allograft function after KT.

PUB474
Immunosuppressive Regimen Adjustment Has No Effect on Serum Cystatin C Concentration in Patients with Severe Pulmonary Infection after Renal Transplantation Fei Liu, Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China.

Background: Assessment of renal function is of vital importance for patients with renal transplants. Cystatin C has the characteristics of an ideal marker to assess renal function.

Methods: A descriptive, analytical and prospective study was conducted between January 1, 2010 and January 31, 2013 on 27 renal transplant recipients with severe pulmonary infection.

Results: Immunosuppressive drugs was discontinued in 27 cases of the them and the methylprednisolone 40 mg only used by intravenous drips once a day. The forbidden course of immunosuppression was 7 to 20 days. The dose of immunosuppressive drugs was decreased in 13 cases of them. No patients had rejection during the forbidden course of immunosuppression and followed for a median of 4.8 months (range=3-7 months). Clinical improvement in renal function was noted even in patients with chronic allograft fibrosis and tubule atrophy.

Conclusions: Our results showed no significant difference for serum cystatin C was obtained between before and after adjustment of immunosuppressive regimen. Adjustment of immunosuppressive regimen was effective and safe for patients with severe infection after renal transplantation. Serum cystatin C may be considered as a sensitive predictive parameter of kidney function in renal transplant recipients with infection.

PUB475
Improvement in Renal Function in High Immunologic Risk Kidney Transplant Recipients Switched from Tacrolimus to Belatacept Gaurav Gupta1, Stacey Posner, Dhiren Kumar, Qing Ren, Marc P. Posner, Amit Sharma, Anne L. King. 1Nephrology, Virginia Commonwealth Univ, Richmond, VA; 2Transplant Surgery, Virginia Commonwealth Univ, Richmond, VA.

Background: Belatacept might be an alternative to Calcineurin Inhibitors (CNI) to avoid short- and long-term nephropathy. Prior data on low immunologic risk de-novo kidney transplant recipients (KTx) switched from a CNI to belatacept demonstrated improved renal function. There is no literature on the use of belatacept for sensitized patients or regrfts.

Methods: All patients were confirmed to be EBV seropositive. Tacrolimus (tac) was tapered and belatacept initiated based upon prior published protocol (Grinyo et al., Transpl Int. 2012 Oct;25). Mycophenolate mofetil dose was increased to a dose of 2-2.5g/d to minimize risk of rejection.

Results: Five patients, of whom 60% (3/5) were African-American, were switched from tac to belatacept and followed for a median of 4.8 months (range=3-7 months). Clinical features are listed below:

- Age: 50, 48, 49, 60 and 65 years
- Hyperlipidemia: Yes (50%)
- Hypertension: Yes (50%)
- DM: Yes (40%)
- HTN associated with DM: Yes (40%)
- Scars: Yes (50%)
- Possibility of DVT: No (50%)
- Prior CABG: Yes (20%)
- Prior valve procedure: Yes (20%)
- Prior transplant: Yes (20%)
- Prior HCV: Yes (20%)

Conclusions: The two patients who underwent CABG and the rest of the group (42.9%) required valve procedure in patients with HCS, therefore such patients could be included in KT programs.

PUB476
Metformin Use in Kidney Transplant Recipients in the United States Aisw K. Israni, Sally K. Gustafson, Jon J. Snyder, Bertram L. Kasiskie. 1Scientific Registry of Transplant Recipients, Minneapolis, MN; 2Medicine, Hennepin County Medical Center (HCMC), Univ of Minnesota (UMN).

Background: Metformin is contraindicated in patients with "renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance)" (US Food and Drug Administration) due to the risk of lactic acidosis. The prevalence of metformin use in kidney transplant recipients (KTX) in the US is not known.

Methods: We linked Scientific Registry of Transplant Recipient data for all incident KTX occurring between 2001 and 2012 with pharmacy claims from a database constructed from administrative claims data with the use of pharmacy claims. We then excluded records that were inconsistent between the two databases based on gender, date of birth or state of residence; and required at least one pharmacy claim post-transplant. The final dataset included 123,533 KTX, which represented 82.1% of the initial match and 63.9% of all KTX recipients.

Findings: There were 4,291 patients (3.5%) of KTX who met at least one claim for metformin post-transplant and the number of claims for metformin ranged from 1 to 111 per KTX. Over 50% of these KTX had 5 or more claims. The first claim for Metformin was at a mean of 1116±950 days post-transplant and the creatinine level prior to this first claim was 1.45 mg/dl ±1.22 (Interquartile range, IQR 1-1.5). Characteristics of KTX on metformin versus the remaining 119,242 not on metformin are shown in Table.

<table>
<thead>
<tr>
<th>Baseline characteristics of kidney transplant recipients on metformin versus those not on metformin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (in years)</td>
<td>60.1±12.7 vs. 59.7±12.8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1,222 (84.1%) vs. 23,771 (84.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,244 (85.2%) vs. 24,074 (84.9%)</td>
</tr>
<tr>
<td>Prior diabetes</td>
<td>358 (24.5%) vs. 6,040 (21.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>708 (47.5%) vs. 10,460 (39.6%)</td>
</tr>
</tbody>
</table>

Mean Altered (membrane) SCr levels in mg/dL across treatment groups were 1.9±0.2 vs. 2.4±0.2 (p<0.001).

Conclusions: Metformin has been used in 5.3% of KTX. The KTX on metformin had a lower creatinine than those not on metformin. The KTX on metformin will be compared for morbidity and mortality with diabetic KTX not on metformin.

PUB477

Background: The survival of patients who undergo kidney transplant (KT) has improved considerably over the past three decades, death with a functioning kidney is a major reason for graft loss. Few published studies address renal graft and patient survival in patients with a history of cardiac surgery (HCS), which is important due to pretransplant cardiac disease (CD) is a major risk factor for developing post transplant CD.

Methods: Between 1995-2012, 600 KT were performed in our center including 7 cases with HCS. We compared those cases with 21 patients who did not have HCS. We recorded renal function parameters at baseline (at discharge of KT), 6 and 12 months of follow up. In patients with HCS we analyzed echocardiogram parameters before and 1 year after KT.

Results: The age was significantly higher in HCS group. In HCS group the principal etiology of ESRD was diabetes (57%). Concerning anamnesis of medical procedures, most patients (57.1%) underwent CABG and the rest of the group (42.9%) required valve replacement including one case with three cardiac valve replacement. All patients underwent first KT. The median time between cardiac surgery and KT was 8 months (25-75% IQR: 7-28). At 12 months of follow up serum creatinine were no significantly different between groups (1.4±0.12 vs. 1.5±0.4 mg/dL in HCS and no-HCS group respectively). One-year patient and graft survival in both groups was 100%. In HCS group the ejection fraction increased after KT (45.3±13.5 vs. 51.3±18.5%, p<NS, before and one year after KT respectively).

Conclusions: In dialysis patients, the estimated survival after CRV is 40-54% and after CABG is 56% at 2-year. Debska reported a one year survival of 93% in 16 dialysis patients who had HCS and underwent KT. We found one-year graft and patient survival of 100% which is better compared with others reports. At one year of follow up we observed improvement of ejection fraction, no significant maybe due to sample size. Kidney allograft function was similar between groups at the end of follow up, thus it seems probable that patients with HCS have a favorable long term prognosis. We consider that KT is a safe procedure in patients with HCS, therefore such patients could be included in KT programs.
not requiring dialysis. This study evaluates the association between the velocity of initial kidney graft recovery estimated by the change in plasma creatinine (p-creatinine) and graft function after one year.

Methods: A single center, observational, cohort study including 100 kidney transplants followed for one year at Aarhus University Hospital. p-Creatinine was registered immediately before transplantation, daily the first seven days post transplant and finally after one year along with relevant patient characteristics. Patients with no improvement in graft function or requiring dialysis within the first week of transplantation were excluded. A total of 80 patients remained in the analysis. Time to a 50% drop in p-creatinine after transplantation was calculated based on whether an exponential or logistic decrease of p-creatinine over time, depending on which model fitted the single patient data best. A multiple linear regression model was used to analyse the association between the time to a 50% drop in p-creatinine and p-creatinine after one year.

Results: The time to a 50% drop in p-creatinine correlated positively with p-creatinine at one year (r=0.31, p=0.0052). The correlation persisted when corrected for donor type and recipient age, initial p-creatinine level, sex, number of rejections and use of calcineurin inhibitors (p=0.0468).

Conclusions: The initial change in p-creatinine is independently associated with one year kidney graft function indicating 1) that non dialysis dependent differences in early graft function may be important for long term outcome and 2) that this may be used as surrogate marker in studies aimed at enhancing long term outcome by improvement of early graft function.

**PUB479**

Basal Creatinine as Predictor of Graft Dysfunction a Postransplant Year


Background: In renal transplant (RT) an increase of serum creatinine (SCr) ≥1.5mg/dl at 1yr of RT predict graft loss at 3yrs in almost 20%. The objective was to establish whether the creatinine at discharge postsurgical unit (SCrbasal) could predict the presence of graft dysfunction (GD) at 1yr post-RT in a Mexican population.

Methods: This is a retrospective cohort study performed between January 2009-June 2011 in 561 RT receptors; GD was defined as SCr ≥1.5mg/dl at 1yr.

Results: 71% were male receptors, living related donor in 92%, negative crossmatch 16.34%. Patients were divided according to SCrbasal values in quartiles. Risk SCrbasal was defined as that with a value >1.2mg/dl because showed a value of SCr of 1.67mg/dl at 1yr post-RT. Changes in SCr and comparison between quartiles variables are shown in table and figure *(p<0.05, **p<0.001)*.

**PUB480**

Late Onset De Novo Thrombotic Microangiopathy after Solid Organ Transplant

Mohamad Alhossaini, Krishna Pothugunta, Susan H. Hou, Kavitha Vellanki. Div of Nephrology and Hypertension, Loyola Univ Medical Center, Maywood, IL.

Background: De novo thrombotic microangiopathy (TMA) is a well-described complication with calcineurin inhibitors (CNI) and mammalian target of rapamycin inhibitors (mTORI). The vast majority of the reported cases occurred within the first year post solid organ transplant. Here we report our center’s experience with late onset TMA.

Methods: Since March 2010, we had 4 patients with solid organ transplant develop late onset de novo TMA. The patient characteristics are as shown in Table 1.

**PUB481**

Indian Transplantation of Human Organs Act (THOA) and Rules: Practical Problems

Bharat V. Shah. Nephrology, Global Hospital, Mumbai, Maharashtra, India.

Background: Transplantation of Human Organs Act (THOA) was passed to regularize organ transplant and prevent commercial dealing in transplant. While this has been achieved to a great extent, it has made living donor transplant very difficult and deceased donor transplant has not picked up. The aim of this study is to highlight with examples the problems faced in transplantation due to THOA and rules.

Methods: A detailed study of THOA and rules and their amendments has been made (http://www.orbo.org.in/Doc/Ann%204%20THOA%20ACT%202011.pdf). Further, check-list of documents to be submitted as per Directorate of Health Services, is studied. The problems are divided into those pertaining to regulation of professionals and institutions and those pertaining to patients to obtain approval of Authorization committee.

Results: Problems for professionals and institutions: 1. If a professional registered at 1 center wishes to perform transplants at another center, he/she again has to apply from that center – a process which takes months. 2. An institution is recognized for transplant purposes only in the state of its domicile. 3. An institution cannot perform any organ transplant without an Authorization committee. 4. Authorization committee often questions medical evaluation of the transplant team.

Conclusions: Late onset TMA should be considered in the differential diagnosis of acute kidney injury in solid organ transplant patients on CNI or mTORI therapy for immunosuppression after solid organ transplant.

**PUB482**

Comparing 10 Year Renal Function Outcomes in Patients with Live Donor and Deceased Donor Liver Transplant: A Single Center Retrospective Study


Background: Incidence of chronic kidney disease is approximately 25% by 10 years after an orthotopic liver transplantation (OLT). Long term survival of patients undergoing living donor liver transplant (LDLT) compared to those undergoing deceased donor liver transplant (DDLT) have yielded mixed results and no literature exists comparing the long
term renal outcomes in this patient population. LDLT have become rare at our institution. The purpose of this study is to compare longterm renal outcomes in patients who underwent LDLT to DDLT.

Methods: A retrospective analysis of patient who received an OLT in years 2000 and 2001 was conducted. Data was obtained from databases UNOS, EPIC and OTTR.

Results: A total of 229 OLT were performed in the years 2000 and 2001, of which 82 were LDLT and 137 were DDLT. 1 combined liver and kidney transplant was excluded. Overall patient survival was: 87.7% at 6 months (87.8% for LDLT and 87.6% for DDLT), 84.5% at 1 year (84.1% for LDLT and 84.7% for DDLT), 69.9% at 5 years (74.4% for LDLT and 67.1% for DDLT) and 53% at 10 years (57.3% for LDLT and 50.3% for DDLT).

Graft survival was: 80.8% at 6 months (80.5% for LDLT and 81% for DDLT), 76.2% at 1 year (75.6% for LDLT and 76.6% for DDLT), 61.6% at 5 years (63.4% for LDLT and 60.6% for DDLT) and 47.5% at 10 years (47.6% for LDLT and 47.4% for DDLT). 9.1% patients needed some form of RRT prior to the transplant and 25.1% in the immediate post transplant period. Our preliminary data suggest no significant difference in the average GFR of patients who received LDLT versus DDLT at 6 months, 1 year, 5 years and 10 years. We await more robust statistical analysis of this data.

Conclusions: Preliminary data shows that patients who receive LDLT and DDLT may have similar 10 year renal function outcomes.

PUB483
The Effect of Weight Loss Surgery before Kidney Transplant on Recipient Outcomes

Julie Ann T. Limatoc, Haidri Sabah Agha, Qing Ren.
Virginia Commonwealth Univ.

Background: Obese patients with a body mass index (BMI) greater than 35 are often denied kidney transplantation. Obesity is associated with poor graft and patient survival and higher risk of wound infection. Weight loss surgery before kidney transplant may be a solution in this clinical scenario.

Methods: We retrosively studied patients from January 2004 to June 2013 who underwent weight loss surgery, either laparoscopic gastric banding (LGB) or Roux-en-Y gastric bypass (GBP) prior to kidney transplant.

Results: Our series included 9 patients. Eight of 9 patients had a BMI below 30 at the time of kidney transplant and maintained BMI less than 35 post transplant. Waiting time for 4 deceased donor (DD) kidney transplants was between 2 to 11 months. Only 1 of 5 recipients who were not diabetic prior to transplant developed new onset diabetes mellitus. All patients have excellent allograft kidney function with no wound infection or cardiovascular complications.

Conclusions: Weight loss surgery before kidney transplant could be used effectively to control obesity and allow these obese renal failure patients to have the opportunity of successful kidney transplantation with excellent outcomes.

PUB484
Perceived Bias in the Kidney Allocation System Predicts Mortality among Black Hemodialysis Patients

Avram Gillespie, Vladimir Ouzienko, Jeanne Dreier, Teri Browne, Zoran Obradovic.
Temple Univ School of Medicine, Philadelphia, PA; Center for Data Analytics and Biomedical Informatics, Temple Univ, Philadelphia, PA; 1st SRBI, Silver Springs, MD; College of Social Work, Univ of South Carolina, SC.

Background: Perceived racism has been associated with disparities in renal transplantation and poorer health outcomes for African American hemodialysis patients. This study aimed to determine if perception of the kidney transplant allocation system as racially biased predicts mortality independent of biomarker data in a cohort of urban, African American hemodialysis patients.

Methods: In this study of the 101 end-stage renal disease (ESRD) patients who self-identified as black or African American in a hemodialysis clinic survey, perceived racism and other subjective variables were measured with the Dialysis Patient Transplant Questionnaire (DPTQ) and merged with prospective biomarker and mortality data. The predictive association with mortality was measured using chi-square, Fisher’s exact test, and multivariate logistic regression.

Results: Twenty-two patients (21.8%) died during the study period. Fisher’s exact tests showed that patients who thought the kidney transplant allocation system was definitely or mostly biased against blacks were 2.49 times more likely to die compared to those less certain (P=0.001). Serum albumin was also associated with mortality, however, in general, patients that perceived racism were more likely to die independent of their biomarkers.

Conclusions: This is the first study to validate the link between perceived racism in the kidney allocation system among African American hemodialysis patients.

PUB485
Effect of mTOR Inhibitors in Patients with Severe Posttransplantation Encapsulating Peritoneal Sclerosis

Edin Colic, Claus Bistrup, Helle C. Thissen, Niels Marcussen, Martin Tepel.
Nephrology, Odense Univ Hospital, Odense, Denmark; Pathology, Odense Univ Hospital, Odense, Denmark.

Background: Posttransplantation encapsulating peritoneal sclerosis is a live threatening complication seen in patients after kidney transplantation who had previously been treated with peritoneal dialysis. In the present study we investigated the effects of mTOR inhibitors on outcome in patients with severe posttransplantation encapsulating peritoneal sclerosis.

Methods: Using the transplantation registry of the Odense University Hospital of Southern Denmark, we identified all patients with kidney transplantation between 2006 and 2012. The risks of encapsulating peritoneal sclerosis as diagnosed by radiological or histological signs and need for laparotomic or laparoscopic interventions were estimated. In addition, the effects of treatment with mTOR inhibitors during follow up were evaluated. Major outcome measures were patients’ survival, graft survival, number of acute rejections and relapse of encapsulating peritoneal sclerosis.

Results: A total of 341 transplanted patients were evaluated. Five (4 female and 1 male) out of 94 patients with previous peritoneal dialysis (5.3 percent) developed posttransplantation encapsulating peritoneal sclerosis. Median age was 54 years (range, 46-59). Median duration of peritoneal dialysis was 63 months (range, 36-107). Median time for development of encapsulating peritoneal sclerosis after transplantation was 13 months (range, 1-38). 1 patient was shifted to capamycine, whereas 4 patients were shifted to everolimus. During a median follow up period of 21 months, 2 patients developed a relapse of encapsulating peritoneal sclerosis necessitating additional surgical interventions. Graft loss was observed in 2 other patients. There were no acute rejections. All 5 patients are still alive.

Conclusions: This retrospective observational study in patients with severe posttransplantation encapsulating peritoneal sclerosis with need of surgical intervention shows that shifting from calcineurin inhibitors to mTOR inhibitors did not ameliorate ongoing fibrosis. However, altered speed of progression can not be excluded.

PUB486
Assessing the Quality of Deceased Donor Kidneys by Simple and More Accurate Prognostic Factors

Ana Pinho, Ínês Castro Ferreira, Isabel Tavares, Susana Moreira Norton.
Nephrology, Faro Hospital, Faro, Portugal; Nephrology, São João Hospital, Oporto, Portugal.

Background: Since the increasing use of lesser quality kidneys, both survival benefit and a quality of life advantage of kidney transplantation over dialysis is known a difficult question of patients to their transplant team. In order to clarify, several Donor Risk Indexes (KDI) were derived from many potential donor factors that need to be validated. The aim of this study was to determine which donor factors predict poorer transplant outcome.

Methods: Data from transplant registry on 273 adult recipients of adult deceased donor kidney transplants, performed consecutively between 2009 and 2012 were analyzed. Donor factors potentially influencing transplant outcome were investigated using Cox regression, adjusting for significant recipient and transplant factors.

Results: Donor hypertension was the most significant factor predicting poor transplant outcome (hazard ratio [HR] 4.96; 95% confidence interval [CI] 1.81 to 13.55). The cause of death by cerebrovascular accident (HR 3.85; 95% CI 1.49 to 9.92) and Donor age (HR for a 10-yr increase 1.44; 95% CI 1.1 to 1.78) were also associated with increased risk with poorer outcomes up to 4 years posttransplant. Other donor factors including diabetes history, longer hospital stay before death, use of adrenaline, previous infection and terminal creatinine were not significant.

Conclusions: This finding corroborates the relevance of donor risk factors, such as age, cause of death and hypertension; that may be of value for researchers and clinicians in provide a clinically useful tool that help with organ allocation and informed consent.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Complications Associated with Failed Pediatric Renal Allograft

Murty Adabala,1 Tej K. Matteo,1 Gaurav Kapur,1 Rossana Baracco,1 Amrish Jain.1 1Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 2Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 3Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 4Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 5Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI.

Background: NAPRTCS data reports 18-30% graft loss in the 1st 5 years post transplant. The failed graft in adult is associated with increased morbidity and mortality. However, there is paucity of pediatric reports on complications associated with failed renal allograft and their outcome.

Methods: Retrospectively reviewed medical records of patients with failed renal transplant over last 10 years (2001-2011). For study purpose, graft intolerance was defined by presence of chronic inflammatory state, pain at the graft site or hematuria.

Results: Of the 470 KTRs studied (mean age =36.5±12.1 years; M:F = 3.3:1), 9.6% received deceased donor grafts, Basillitximab induction in 62.7% with prednisone + Tacrolimus + Mycophenolate in 61.6% and Valganciclovir (3 months) in 62.4%. The overall incidence of CMV disease was 14.9 %. Valganciclovir effectively reduced CMV disease (10.9% vs. 21.5%; p<0.01; NNT=10), delaying its onset (median time of 11.9 vs 3.7 months) and reduced the degree of viremia. However, Valganciclovir was not associated with any difference in tissue invasive disease, recurrence or CMV associated mortality. There was however, a reduction in coincident infections such as Post transplant TB, varicella zoster virus and Hepatitis C virus infections as well as mortality. Graft survival was better in Valganclovir group (p<0.01) despite no difference in rejection rates, probably associated with effective immunosuppression as well as control of the indirect effects of CMV. Within the Valganclovir group also, CMV disease was significantly and independently associated with co-incident infection and mortality indicating a generalised immunosuppressed state.

Conclusions: Valganciclovir prophylaxis reduces incidence of CMV disease by 50%, delays its onset, decreases viremia and is associated with better graft and patient survival probably by controlling both the direct and indirect effects of CMV in KTRs.

PUB487

Combination Therapy of Lefunomide and Ciprofloxacin for Treatment of (Suspected) Polyomavirus BK-Associated Nephropathy in Kidney Transplant Recipient Lacking Graft Biopsy (Single Center Experience)

Seddeeg Younis, Dujanah Hassan Moussa, Ebudah Raman, Naveed Aslam, Rachas Farhan Mushtaq, Madhoud Abdulghafour Nada, Nader Mohamed Omran, Ahmad Salimian, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.

Background: Polyoma virus type BK Nephropathy (BVKN) occurs in 1-10% of Renal Transplant Recipients. Progression to Graft Failure in the First year is up to 70%. Immunosuppression Reduction (ISR) is the Treatment of BKVN. Diagnosis of BKVN is Based on BKV Replication in Blood and Histological Evidence of BKV Involvement. In this Prospective Study, we Reported 7 Patients with Graft dysfunction and Significantly High BK Viral Load, declined to do Graft Biopsy, were treated Blindly as BKVN, with addition of Lefunomide & Ciprofloxacin to Improve Graft Survival.

Methods: Blood BKV Quantitative Polymerase Chain Reaction (PCR) and Graft Biopsy for all Patients with Unexplained Graft dysfunction. Between Jan 2011 to May 2012. Seven Patients Presented with Slowly Rising Creatinine and high BK Viral Load, refused to do Graft Biopsy. The Median Creatinine at Baseline was 121 ±01 (68-174), and the Median Peak Viral Load was 7X10^4 copies/ml (1.2X10^4-3X10^5). They were treated with ISR and Combination of Lefunomide and Ciprofloxacin. Lefunomide Loading dose was 40mg daily for One Week, Lowered to 20mg Until Complete Viral Clearance or Progressive Reduction in Viral Load, then Continued at 10mg. Ciprofloxacin, 500mg twice daily for 6 Week. The treatment Monitored by Serial Measurement of LFT, FBC, Serum Creatinine, and BKV PCR. Graft Function and Viral Clearance were Followed.

Results: After 22 months (19-22) follow up, Median creatinine was 152±41 ml/(4.8-273). Creatinine was Stable in 3/7 (42.9%) and deteriorated in 4/7(57.1%), but there was no Graft Loss on follow up. Complete viral clearance Occurred in 2/7, and Significant Reduction in 5/7(5p<0.0001). There were no Serious Adverse effects.

Conclusions: Despite Good Response to Treatment of (Suspected) BKVN with ISR and Combination Therapy of Low Dose Lefunomide and Ciprofloxacin the Decline in Graft is not Determined, this Highlights the Importance of Graft Biopsy in the Diagnosis of BKVN and Alternative Etiology.

PUB490

Chronic Opioid Use, Pain and Outcomes of Kidney Transplantation

Santosh Varughese, Chakko Korula Jacob, Veerasamy Tamilarasi.1 Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 2Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI; 3Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI.

Background: Chronic opioid usage (COU) is relatively common among patients with end stage renal disease qualified for kidney transplantation. The prevalence of continued COU after kidney transplantation and its impact on transplant outcomes remains unknown.

Methods: We conducted a retrospective single center study to describe the prevalence of COU during the first year after transplantation, to identify the predictors of COU and to determine the effect of COU on patient and kidney transplant survival.

Results: Among 1045 kidney transplant patients, 114 (10.8%) had COU during the first year. The most common cause of pain was surgery-related (39.9%) and the most commonly prescribed opioid analgesic was hydrocodone (59.2%). A history of chronic opioid usage was an independent predictor of COU during the first year (AOR 2.25, 95% CI 1.35, 3.76, p=0.002) for 1 or 2 readmissions, and AOR 5.52, 95% CI 3.13, 9.76, p<0.0001 for >3 readmissions, respectively), but similar patient and kidney graft survival, both within the first year and during subsequent follow-up.

Conclusions: Clinically indicated COU early post-transplantation does not appear to increase the risk of death and death censored graft failure.

PUB491

Comparison of Cadaveric Kidney Transplantation from In-Center and External Hospital Donors

Ajin Cho, Hye Ryoun Jang, Jung Eun Lee, Woosong Huh, Yoon-Goo Kim, Ha Young Oh, Dae Joong Kim.1 Div of Nephrology, Univ of Michigan, Ann Arbor, MI; 2Nephrology, Presbyterian Kidney Transplant Center, Albuquerque, NM.

Background: Renal transplantation is the best treatment modality for end-stage renal disease. We investigated the effects of cadaver donor sources, inside vs. outside of transplantation center, on renal allograft and patient survival.
Methods: We retrospectively analyzed 190 cadaver kidney transplants carried out in our center from January 2000 to December 2009, 136 cadaver harvested in our transplant center and 54 harvested in external hospital. All patients received induction therapy and standard triple immunosuppressive protocols with cyclosporine or tacrolimus (FK506), mycophenolate-mofetil, and prednisone. Variables on this study were donor and recipient age, sex, body mass index (BMI), presence of diabetes mellitus, HLA-mismatching, dialysis duration, cold ischemic time, donor from external hospital, acute rejection episodes, delayed graft function (DGF) and panel reactive antibody (PRA) > 30%. Graft and patient survival were assessed with the Kaplan-Meier method and the significance of possible variables with the Cox proportional hazard model.

Results: Donor and recipient ages, recipient BMI, duration of dialysis, presence of DGF and PRA > 30% were not significantly different. Cold ischemic time was shorter in recipients of cadaver from our center, 288 min, than external hospital, 388 min (P<0.001). Twenty recipients lost their grafts (14 cadaver from external hospital and 6 cadaver from our center). Graft survival at 1, 3, and 5 years were 99.2%, 97.3%, and 95.5% for our center donors while 98.1%, 88.9%, and 86.2% for external hospital donor transplants (P=0.01). Total of 8 patients died (2 from external hospital and 6 from our center). No difference in patient survival rates was found. Acute rejection episodes (hazard ratio [HR] =13.8; P<0.001) and location of harvest (HR ~7.0; P=0.02) were independent associating factors for graft failure.

Conclusions: Graft survival rate of cadaveric transplants from external hospital donor was lower than that from donor harvested in our center. Acute rejection episodes and location of harvest were significant factors for graft survival.

PUB492
Adult Kidney Transplantation with Allografts from Pediatric Cardiac Death Donors in China – A Single-Center Experience Ying Xu, Jianghua Chen. The Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.

Background: Current transplant experience with cardiac death donors (DCD) organs has focused on the adult donor population, little is known about the outcome of pediatric donor organs used in adult recipients. The abstract is aimed to report clinical outcomes of kidney transplantation from pediatric DCD in China, and to investigate its feasibility to expand the organ donor pool.

Methods: We retrospectively reviewed the clinical data of 45 DCD kidneys from 27 donors from 1/January 2012 to 30/November 2012 in our center. Recipients were followed for patient and graft survival.

Results: There were seven pediatric DCD donors (age ≤18) and twenty adult DCD donors (age >18 years). All the eleven recipients who received the pediatric donors were alive. The age of the pediatric DCD donors ranged from 31 months to 17 years old (31 months, 50 months, 12 years, 13 years, 14 years, 15 years and 16 years respectively). The average weight of the donated kidneys was 126 grams (ranged from 46 to 160 grams). The incidence of delayed graft function was 18.2% (2/11); these two recipients received the kidneys from the youngest donor (31 months, 46 grams), their allograft function recovered to normal range within 3 months post-transplant. The function of the allograft from the 50-month-old donor recovered with a slow rate to the normal range. All other recipients survived with good allograft function.

Conclusions: Although kidney transplantations from younger pediatric DCD donors showed a higher rate of DGF with a longer duration of graft recovery, we achieved favorable short-term clinical outcome in terms of graft survival and function. Donation after pediatric cardiac death could expand the organ donor pool in China.

Funding: Government Support - Non-U.S.

PUB493
The Effect of Kidney Transplantation on Left Ventricular Function and Valvular Regurgitation in End Stage Renal Disease Patients Prabhlakar Doddi,1 Harbir Singh Kohli,2 Ajay Bahl.1,2.1Nephrology, PGIMER, Chandigarh, India; 2Cardiology, PGIMER, Chandigarh, India.

Background: Most patients with chronic kidney disease suffer frequently from cardiac abnormalities including valvular disorders and left ventricular(LV) systolic and diastolic dysfunction. At present, little information is available regarding the effect of kidney transplantation on LV function and valvular regurgitation in End Stage Renal Disease (ESRD) patients.

Methods: This is a prospective study in which 250 patients with ESRD on maintenance hemodialysis were enrolled between July 2010 to June 2011 and 30 patients were studied who subsequently underwent kidney transplantation. Base line LV function and valvular abnormalities were evaluated by using conventional echocardiography 4 weeks before kidney transplantation and same was repeated at 12 weeks after transplantation.

Results: In this study we found that 4 weeks prior to renal transplant, out of 30 patients, 15(50%) had low ejection fraction (EF), 13(43.3%) patients had moderate and 1(3.3%) patient had severe mitral regurgitation (MR). There were 13(43.3%) patients with moderate tricuspid regurgitation (TR) and 26.7% with severe TR. Twelve weeks post transplantation it was observed that there was significant improvement in EF(0.001) and valvular regurgitation(P<0.001 for MR and 0.001 for TR). Of 13 patients with moderate MR, 6 improved to mild MR and in rest 7 MR disappeared. One patient with severe MR had complete disappearance of MR after transplantation. Of 13 patients with moderate TR, 8 improved to mild, in 4 TR disappeared and one patient it persisted. Out of 2 patients with severe TR, one improved to mild and in other TR disappeared. Of 15 patients with low EF, 14 improved.

Conclusions: In this study we found that there was significant improvement in LVEF and valvular regurgitation after kidney transplantation and it implies that poor LV function and valvular regurgitation should not be contraindications for kidney transplantation.

PUB494

Background: Organ shortage is a universal thorny issue. Living related transplantations (LRT) are offered free of charge for all citizens. Law bans commercial transplants. Commercial renal transplants (CRT) are still practiced in some low-income countries. The declaration of Istanbul (DoI) formulated in April 2008 constitutes the global framework for transplantation practice rejects and combats this practice. We analyzed the impact of the DoI on LRT and CRT dynamics in Oman.

Methods: Registry data analysis for the period 2007 till June 2013 of local LRT and CRT. The chi-square proportion test was applied to look for significance before (year 2007) and after the DoI (2008-June 2013). We used Stata12,1,Tx, USA.

Results: Dynamics of Living related (LRT) and Commercial (CRT) transplants in Oman before and after DoI are shown on the table below:

<table>
<thead>
<tr>
<th>Year</th>
<th>LRT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>2008</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>2009</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>2010</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>2011</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>2012</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>2013</td>
<td>16</td>
<td>24</td>
</tr>
</tbody>
</table>

In 2007 the proportion of LRT to CRT was 24%. The proportion increased significantly to reach a peak of 62% in 2009. Also, CRT from Pakistan decreased from 84% in 2007 to 38% and 51% in 2008 and 2009 respectively. Painfully, Commercialism resurged, grows and affects negatively the local program.

Conclusions: Oman enjoyed a significant positive impact of the DoI till 2011. However, the effect seems to lessen due to the resurgence of commercial transplants. Mechanisms of resurgence should be analyzed meticulously. Concomitantly, an active deceased donor program and further development of the living donor program to ensure self-sufficiency would be effective means to deter this phenomenon and reinforce the Declaration.

Funding: Government Support - Non-U.S.

PUB495
Long-Term Effects of Renal Transplantation on Cardiac Autonomic Dysfunction Eduardo Cruz, Fadi Tohni, Roberto S. Kallil, Harald M. Stauss. Medicine/Nephrology, Univ of Iowa; 1Exercise Physiology, Univ of Iowa.

Background: It has been suggested that uremic autonomic neuropathy in patients with end-stage renal disease (ESRD) contributes to cardiac autonomic dysfunction that has been associated with increased cardiovascular morbidity and mortality. With this regard, it has been demonstrated that reduced low frequency to high frequency (LF/HF) ratio of heart rate variability (HRV) is associated with a higher probability of cardiovascular disease events in patients with chronic kidney disease (Chandra P. et al., 2011). We hypothesized that renal transplantation (RTX) in patients with ESRD will improve autonomic dysfunction (indicated by an increase in the LF/HF ratio of HRV) and, thus, reduces the probability of cardiovascular disease events.

Methods: To test this hypothesis, we studied cardiac autonomic function by frequency domain HRV analysis (power spectral analysis) in patients with ESRD before and 3 months, 12 months, and 36 months following renal transplantation.

Results: 28 patients were studied. Mean age was 51.6 ±17.4 years with 20 males. Mean cGFR was 56.4 ±17.9. Low frequency to high frequency ratio of HRV increased significantly before (year 2007) compared to after RTX (P<0.001). In the DoI period on LRT and CRT dynamics in Oman.

Conclusions: Oman enjoyed a significant positive impact of the DoI till 2011. However, the effect seems to lessen due to the resurgence of commercial transplants. Mechanisms of resurgence should be analyzed meticulously. Concomitantly, an active deceased donor program and further development of the living donor program to ensure self-sufficiency would be effective means to deter this phenomenon and reinforce the Declaration.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
patients not on dialysis, there was a significant difference between the two groups' in terms of distance from their respective homes to the transplant center, their level of education, and presence of specific medical co-morbidities.

Conclusions: We believe that through targeted interventions such as timely referral, providing appropriate educational resources and development of adequate support systems, all patients with advanced CKD, including those on dialysis, can be motivated to complete their pre-transplant workup.

PUB499

Early Belatacept Conversion for Slow Renal Allograft Function


Background: Slow renal allograft function (SGF), which we define as the need for HD or a Cr >2 mg/dL > 14 days post-transplant, has a negative impact on long-term graft outcome. Tacrolimus is postulated to prolong SGF. We investigated belatacept conversion from tacrolimus as a novel treatment strategy for SGF.

Methods: Retrospective single center analysis of the first 8 patients converted to belatacept for SGF (Group 1) compared to a historical control group of 16 SGF patients remaining on tacrolimus (Group 2) matched for the following variables: type of kidney transplant, cause of ESRD, and CIT. Primary outcome: eGFR at 6 months; secondary outcomes: rates of rejection and infection.

Results: Table: Baseline demographic and transplant characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (8)</th>
<th>Group 2 (16)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race, n</td>
<td>Male 4, Female 4</td>
<td>Male 4, Female 6</td>
<td>0.5</td>
</tr>
<tr>
<td>Age, years</td>
<td>57 (13.1)</td>
<td>56 (13.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>PRA, mean (SD)</td>
<td>53.5 (35.4)</td>
<td>45 (21.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>CIT, hours</td>
<td>11.5 (6.6)</td>
<td>11.2 (5.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Standard</td>
<td>100%</td>
<td>100%</td>
<td>—</td>
</tr>
<tr>
<td>cPRA, mean (SD)</td>
<td>23.1 (14.4)</td>
<td>13.4 (7.2)</td>
<td>0.53</td>
</tr>
<tr>
<td>Donor type</td>
<td>ECD/DCD 3, Standard 5</td>
<td>ECD/DCD 3, Standard 6</td>
<td>0.22</td>
</tr>
<tr>
<td>Donor age</td>
<td>53 (21)</td>
<td>60 (18)</td>
<td>0.1</td>
</tr>
<tr>
<td>TCM, n</td>
<td>0.67</td>
<td>0.67</td>
<td>—</td>
</tr>
<tr>
<td>Race, n</td>
<td>Male 4, Female 4</td>
<td>Male 4, Female 6</td>
<td>0.5</td>
</tr>
<tr>
<td>Age, years</td>
<td>57 (13.1)</td>
<td>56 (13.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>PRA, mean (SD)</td>
<td>53.5 (35.4)</td>
<td>45 (21.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>CIT, hours</td>
<td>11.5 (6.6)</td>
<td>11.2 (5.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Standard</td>
<td>100%</td>
<td>100%</td>
<td>—</td>
</tr>
<tr>
<td>cPRA, mean (SD)</td>
<td>23.1 (14.4)</td>
<td>13.4 (7.2)</td>
<td>0.53</td>
</tr>
<tr>
<td>Donor type</td>
<td>ECD/DCD 3, Standard 5</td>
<td>ECD/DCD 3, Standard 6</td>
<td>0.22</td>
</tr>
<tr>
<td>Donor age</td>
<td>53 (21)</td>
<td>60 (18)</td>
<td>0.1</td>
</tr>
<tr>
<td>TCM, n</td>
<td>0.67</td>
<td>0.67</td>
<td>—</td>
</tr>
</tbody>
</table>

Mean POd of conversion was 46.6 (range: 21-74). Mean number of HD treatments (SD) for Groups 1 and 2 was 8.4 (3.5) and 6.6 (6.5), respectively (P = 0.57). Mean eGFR mL/min/1.73m² (SD) for Groups 1 and 2 were 54.3 (35.4) and 45 (21.7); P = 0.43 at 3-months and 56.1 (28) and 46.8 (21.6); P = 0.38 at 6-months post-transplant, respectively. No clinical rejection occurred, however subclinical rejection occurred in 3 patients in Group 1 (all type 1a) and 1 patient in Group 2 (type 2a), all diagnosed on a 6-month post-transplant surveillance biopsy. Similar rates of CMV and BK viremia, and UTIs occurred between the groups.

Conclusions: Belatacept conversion for SGF is a novel strategy that resulted in numerically higher eGFR 6 months post-transplant compared to a historical control group. Expansion of this cohort with longer follow-up is necessary to further define efficacy and safety.

Funding: Clinical Revenue Support

PUB500

Early Identification of Skin Cancer in Renal Transplant Recipients through a Nurse-Led Skin Surveillance Service


Background: Non-melanoma skin cancer (NMSC), has become one of the major causes of morbidity and mortality in renal transplant recipients (RTRs), with a 20 fold increase of NMSC rates in RTRs. Previous studies predominantly address the incidence of these cancers in white populations while little is available to compare ethnically diverse populations such as that found in London. This study was to determine the incidence of skin lesions occurring in RTRs and the impacts of skin surveillance screening clinics.

Methods: 152 RTRs were seen in our renal and transplant unit nurse-led skin screening clinic between September 2010 and November 2011, 27 were excluded (16 did not attend; 5 declined, 3 reviewed elsewhere, 1 death, 1 notes were unavailable). A total of 125 RTRs were reviewed for diagnosis of de novo skin lesions in consultant/nurse led clinics. Diagnoses of de novo skin lesions, demographics and clinical data were collected retrospectively from patients’ notes.

Results: Male to female ratio 2:1, mean age 53.4yrs. 65% White, 17.6% Asian, 15.2% Black and 1.6% not stated. NMSC were found in 13 patients (12 basal cell carcinoma, 1 squamous cell carcinoma), no melanoma was found. There were 17 pre-malignant lesions

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

Underline represents presenting author.

984A
Hypercalcaemia Post Renal Transplantation Does Not Affect Affected Renal Transplant Function: A Retrospective Single Centre Study

**Aim:**
This retrospective study determined the natural history of hypercalcaemia and the effect of calcitriol post RT.

**Methods:**
210 patients’ notes were reviewed between 2007-2012. Corrected calcium (Ca), parathyroid hormone (PTH), phosphate (P) levels were collected over time, with particular attention to those hypercalcaemic pre-RT. eGFR was calculated as corrected calcium >2.60mmol/L at 1 month post RT.

**Results:**
13/210 (6.2%) developed hypercalcaemia by 1 month post RT, 6 were LD and 7 DCD. 14/19 (73.7%) patients were on immunosuppressive regimens with prednisone at time of diagnosis with eGFR 14/160 (6.8%) RT on P basedefined regimens, developed NOAK whereas 5/90 (5.6%) on P free regimen developed NOAK (p=0.08).

**Conclusions:**
This retrospective study determined that the natural history of hypercalcaemia and the effect of calcitriol post RT. The incidence of NOAK and PMLs in 15 RTRs (11 actinic keratosis, 5 Bowen’s disease, 1 lentigo maligna). Total NMSC and PMLs in this cohort was 10.4% with total PML of 12%. The incidence of NMSC in this cohort was 6.8%, and of PML 9%. Both NMSC and PML occurred in less than 5 years and more than 10 years post 1st renal transplant.

**Conclusions:**
PreRT hypercalcaemia does not predict post RT Ca levels. High Ca levels at 1 month post RT are maintained at 1 year with no effect on eGFR. eGFR is unaffected by hypercalcaemia up to 3 years later. Treatment with Cinacalcet affects beneficial effect on eGFR whilst reducing PTH. This cohort had small numbers on this treatment and further studies are needed to confirm these initial findings. The effects of maintained hypercalcaemia on cardiac function, vascular calcification and bone status have not been addressed in this study and may warrant investigation to its possible implication.

**Conclusions:**
A retrospective study to determine whether the natural history of hypercalcaemia differs in LD or DCD RT.

**Methods:**
210 patients’ notes were reviewed between 2007-2012. Corrected calcium(Ca), parathyroid hormone(PTH), phosphate(P) levels were collected over time, with particular attention to those hypercalcaemic pre-RT. Immunosuppressive regimens with prednisone at time of diagnosis with eGFR 14/160 (6.8%) RT on P basedefined regimens, developed NOAK whereas 5/90 (5.6%) on P free regimen developed NOAK (p=0.08).

**Results:**
PreRT hypercalcaemia was diagnosed if random blood glucose was >11.1mmol/L. 14/19 (73.7%) patients were on immunosuppressive regimens with prednisone at time of diagnosis with eGFR 14/160 (6.8%) RT on P basedefined regimens, developed NOAK whereas 5/90 (5.6%) on P free regimen developed NOAK (p=0.08).

**Conclusions:**
This retrospective study determined that the natural history of hypercalcaemia and the effect of calcitriol post RT. The incidence of NOAK and PMLs in 15 RTRs (11 actinic keratosis, 5 Bowen’s disease, 1 lentigo maligna). Total NMSC and PMLs in this cohort was 10.4% with total PML of 12%. The incidence of NMSC in this cohort was 6.8%, and of PML 9%. Both NMSC and PML occurred in less than 5 years and more than 10 years post 1st renal transplant.

**Conclusions:**
PreRT hypercalcaemia does not predict post RT Ca levels. High Ca levels at 1 month post RT are maintained at 1 year with no effect on eGFR. eGFR is unaffected by hypercalcaemia up to 3 years later. Treatment with Cinacalcet affects beneficial effect on eGFR whilst reducing PTH. This cohort had small numbers on this treatment and further studies are needed to confirm these initial findings. The effects of maintained hypercalcaemia on cardiac function, vascular calcification and bone status have not been addressed in this study and may warrant investigation to its possible implication.

**Conclusions:**
A retrospective study to determine whether the natural history of hypercalcaemia differs in LD or DCD RT.

**Methods:**
210 patients’ notes were reviewed between 2007-2012. Corrected calcium(Ca), parathyroid hormone(PTH), phosphate(P) levels were collected over time, with particular attention to those hypercalcaemic pre-RT. Immunosuppressive regimens with prednisone at time of diagnosis with eGFR 14/160 (6.8%) RT on P basedefined regimens, developed NOAK whereas 5/90 (5.6%) on P free regimen developed NOAK (p=0.08).

**Results:**
PreRT hypercalcaemia was diagnosed if random blood glucose was >11.1mmol/L. 14/19 (73.7%) patients were on immunosuppressive regimens with prednisone at time of diagnosis with eGFR 14/160 (6.8%) RT on P basedefined regimens, developed NOAK whereas 5/90 (5.6%) on P free regimen developed NOAK (p=0.08).

**Conclusions:**
This retrospective study determined that the natural history of hypercalcaemia and the effect of calcitriol post RT. The incidence of NOAK and PMLs in 15 RTRs (11 actinic keratosis, 5 Bowen’s disease, 1 lentigo maligna). Total NMSC and PMLs in this cohort was 10.4% with total PML of 12%. The incidence of NMSC in this cohort was 6.8%, and of PML 9%. Both NMSC and PML occurred in less than 5 years and more than 10 years post 1st renal transplant.

**Conclusions:**
PreRT hypercalcaemia does not predict post RT Ca levels. High Ca levels at 1 month post RT are maintained at 1 year with no effect on eGFR. eGFR is unaffected by hypercalcaemia up to 3 years later. Treatment with Cinacalcet affects beneficial effect on eGFR whilst reducing PTH. This cohort had small numbers on this treatment and further studies are needed to confirm these initial findings. The effects of maintained hypercalcaemia on cardiac function, vascular calcification and bone status have not been addressed in this study and may warrant investigation to its possible implication.
Methods: We retrospectively reviewed blood BK PCR for recipients 48 months post-transplant. For the purpose of this study, we classified BK viremia according to viral copies as follows: Low grade transient (<5000 lasting less than 3 months); Low grade persistent (<5000 lasting more than 3 months); High grade transient (>5000 lasting less than 3 months); High grade persistent (>5000 viral copies lasting more than 3 months).

Results: Records of 78 transplant recipients were reviewed. 13% demonstrated BK viremia. Of these, 20% showed evidence of allograft dysfunction, while 80% did not. Of the total sample, 3% showed allograft dysfunction attributable to BK virus nephropathy (BKVN) on biopsy, and these patients belonged to the high-grade persistent group. Patients with BKVN are almost always found to have BK viremia. Our analysis of a limited sample revealed that a persistent high-grade viremia is probably more likely to be associated with BKVN, unlike transient BK viremia detected on prospective monitoring without allograft dysfunction. The impact of low-grade persistent viremia remains to be determined.

<table>
<thead>
<tr>
<th>Patients with BK viremia (%)</th>
<th>Total Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade transient</td>
<td>30</td>
</tr>
<tr>
<td>Low grade persistent</td>
<td>0</td>
</tr>
<tr>
<td>High grade transient</td>
<td>40</td>
</tr>
<tr>
<td>High grade persistent</td>
<td>20</td>
</tr>
</tbody>
</table>

Conclusions: High-grade persistent BK viremia post transplant with allograft dysfunction is most likely suggestive of BKVN. Transient BK viremia without allograft dysfunction may be less likely to be associated with BKVN.
dialysis outcomes (continued) .............. SA-PO502, SA-PO503, SA-PO505, SA-PO517, SA-PO521, SA-PO530, SA-PO555, SA-PO590, SA-PO913, SA-PO917, SA-PO922, SA-PO941, SA-PO1034, PUB009, PUB107, PUB165, PUB167, PUB169, PUB184, PUB200, PUB227, PUB228, PUB237
diabetes related amyloidosis .............. SA-PO404, SA-PO518
diabetes volume ............................. FR-OR031, FR-PO332, FR-PO396, SA-PO938, PUB161, PUB189, PUB224
diabetes withholding ...................... SA-OR056
diastolic boundary ......................... TH-OR126, TH-OR127, TH-OR129, TH-PO277, FR-PO732, FR-PO735, FR-PO737, FR-PO738, FR-PO744
diuretics .................. TH-PO632, TH-PO636, TH-PO693, TH-PO743, FR-OR014, FR-OR022, FR-OR071, FR-OR076, FR-PO496, FR-PO516, FR-PO733, FR-PO735, FR-PO752, SA-PO361, SA-PO591, SA-PO943, SA-PO1011, PUB269, PUB289, PUB296, PUB400
drug delivery .............................. TH-PO812, FR-PO417, FR-PO713
drug excretion ....... TH-PO832, TH-PO1093, SA-OR015, PUB055
drug interactions ......................... TH-OR136, TH-PO054, TH-PO1110, FR-PO473, FR-PO915, SA-PO796, SA-PO918, PUB011, PUB452, PUB456, PUB487
drug metabolism ....... TH-PO832, TH-PO1102, TH-PO1105, TH-PO1106, TH-PO1107, TH-PO1108, FR-PO264, SA-PO529, PUB140, PUB160, PUB283, PUB367, PUB452
drug nephrotoxicity ............... TH-PO007, TH-PO017, TH-PO032, TH-PO073, TH-PO059, TH-PO069, TH-PO081, TH-PO087, TH-PO0810, TH-PO1102, TH-PO1126, TH-PO283, TH-PO334, TH-PO343, TH-PO1014, FR-OR036, FR-PO320, SA-PO111, SA-PO308, SA-PO309, SA-PO407, SA-PO508, SA-PO5083, SA-PO524, SA-PO667, SA-PO671, PUB004, PUB006, PUB011, PUB038, PUB068, PUB333, PUB362, PUB371, PUB419, PUB444
drug transporter ...................... TH-PO1106, TH-PO1107, TH-PO1115
dyslipidemia ............................. TH-PO395, TH-PO405, SA-PO329, SA-PO367, PUB451
echocardiography ............... TH-PO176, TH-PO426, FR-OR143, FR-PO393, SA-PO998, SA-PO251, SA-PO433, SA-PO442, SA-PO448, SA-PO457, SA-PO468, SA-PO470, SA-PO923, PUB050, PUB221, PUB329, PUB493
economic analysis ............... TH-OR123, TH-OR140, TH-PO319, FR-PO339, FR-PO340, FR-PO341, FR-PO426, FR-PO980, FR-PO982, FR-PO1011, SA-OR041, SA-PO709, SA-PO896
economic impact .................. TH-OR140, TH-PO497, SA-OR045, SA-PO187, SA-PO243, PUB092
edematous disorders .......... FR-PO358, PUB436

education ...................... TH-OR004, TH-PO314, TH-PO323, TH-PO333, TH-PO481, TH-PO531, TH-PO699, TH-PO853, TH-PO854, TH-PO855, TH-PO856, TH-PO861, TH-PO863, TH-PO864, TH-PO865, TH-PO866, TH-PO867, TH-PO868, TH-PO869, TH-PO870, TH-PO871, TH-PO874, TH-PO877, TH-PO879, TH-PO880, TH-PO1052, TH-PO1084, TH-PO1141, FR-OR079, FR-OR082, FR-OR083, FR-OR084, FR-PO046, FR-PO149, FR-PO164, FR-PO327, FR-PO459, SA-PO155, SA-PO376, SA-PO402, SA-PO550, SA-PO809, SA-PO1022, PUB086, PUB094, PUB095, PUB113, PUB207, PUB242, PUB321, PUB446
elderly ...................... TH-PO303, TH-PO267, TH-PO268, TH-PO269, TH-PO277, TH-PO530, TH-PO619, TH-PO669, TH-PO675, TH-PO679, TH-PO692, TH-PO696, TH-PO697, TH-PO964, TH-PO1150, FR-OR032, FR-OR040, FR-PO139, FR-PO167, FR-PO235, FR-PO415, SA-PO292, SA-PO505, SA-PO649, PUB227, PUB239, PUB264, PUB286
electrolytes ............... TH-OR133, TH-OR143, TH-OR103, TH-PO106, TH-PO613, TH-PO614, TH-PO615, TH-PO618, TH-PO621, TH-PO623, TH-PO624, TH-PO704, TH-PO743, TH-PO783, TH-PO809, TH-PO823, TH-PO825, TH-PO833, TH-PO841, TH-PO844, FR-PO046, FR-PO361, FR-PO448, FR-PO449, FR-PO736, FR-PO740, FR-PO767, FR-PO1100, FR-PO1141, SA-OR015, SA-PO157, SA-PO452, PUB211, PUB263, PUB268, PUB272, PUB309, PUB332, PUB337, PUB355, PUB370, PUB379
electron microscopy .... TH-PO962, TH-PO1056, TH-PO1119, FR-PO464, FR-PO856
electrophysiology ....... TH-PO633, SA-PO593
end-stage kidney disease .......... TH-OR052, TH-OR138, TH-PO483, FR-OR444, FR-OR130, FR-PO326, FR-PO413, FR-PO1065, SA-PO317, SA-PO541, SA-PO938, PUB079, PUB126, PUB149, PUB150
end-stage renal disease (ESRD) ... TH-OR049, TH-OR110, TH-OR117, TH-OR120, TH-OR140, TH-OR144, TH-PO192, TH-PO210, TH-PO247, TH-PO29, TH-PO444, TH-PO455, TH-PO469, TH-PO483, TH-PO504, TH-PO512, TH-PO539, TH-PO688, TH-PO755, TH-PO935, TH-PO1142, TH-PO1148, TH-PO1150, FR-OR046, FR-OR092, FR-OR134, FR-OR143, FR-PO133, FR-PO159, FR-PO219, FR-PO291, FR-PO309, FR-PO311, FR-PO325, FR-PO368, FR-PO412, FR-PO426, FR-PO428, FR-PO429, FR-PO446, FR-PO455, FR-PO457, FR-PO461, FR-PO462, FR-PO487, FR-PO895, FR-PO939, FR-PO950, FR-PO957, FR-PO960, FR-PO965, FR-PO975, FR-PO997, FR-PO1002, FR-PO1071, FR-PO1073, FR-PO1094, FR-PO1096, FR-PO1110, FR-PO1114, FR-PO1116,

glomerulonephritis (continued) ...... SA-PO627,
SA-PO628, SA-PO636, SA-PO664,
SA-PO670, SA-PO671, SA-PO672,
SA-PO676, SA-PO677, SA-PO686,
SA-PO687, SA-PO691, SA-PO692,
SA-PO694, SA-PO696, SA-PO698,
SA-PO704, SA-PO707, SA-PO714,
SA-PO750, SA-PO768, SA-PO798,
SA-PO812, SA-PO819, SA-PO822,
SA-PO835, SA-PO854, SA-PO861,
SA-PO865, SA-PO881, PUB109, PUB329,
PUB335, PUB377, PUB416, PUB418
glomerulopathy ............. TH-PO573, TH-PO981,
TH-PO1010, TH-PO1030, TH-PO1033,
TH-PO1036, TH-PO1047, FR-PO250,
FR-PO579, FR-PO692, FR-PO1049,
SA-OR095, SA-PO348, SA-PO643,
SA-PO655, SA-PO776, SA-PO777,
SA-PO779, SA-PO787, SA-PO806,
PUB346, PUB359, PUB420, PUB426
glomerulosclerosis ......... TH-PO402, TH-PO564,
TH-PO1015, FR-OR001, FR-OR118,
FR-PO245, FR-PO774, FR-PO834,
FR-PO840, FR-PO850, FR-PO851,
FR-PO1133, SA-OR022, SA-OR028,
SA-OR029, SA-PO855, PUB138, PUB395
glomerulus ..................... TH-PO092, TH-PO334,
TH-PO357, FR-PO481, FR-PO872,
FR-PO904, FR-PO916, SA-OR106,
SA-PO757, SA-PO758, PUB104, PUB136
glucose ........ TH-PO446, TH-PO522, TH-PO610,
FR-OR061, FR-OR072, FR-PO776,
FR-PO911, FR-PO928, SA-PO304,
SA-PO341, SA-PO349, SA-PO350,
SA-PO352, SA-PO371, SA-PO792,
PUB140, PUB152, PUB187, PUB289
glycation .........................TH-OR087, TH-PO165,
TH-PO455, TH-PO456, TH-PO916,
FR-PO428, FR-PO432, FR-PO546,
FR-PO941, SA-PO375, SA-PO461
glycocalyx ....TH-PO192, TH-PO398, FR-PO926,
FR-PO927, SA-PO335, SA-PO1052
Goodpasture syndrome..................... FR-PO563,
FR-PO570, FR-PO571, SA-PO608,
SA-PO612, SA-PO613, PUB433
growth factors............... TH-OR036, TH-OR037,
TH-PO340, TH-PO386, FR-OR115,
FR-PO190, FR-PO211, FR-PO831,
SA-OR017, SA-PO074, SA-PO133,
SA-PO274, SA-PO378, SA-PO396,
SA-PO791, PUB144
H/K-ATPase ........................................TH-PO628
H-ATPase ........................ TH-PO635, TH-PO663
health status ............... TH-PO1030, TH-PO1144,
FR-PO337, FR-PO800, SA-PO597,
PUB088, PUB384
heart disease ..................TH-OR039, TH-PO164,
TH-PO450, TH-PO720, TH-PO721,
TH-PO1137, FR-PO105, FR-PO1109,
SA-PO872, PUB219, PUB477
heart failure ...................TH-OR051, TH-PO035,
TH-PO036, TH-PO037, TH-PO220,
TH-PO708, TH-PO997, FR-OR140,
FR-PO235, FR-PO349, FR-PO365,
FR-PO366, FR-PO381, FR-PO404,
FR-PO966, FR-PO1116, SA-PO249,
SA-PO253, SA-PO459, SA-PO1042,
PUB071, PUB269, PUB275

heme oxygenase .............TH-PO160, SA-OR024,
SA-PO045, SA-PO076, PUB407
hemodialysis.................. TH-OR028, TH-OR114,
TH-OR118, TH-OR136, TH-OR142,
TH-OR143, TH-OR144, TH-PO033,
TH-PO096, TH-PO101, TH-PO102,
TH-PO103, TH-PO105, TH-PO255,
TH-PO325, TH-PO445, TH-PO453,
TH-PO457, TH-PO462, TH-PO468,
TH-PO471, TH-PO472, TH-PO480,
TH-PO498, TH-PO510, TH-PO511,
TH-PO517, TH-PO518, TH-PO526,
TH-PO537, TH-PO686, TH-PO694,
TH-PO808, TH-PO813, TH-PO819,
TH-PO874, TH-PO878, FR-OR027,
FR-OR088, FR-OR136, FR-PO016,
FR-PO037, FR-PO142, FR-PO144,
FR-PO162, FR-PO165, FR-PO325,
FR-PO327, FR-PO330, FR-PO340,
FR-PO341, FR-PO343, FR-PO354,
FR-PO363, FR-PO366, FR-PO373,
FR-PO374, FR-PO377, FR-PO379,
FR-PO380, FR-PO381, FR-PO387,
FR-PO388, FR-PO389, FR-PO390,
FR-PO396, FR-PO400, FR-PO402,
FR-PO404, FR-PO405, FR-PO409,
FR-PO416, FR-PO418, FR-PO419,
FR-PO424, FR-PO433, FR-PO435,
FR-PO439, FR-PO443, FR-PO451,
FR-PO454, FR-PO460, FR-PO464,
FR-PO502, FR-PO523, FR-PO605,
FR-PO610, FR-PO624, FR-PO625,
FR-PO669, FR-PO682, FR-PO786,
FR-PO795, FR-PO799, FR-PO804,
FR-PO807, FR-PO968, FR-PO978,
FR-PO983, FR-PO984, FR-PO986,
FR-PO994, FR-PO999, FR-PO1001,
FR-PO1002, FR-PO1007, FR-PO1010,
FR-PO1102, FR-PO1112, FR-PO1126,
SA-OR081, SA-PO164, SA-PO202,
SA-PO205, SA-PO213, SA-PO222,
SA-PO381, SA-PO387, SA-PO392,
SA-PO394, SA-PO399, SA-PO405,
SA-PO406, SA-PO421, SA-PO422,
SA-PO431, SA-PO437, SA-PO438,
SA-PO439, SA-PO440, SA-PO441,
SA-PO449, SA-PO450, SA-PO451,
SA-PO456, SA-PO460, SA-PO482,
SA-PO488, SA-PO502, SA-PO504,
SA-PO505, SA-PO507, SA-PO508,
SA-PO512, SA-PO520, SA-PO523,
SA-PO526, SA-PO532, SA-PO539,
SA-PO549, SA-PO566, SA-PO567,
SA-PO574, SA-PO575, SA-PO597,
SA-PO817, SA-PO903, SA-PO1032,
PUB023, PUB122, PUB149, PUB150,
PUB151, PUB155, PUB156, PUB167,
PUB171, PUB180, PUB182, PUB198,
PUB202, PUB213, PUB214, PUB215,
PUB223, PUB226, PUB228, PUB232,
PUB233, PUB235, PUB273, PUB305,
PUB316, PUB338, PUB384, PUB385,
PUB391, PUB453

1047A

hemodialysis access .......TH-OR005, TH-PO328,
TH-PO461, TH-PO465, TH-PO467,
TH-PO470, TH-PO477, TH-PO478,
TH-PO489, TH-PO791, FR-OR090,
FR-PO138, FR-PO139, FR-PO140,
FR-PO142, FR-PO148, FR-PO160,
FR-PO162, FR-PO163, FR-PO165,
SA-OR128, PUB173, PUB174, PUB176,
PUB178, PUB181, PUB182, PUB183,
PUB199, PUB222, PUB445
hemodialysis adequacy .................... TH-OR142,
TH-PO099, TH-PO1079, FR-PO353,
FR-PO981, FR-PO982, FR-PO989,
FR-PO992, FR-PO995, FR-PO1008,
SA-OR042, PUB185, PUB189, PUB246
hemodialysis biocompatibility..........TH-PO096,
TH-PO099, TH-PO473, FR-PO350,
FR-PO969, FR-PO972, SA-PO403
hemodialysis hazards .. TH-PO1080, FR-PO338,
FR-PO359, FR-PO1003, SA-PO396,
SA-PO398, PUB336
hemodialysis patients ....TH-OR137, TH-PO101,
TH-PO456, TH-PO458, TH-PO488,
TH-PO509, TH-PO519, TH-PO522,
TH-PO528, TH-PO535, TH-PO731,
TH-PO766, FR-OR047, FR-OR081,
FR-PO370, FR-PO399, FR-PO430,
FR-PO434, FR-PO453, FR-PO458,
FR-PO459, FR-PO650, FR-PO652,
FR-PO673, FR-PO676, FR-PO772,
FR-PO789, FR-PO974, FR-PO989,
FR-PO1009, SA-OR079, SA-PO144,
SA-PO148, SA-PO390, SA-PO400,
SA-PO430, SA-PO445, SA-PO446,
SA-PO454, SA-PO464, SA-PO467,
SA-PO470, SA-PO484, SA-PO494,
SA-PO529, PUB072, PUB157, PUB169,
PUB185, PUB192, PUB195, PUB217,
PUB218, PUB219, PUB224, PUB225,
PUB236, PUB387, PUB445
hemodynamics ............... TH-PO104, TH-PO282,
TH-PO742, FR-OR085, FR-PO093,
FR-PO373, FR-PO374, FR-PO400,
FR-PO501, SA-PO445, SA-PO1057,
SA-PO1061, SA-PO1066, PUB305, PUB350
hemodynamics and vascular regulation .............
FR-PO403, FR-PO973, SA-PO471
hemoglobin..................... TH-PO200, TH-PO493,
TH-PO502, TH-PO504, FR-OR011,
FR-OR044, FR-PO025, FR-PO1005,
SA-PO383, SA-PO388, SA-PO746,
SA-PO944, PUB149, PUB197
hemolytic uremic syndrome ............ TH-OR064,
TH-PO012, TH-PO665, TH-PO1036,
FR-OR056, FR-OR057, FR-PO690,
FR-PO823, FR-PO912, SA-PO039,
SA-PO040, SA-PO041, SA-PO043,
SA-PO047, SA-PO613, SA-PO635,
SA-PO641, SA-PO849, SA-PO850,
SA-PO851, SA-PO852, SA-PO853,
SA-PO890, SA-PO892, SA-PO893,
PUB110, PUB111, PUB114, PUB115,
PUB125, PUB375
hemoperfusion .................................. FR-PO1010
heme oxygenase ............. TH-PO065, FR-PO095,
FR-PO905, FR-PO933, SA-PO067
Henoch-Schonlein Purpura ..............TH-PO963,
SA-PO615, SA-PO840, SA-PO869, PUB421


malnutrition

MDCK

medical education

MCP-1

microalbuminuria

malnutrition


metabolic acidosis

metabolic alkalosis

mesangial cells

membranoproliferative glomerulonephritis (MPGN)

membranous nephropathy

mitochondria

microarrays

microcirculation

microRNAs

molecular biology

molecular diagnostics

molecular genetics

mortality

mouse model

mRNA

multiple myeloma
nanotechnology
nephron
nephropathy
Na/H exchangers

Na transport

nephrotoxicity

next generation sequencing

nephritogenic

novel dialysis technologies

nutrition

neprhony

neprhopathy

neprhopathic (NPH)

neprhotic syndrome

obstructive uropathy

omega-3 fatty acids

organ transplant

organic anion transporter

FR-PO1068, SA-OR023, SA-PO313, TH-PO879, TH-PO889, TH-PO892, TH-PO959, TH-PO973, TH-PO979, TH-PO982, TH-PO987, TH-OR077, TH-OR104, TH-PO448, TH-PO755, PUB254

outcomes

FR-PO214, FR-PO255, FR-PO578, FR-PO704, FR-PO768, FR-PO781, FR-PO757, FR-PO908, SA-PO002, SA-PO005, SA-PO009, SA-PO026, SA-PO063, SA-PO078, SA-PO237, SA-PO058, SA-PO1007, PUB113, PUB466

organic anion transporter

organic solutes

osmolality


nephrology

nephritis

nephrectomy

nephrotoxic
	nitric oxide

nephrotic syndrome (continued)

nephrotic syndrome

nephrin

Na/H exchangers

NADPH oxidase

nanotechnology

mycophenolate mofetil
phosphorus

proteinuria

pulmonary

primary glomerulonephritis

potassium channels

progression of chronic renal failure

progression of renal failure

platelets

polycystic kidney disease (PKD)

cardiovascular

prognosis

calciuria

pulmonary

phosphorus

cardiovascular
pyelonephritis

renal biopsy

randomized controlled trials

reactive oxygen species

recurrent disease

rejection

renal ablation

renal agenesis

renal artery stenosis

renal biopsy

renal carcinoma

renal cell biology

renal dialysis

renal dysfunction

renal epithelial cell

renal failure

renal fibrosis

renal function

renal function decline

renal hypertension

renal injury

renal ischaemia

renal morphology

renal osteodystrophy

renal proximal tubule cell

renal transplantation

renal tubular acidosis

renal tubular epithelial cells
VEGF ........ TH-OR030, TH-OR098, TH-PO392, FR-PO030, FR-PO177, FR-PO834, FR-PO936, SA-PO271, SA-PO273, PUB141, PUB302
vesico-ureteral reflux .... TH-OR059, FR-PO707, SA-PO870, SA-PO871
virology ...... FR-PO1129, SA-PO951, SA-PO955, SA-PO956, SA-PO960, SA-PO961, SA-PO962, SA-PO963
vitamin C ...................... TH-PO503, FR-PO799
vitamin D ..................... TH-OR023, TH-PO018, TH-PO029, TH-PO050, TH-PO175, TH-PO191, TH-PO439, TH-PO515, TH-PO753, TH-PO776, TH-PO777, TH-PO779, TH-PO846, TH-PO1070, FR-OR137, FR-PO134, FR-PO183, FR-PO259, FR-PO443, FR-PO644, FR-PO673, FR-PO675, FR-PO677, FR-PO679, FR-PO681, FR-PO682, FR-PO806, FR-PO818, FR-PO841, FR-PO867, FR-PO1064, SA-OR053, SA-OR077, SA-OR091, SA-PO066, SA-PO082, SA-PO083, SA-PO084, SA-PO202, SA-PO230, SA-PO296, SA-PO336, SA-PO353, SA-PO362, SA-PO555, SA-PO559, SA-PO565, SA-PO573, SA-PO584, SA-PO585, SA-PO587, SA-PO588, SA-PO589, SA-PO590, SA-PO597, SA-PO598, SA-PO718, SA-PO730, SA-PO754, SA-PO769, SA-PO785, SA-PO794, SA-PO841, SA-PO884, SA-PO926, SA-PO975, SA-PO995, PUB036, PUB052, PUB060, PUB302, PUB320
VLDL ..................................................SA-PO924
water channels ............. TH-PO141, TH-PO145, TH-PO350, TH-PO532, TH-PO591, TH-PO592, TH-PO593, TH-PO594, TH-PO595, TH-PO606, TH-PO828, TH-PO905, TH-PO1117, FR-OR068, FR-OR069, FR-OR071, FR-PO953, SA-PO996, PUB275
water permeability ..................FR-OR069
water transport ........... TH-PO591, TH-PO604, FR-PO940, FR-PO953, PUB260, PUB267
water-electrolyte balance ............. TH-PO343, TH-PO596, TH-PO598, TH-PO609, TH-PO727, FR-PO754, FR-PO998, SA-OR016, SA-PO920, PUB254, PUB257, PUB258, PUB259, PUB263
whole exome sequencing (WES) ............ TH-OR064, TH-PO650, TH-PO929, FR-OR131, FR-PO685, FR-PO690, SA-OR109, SA-PO379, SA-PO870
HI-OR01

Acute Kidney Injury from Off-Pump or On-Pump Coronary Bypass Grafting and Kidney Function One Year Later  
Amit X. Garg,1 Philip J. Devereaux,2 Salim Yusuf,3 Meghan S. Cuerden,4 Chirag R. Parikh,5 Steven G. Coca,1 Michael Walsh,1 Richard J. Cook,1 Richard P. Whitlock,6 Richard J Novick,3 Yongping Ou,7 Xiabing Pan,8 Sirish Parvathaneni,9 Andre Lamy,10 London Kidney Clinical Research Unit, London, ON, Canada; Population Health Research Institute, Hamilton, ON, Canada; “On Behalf of the CORONARY Investigators.

Background: Most acute kidney injury (AKI) observed in hospital is defined by sudden mild or moderate increases in serum creatinine which may persist for several days. It is unknown whether an intervention which reduces the risk of such AKI better preserves long term kidney function.

Methods: Within the CORONARY trial we assessed kidney function in 2932 patients (from 63 sites, 16 countries) who were randomly assigned to coronary-artery bypass grafting (CABG) either with a beating-heart technique (off-pump) or with cardiopulmonary bypass (on-pump) (CORONARY kidney protocol published BMJ Open 2012; 2:e001080). The primary outcomes were AKI within 30 days of surgery (≥50% increase in serum creatinine from baseline) and loss of kidney function at one year (≥20% loss in estimated glomerular filtration rate from pre-randomization value).

Results: Off-pump (n=1472) vs. on-pump (n=1460) CABG reduced the risk of AKI (17.5% vs. 20.8%, relative risk 0.85 (95% confidence interval [CI] 0.72 to 0.95); p=0.01); however, there was no significant difference between the two groups in the loss of kidney function at one year (17.0% vs. 15.3%, relative risk 1.09 (95% CI 0.93 to 1.28); p=0.29).

Results were consistent with multiple alternate continuous and categorical definitions of AKI or kidney function loss.

Conclusions: The use of off-pump vs. on-pump CABG reduced the risk of postoperative AKI with no significant difference in kidney function between the two groups at one year. The findings emphasize that an intervention which reduces the risk of mild AKI may not necessarily improve long term kidney function.

Funding: Government Support - Non-U.S.

HI-OR02

The Effect of Bardoxolone Methyl in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease  

Background: Although inhibitors of the renin-angiotensin-aldosterone system can slow the progression of diabetic kidney disease, residual risk is high. Whether antioxidant-inflammation modulators further reduce this risk is unknown.

Methods: We randomized 2185 patients with type 2 diabetes mellitus (T2DM) and CKD stage 4 (estimated glomerular filtration rate (eGFR) 15 to ≤30 mL/min/1.73m²) to bardoxolone methyl (20 mg daily) or placebo. The primary composite outcome was end-stage renal disease (ESRD) or cardiovascular death.

Results: The Sponsor and Steering Committee terminated the trial as recommended by the Independent Data Monitoring Committee; median follow-up was 9 months. Sixty-nine of 1088 (6.3%) patients randomized to bardoxolone methyl and 69 of 1097 (6.3%) patients randomized to placebo experienced a primary composite outcome (hazard ratio 0.98, 95% confidence interval [CI] 0.70 to 1.37; p=0.92). In the bardoxolone methyl group, 43 patients developed ESRD and 27 experienced cardiovascular death; in the placebo group, 51 patients developed ESRD and 19 experienced cardiovascular death. Ninety-six patients were hospitalized with or died from heart failure in the bardoxolone methyl group compared with 55 in the placebo group (hazard ratio 1.83, 95% CI 1.32 to 2.55, p<0.001). Estimated GFR (6.4 mL/min/1.73m², 95% CI 5.9 to 6.9 mL/min/1.73m²), blood pressure and albuminuria increased significantly and body weight decreased significantly in the bardoxolone methyl group relative to placebo.

Conclusions: In patients with T2DM and stage 4 CKD, bardoxolone methyl did not reduce the risk of ESRD or cardiovascular death. More frequent cardiovascular events prompted termination of the trial.

Funding: Pharmaceutical Company Support - Reata Pharmaceuticals, AbbVie, Inc.

HI-OR03

Combined Angiotensin Inhibition for Treatment of Diabetic Nephropathy: VA Nephron D  
Linda F. Fried,1 Nicholas Emanuele,2 Jane Hongyuan Zhang,3 Mary Brophy,4 Todd Conner,5 William Duckworth,6 David J. Leechy,7 Peter A. McCullough,8 Theresa Z. O’Connor,9 Paul M. Palevsky,2 Robert F. Reilly,10 Stephen L. Seliger,11 Stuart Warren,12 Suzanne Watnick,13 Peter Peduzzi,3 Peter Guarino,3 VA Pittsburgh HCS, Pittsburgh, PA; ‘Hines VA, Hines, IL; ‘Cooperative Studies Program Coordinating Center, VA Connecticut HCS, West Haven, CT; ‘VA Boston HCS, Boston, MA; ‘VA Cooperative Studies Program Research Pharmacy, Albuquerque, NM; ‘Carl T. Hayden VA Medical Center, Phoenix, AZ; ‘St John Providence Health System, Novi, MI; ‘VA North Texas HCS, Dallas, TX; ‘VA Kentucky HCS, Baltimore, MD; ‘Portland VA Medical System, Portland, OR.

Background: Combination therapy with angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) decreases proteinuria; however its safety and impact on progression of kidney disease is uncertain.

Methods: Patients with type 2 diabetes, urine albumin excretion ≥300 mg/24h and estimated glomerular filtration rate (eGFR) 30-89.9 mL/min/1.73m² were treated with losartan 100 mg/day and then randomized to lisinopril (10 to 40 mg/day) or placebo. The primary endpoint was the composite of change in eGFR (decline of ≥30 mL/min/1.73m² if initial eGFR ≤50 or ≥50% decline if initial eGFR ≤60 mL/min/1.73m²), end-stage renal disease (ESRD), or death. Change in eGFR or ESRD was a secondary renal safety endpoint. Safety outcomes included mortality, hyperkalemia, and acute kidney injury.

Results: The study was stopped early for safety concerns. Among 1448 randomized patients with a median follow-up of 2.2 years, there were 152 primary endpoints in the monotherapy arm and 132 in the combination arm (HR 0.88 [95% CI 0.70 to 1.12], p=0.30). A trend towards benefit in renal endpoint [HR 0.78 (0.58 to 1.05), p=0.10] decreased with time (non-proportionality p-value = 0.02). There was no benefit on mortality [HR 1.04 (0.73 to 1.49), p=0.75] nor cardiovascular events. Combination therapy increased the risk of hyperkalemia [6.3 vs. 2.6 per 100 person years, p<0.001] and acute kidney injury [12.2 vs. 6.7 per 100 person years, p<0.001].

Conclusions: Combination ACEI and ARB therapy is associated with increased risk of adverse events in patients with diabetic nephropathy.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Merck (study drug donation)

HI-OR04

Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL): A Randomized Controlled Trial  
Rajiv Agarwal,12 Arjun D. Sinha,12 Maria K. Pappas,2 Terri N Abraham,2 Getachew G. Tsegene,13 1Medicine, Indiana University, Indianapolis, IN; 2Medicine, VAMC, Indianapolis, IN.

Background: To evaluate the comparative safety and efficacy of an ACE inhibitor-based to a β-blocker-based antihypertensive treatment, we conducted a randomized, open-label, parallel-group, single-center trial.

Methods: Subjects on maintenance hemodialysis with echocardiographic left-ventricular hypertrophy and hypertension confirmed by interdiastolic 44-hour ambulatory blood pressure (BP) monitoring were randomized to lisinopril (LIS) (n=100) or atenolol (ATL) (n=100) each administered 3 times weekly after dialysis. Home BP was controlled to <140/90 mmHg. The primary outcome was the change in left ventricular mass index (LVMI) from baseline to 12 months.

Results: Average age was 52.7 y, 33% were women, and 85% black. At baseline, 44 ambulatory BP was 151.5/87.1 mmHg in the ATL group. BP was similar in the LIS group, improved over time in both groups, and no statistical difference between drugs was noted. An independent data safety monitoring board recommended termination of the study when a clear signal for cardiovascular safety emerged. Serious cardiovascular events in the ATL group occurred in 14 subjects who had 18 events (22.2/100 patient-years (PY)) and in the LIS group in 26 subjects who had 40 events (54/100 PY; incidence rate ratio (IRR) 2.29 [95% CI 1.28-4.24, p=0.003). Combined serious adverse event of myocardial infarction, stroke, hospitalization for heart failure or cardiovascular death in the ATL group occurred in 10 subjects who had 11 events (13.5/100 PY) and in the LIS group in 17 subjects who had 23 events (31.0/100 PY; IRR 2.29 (p=0.021). All-cause hospitalizations in the ATL group occurred in 37 subjects who had 73 hospitalizations (48.9/100 PY) and in the LIS group in 59 subjects who had 107 hospitalizations (144.3/100 PY; IRR 1.61 (95% CI 1.18-2.19, p<0.001). LVMI improved with time; no difference between drugs was noted.

Conclusions: Atenolol-based antihypertensive therapy may be superior to lisinopril-based therapy in preventing cardiovascular morbidity and all-cause hospitalizations.

Funding: NIDDK Support

Underline represents presenting author/disclosure.
HI-OR05

Safety and Efficacy of ZS-9, a Novel Selective Cation Trap, for Treatment of Hyperkalemia in CKD Patients
Stephen R. Ash,1 Bhupinder Singh,2 Philip T. Lavin,3 Fiona Stotts,4 Henrik S. Rasmussen,4 Indiana University, Lafayette, IN; 5Southwest Research Institute, Tempe, AZ; 6Boston Biostatistics Research Foundation, Framingham, MA; 7ZS Pharma Inc., Fort Worth, TX.

Background: Hyperkalemia is associated with significant mortality and limits use of cardio- and renoprotective RAASi, yet no reliably safe and effective treatment for this condition exits. ZS-9 is a selective cation exchanger designed to preferentially entrap excess cardio- and reno-protective RAASi, yet no reliably safe and effective treatment for this condition exits. ZS-9 was well tolerated and no serious AEs were reported; no patients withdrew. Only one ZS-9 AE (mild constipation, 3g) was considered at least possibly drug related. No significant hypokalemia, hypomagnesemia, or hypocalcemia was observed. At baseline, mean ± s-K+ was 5.1 mmol/L across groups. ZS-9 demonstrated significant dose-dependent reductions in s-K+; the primary efficacy endpoint was met in the 10g and 3g cohorts (p=0.0001 and p=0.048 vs PBO, respectively) (Fig).

Conclusions: In CKD patients with hyperkalemia, ZS-9 was safe and well tolerated and led to a rapid and sustained s-K+ reduction. Consequently, ZS-9 is being evaluated in a large Phase 3 RCT.

HI-OR06

Treatment of Lupus Nephritis with Abatacept Plus Low-Dose Pulse Cyclophosphamide: The Results of the ACCESS Trial
Brad H. Rovin,1 The Access Trial Investigators.2,3 Internal Medicine, Ohio State University Wexner Medical Center, Columbus, OH; 4The Immune Tolerance Network.

Background: CTLA4Ig (abatacept, ABA) plus intravenous cyclophosphamide (IVC) act synergistically to treat murine lupus nephritis (LN). The ACCESS trial tested low-dose IVC (500 mg weekly), with or without ABA, in AAs and EAs. The primary endpoint was all-cause mortality at week 24, defined as UPCR <0.5, serum creatinine normal or within 25% of baseline. Among patients with diabetes, the HR of a renal event was 1.95 (95% CI: 1.39-2.73) in AAs in the ABA risk group and 1.40 (95% CI: 1.10-1.78) in EAs in the ABA risk group, compared each group to its respective non-risk group.

Results: AAs had CRR, but continued in controls who had CRR. This group was followed to week 52. In AAs, 33% of AA ABA patients and 16% (13/21) of ABA and control patients respectively, still met CRR criteria at week 52 (p=NS). Among complete responders at week 24, 50% (11/22) and 62% (13/21) of AAs and EAs, respectively, had CRR at week 52 (p=NS).

Conclusions: AAs have a higher probability of achieving CRR and PRR compared to EAs. Among complete responders, 50% and 62% continued in AAs and EAs, respectively, to week 52.

SA-PO1076

A Randomized Clinical Trial to Evaluate the Efficacy of Cinacalcet to Correct Hypercalcaemia in Renal Transplant Recipients with Autonomic Hyperthymidroidism
Jeffrey DeGroot,1 Kerry Cooper,2 Hallvard Holdaas,3 Piergiorgio Messa,4 Georges J. Mordard,5 Klaus Olgaard,6 Boleslaw Rutkowski,7 Heidi M. Schafer,8 Hongjie Deng,9 Jose-Vicente Torregrosa,2 Rudolf P. Wuthrich,10 Susan V. Yue.2,6 ‘U Ziekenhuizen, Belgium; 8Aamgen, USA; 9Od U Hospital, Norway; 10Fondazione Ca’ Granda IRCCS Policlinico, Italy; 11of Montpellier Hospital Lapeyronie, France; 12Of Copenhagen, Denmark; 13Medical U of Gdansk, Poland; 14Vanderbilt U Medical Center; 15U of Barcelona, Spain; 16U Hospital Zurich, Switzerland.

Background: Autonomic hyperthymidroidism (HPT) after kidney transplantation (KTx) is associated with elevations in serum calcium (Ca) and reductions in serum phosphorus (P). Cinacalcet (Cin) has been shown to reduce Ca and increase P levels in prior studies, our results suggest that Cinacalcet to correct hypercalcaemia (Ca < 10.2 mg/dL; secondary endpoints: to assess the percent change in bone mineral density (BMD) at the femoral neck and the change in serum P levels.

Results: Demographic distribution was similar across groups: 55% male, 82% white, with median (min, max) age of 53 (24, 76) years. The proportion of subjects achieving the primary endpoint was 78.9% and 3.5% for the Cin and placebo groups (p=0.001). BMD mean (SD) percent change from baseline to wk 52 was 2.16 (7.74%) and 0.73 (4.40%) for the Cin and placebo groups, respectively (p<0.001). The rate of decline in Ca was similar among AAs in the Cin group and EAs. Among patients with diabetes, the HR of a renal event was 1.95 (95% CI: 1.39-2.73) in AAs in the ABA risk group and 1.40 (95% CI: 1.10-1.78) in EAs in the ABA risk group, compared each group to its respective non-risk group.

Conclusions: BMD and Ca were not affected by Cinacalcet. There was no effect on serum or urinary sodium.

HI-OR07

APOLI Risk Variants, Race, and Progression of Chronic Kidney Disease
Afshin Parsa,1 Wen Hong Linda Kao,2 the AASK and CRIC Collaborative Research Groups.2,3 1Nephrology, University of Maryland School of Medicine; 2Epidemiology, Johns Hopkins Bloomberg School of Public Health.

Background: African Americans (AAs) are at substantially increased risk for end-stage renal disease (ESRD) compared to European Americans (EAs).

Methods: We examined the effects of APOLI variants on chronic kidney disease (CKD) progression separately in the African American Study of Kidney Disease and Hypertension (AASK) and the Chronic Renal Insufficiency Cohort Study (CRIC). AASK enrolled 693 AAs with CKD attributed to hypertension. CRIC enrolled EAs and AAs with CKD (n=2955, 46% with diabetes). APOLI risk group was defined by two of the highest-risk APOLI variants. In AASK, primary outcomes were ESRD and a composite of ESRD or doubling of serum creatinine. In CRIC, primary outcomes were the slope in estimated glomerular filtration rate (eGFR) and the composite of ESRD or halving of eGFR from baseline.

Results: In AASK, the primary outcome occurred in 58% of participants in the APOLI risk group and 37% in the APOLI non-risk group [adjusted hazard ratio (HR)=1.88, P<0.001]. There was no interaction between APOLI status and trial interventions (3 drugs and 2 BP targets) or baseline proteinuria. In CRIC, the adjusted rate of decline in eGFR was greater among AAs in the APOLI risk group than EAs in participants with diabetes (1.32 ml/min/1.73m²/year, P<0.001) and participants without diabetes (-1.11 ml/min/1.73m²/year, P=0.001). The rate of decline in eGFR was similar among AAs in the APOLI non-risk group and EAs. Among participants with diabetes, the HR of a renal event was 1.95 (95% CI: 1.39-2.73) in AAs in the APOLI risk group and 1.40 (95% CI: 1.10-1.78) in EAs in the risk group, compared each group to its respective non-risk group. Corresponding HRs among participants without diabetes were 2.68 (95% CI: 1.78-4.05) and 1.57 (95% CI: 1.11-2.21).

Conclusions: APOLI renal risk variants increase CKD progression in AAs, even in the setting of variable-controlled BP. These variants explain, in part, the markedly increased risk of ESRD in AAs compared to EAs, regardless of diabetes status. In the context of prior studies, our results suggest that APOLI risk variants increase CKD progression in AAs, irrespective of CKD etiology.

Funding: NIDDK Support

Underline represents presenting author/disclosure.
**Methods:** Patients with newly diagnosed severe AAV were randomised to receive 3 to 6 months of induction with MMF 2-3 g/day (n=70) or 6-10 pulses of IV CYC 15 mg/kg (n=70). Both groups received the same tapering prednisone regimen and azathioprine therapy after remission induction. The primary outcome was remission at 6 months defined as no disease activity for >4 weeks without excess prednisolone. We considered MMF non-inferior to IV CYC if the lower bound of the 90% confidence interval (CI) for remission was not worse than 2% higher for MMF.

**Results:** The groups were similar at baseline. The primary endpoint occurred in 51 (73%) MMF vs 52 (74%) CYC (risk difference -1%, 90% CI -14 to 11%; p=0.08 for non-inferiority). The secondary remission endpoint occurred in 63/70 (90%) MMF vs 56/70 (80%) CYC (risk difference 10%, 90% CI to 0; p=0.001 for non-inferiority). Although, cumulative prednisolone dosing at 6 months did not differ (p=0.9), there was slightly more noncompliance at low doses in the MMF group. At 18 months, 21 patients (35%) in the MMF group and 12 (22%) in the CYC group relapsed (risk ratio 1.57, 95% CI 0.87 to 2.94; p=0.12). Other key secondary outcomes did not differ significantly between groups: estimated glomerular filtration rate (mean difference 2.6 ml/min, 95% CI -7.6 to 12.9; p=0.62), serious adverse events (risk ratio 1.25, 95% CI 0.86 to 1.81; p=0.23), serious infections (risk ratio 1.5, 95% CI 0.78 to 2.88; p=0.22) or deaths (risk ratio 1.25, 95% CI 0.35 to 4.46; p=0.73).

**Conclusions:** Although remission induction rates were similar, we did not demonstrate non-inferiority of MMF vs IV CYC and MMF was not substantially safer. MMF may offer an alternative to cyclophosphamide in select patients but requires particular attention to disease activity and glucocorticoid dosing.

**Funding:** Pharmaceutical Company Support - Roche

---

**SA-PO1080**

**Increased Duration and Dose of Prednisolone (PST) Treatment Does Not Reduce Relapses in Childhood Nephrotic Syndrome**

**Background:** Although prolonged initial steroid treatment has been reported to decrease the risks of relapse in pediatric patients with steroid-sensitive nephrotic syndrome (SSNS), the optimal treatment approach varies considerably. A Cochrane review concluded that although treating patients for up to 7 months appears more effective than 2-month treatment in achieving sustained remissions, additional well-designed and adequately powered randomized clinical trials are required.

**Methods:** We evaluated the hypothesis that prolonging a 2-month initial PST therapy to 6 months using an increasing cumulative dose would not reduce the incidence of frequently relapsing (FR) NS. We conducted a multicenter, randomised, open-label non-inferiority trial at 91 hospitals in Japan and compared a 2-month initial PST trial (cumulative dose 2240 mg/m²) with a 6-month treatment (3885 mg/m²). The primary endpoint was time to FRNS. A prespecified non-inferiority margin was hazard ratio (HR) of 1.3 and significant level was one-sided 5%. We randomly assigned 255 children with an initial episode of SSNS either 2-month treatment (n=128) or 6-month treatment (n=127). The trial consisted of initial treatment and relapse PST treatment as specified in the protocol. Enrolled patients received this for a total of 24 months.

**Results:** The FRNS-free rates at 24 months were 56.2% (95% confidence interval [CI], 47.6-64.4%) in the 2-month treatment group and 58.8% (95% CI, 41.4-59.4%) in the 6-month treatment group. The HR was 0.86 (90% CI, 0.64-1.16) and met the non-inferiority margin (p = 0.11). There was no significant difference in the number of relapses during the 24-month intervention period (1.25 vs. 1.30 person-years; relapse rate ratio 0.94, 95% CI 0.71-1.22, p = 0.649). The incidence of central obesity in the 6-month treatment group was higher than in the 2-month group (p = 0.03). The treatment was well tolerated.

**Conclusions:** This trial shows that extending initial PST treatment from 2 to 6 months with an increasing dose does not reduce the incidence of FRNS.

**Funding:** Government Support - Non-US

---

**SA-PO1078**

**Continuous, Maintenance Iron Therapy Using Soluble Ferric Pyrophosphatase Citrate Chelate (SFP, Triferic™) Infusion via Hemodialysate in CKD-HD:**

**Background:** SFP (Triferic™), a novel, unique, carbohydrate-free, complex iron salt delivered via hemodialysate donates iron rapidly and directly to apotransferrin, bypassing the RE system. The safety and efficacy of this novel dialysate delivery method for maintaining iron balance in adult, CKD-HD, was examined in two identical RCTs.

**Methods:** Iron replete HD patients were randomized to either placebo (standard iron-free dialysate) or dialysate containing SFP at 2 μM (110 μg iron/L), with every hemodialysis for up to 48 weeks while ESA dose changes and IV/oral iron were prohibited. Subjects were attributed to SFP.

**Results:** The primary endpoint was mean change in Hgb from baseline to the end of treatment (last 1/6th of randomized phase), analyzed using ANCOVA with baseline Hgb as covariate. The safety profile and tolerability of SFP were similar to placebo with no anaphylactoid reactions in over 20,000 administrations. AE and SAE were similar and there was no increase in intradialytic hypotension, CV events or infections. No deaths were attributed to SFP.

**Conclusions:** In HD patients, the novel iron salt-SFP infused by hemodialysis for up to 48 weeks is well tolerated with a safety profile similar to placebo. SFP is effective in maintaining hemoglobin by preventing iron deficiency without inducing iron overload.

**Funding:** Pharmaceutical Company Support - Vifor Pharma

---

**SA-PO1079**

**The Antialbuminuric Effects of an Aldosterone Blocker in Hypertensive Patients with Albuminuria: A Double-Blinded, Randomized, Placebo-Controlled (EVALUATE) Trial**

**Background:** The antialbuminuric effects of the MR blockade by adding MR blockers were examined in two randomized trials (CURE-1 CRUSE-2) in patients with hypertension and proteinuria who were already receiving the angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACE-I) and optimal treatment for hypertension.

**Methods:** We evaluated the antialbuminuric effect of the MR blockade by adding eplerenone group and 138.7±12.58 to 129.4±12.87 mmHg in the placebo group. Serum potassium increased from 4.1 (range 3.5-4.6) to 4.2 (3.7-4.7) in the eplerenone group and 4.0 (3.6-4.4) to 4.0 (3.7-4.4) in the placebo group.

**Results:** Treatment with 50 mg of eplerenone, as compared with placebo, reduced the mean albuminuria from 314 patients in this multicenter, double-blinded, randomized, placebo-controlled trial (UMIN#000001803). The primary outcome was a percent reduction in urinary albumin/creatinine ratio. The primary endpoint was time to FRNS. Enrolled patients received this for a total of 24 months.

**Conclusions:** Results of many animal studies but a few human studies suggest that mineralocorticoid receptor (MR) blockers can inhibit albuminuria and renal damage in chronic kidney disease (CDK) patients. The aim of this trial was to evaluate the potential renoprotective capacity of the MR blockade in non-diabetic patients with hypertension and proteinuria who were already receiving the angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACE-I) and optimal treatment for hypertension.

**Methods:** We evaluated the antialbuminuric effect of the MR blockade by adding treatment of low dose (50 mg/day) of eplerenone to optimal antihypertensive therapy including in non-diabetic hypertensive CDK patients who had blood pressure [BP] of 130-180/100-100 mmHg and albuminuria (urinary albumin/creatinine [Cr] ratio: 30-600 mg/g).

**Results:** The patients had estimated glomerular filtration rate ≥ 50 ml/min/1.73m². We enrolled 314 patients in this multicenter, double-blinded, randomized, placebo-controlled trial (UMIN0000001803). The primary outcome was a percent reduction in urinary albumin/Cr, as measured in an early-morning sample, at 12 months.

**Conclusions:** Treatment with 50 mg of eplerenone, as compared with placebo, reduced the mean urinary albumin/Cr -17.5±9.95 [mean(SD)] vs. 8.7±10.49, P=0.05. A small, but significant reduction [both, P<0.05], diastolic BP was further reduced in the eplerenone treatment groups by the end of the study period: 138.7±11.6 to 126.8±11.52 mmHg in the eplerenone group and 138.7±12.58 to 129.4±12.87 mmHg in the placebo group. Serum potassium was similar between the two groups (4.32±0.40 vs. 4.17±0.50 mmol/L, NS), and total numbers of adverse events were also similar in the groups.

**Underline represents presenting author/disclosure.**
Conclusions: Low dose of eplerenone may have renoprotective effects in non-diabetic patients with hypertension and nephropathy who are receiving ARB or ACE-I.

Funding: Pharmaceutical Company Support - Pfizer

SA-PO1082
The DIVINE Trial: Dialysis Infection and Vitamin D in New England
Ishir Bhan, Dorothy A Dobens, Catifin A. Trotter, Julia Beth Wenger, Hector Tamez, Joseph James Deferio, Kathryn J. Lucchesi, Ravi I. Thadhani. Division of Nephrology, Massachusetts General Hospital, Boston, MA.

Background: The role of nutritional vitamin D in ESRD remains uncertain. We performed a randomized, double-blind placebo-controlled trial to assess the safety and efficacy of ergocalciferol in chronic hemodialysis patients.

Methods: We randomized 105 incident dialysis patients with 25(OH)D levels < 32 ng/ml from 32 centers in the northeast US to ergocalciferol 50,000 IU weekly (n=36), monthly (n=33), or placebo (n=36) for a 12 week treatment period. Follow-up was at 20 weeks and one year. The primary outcome was 25(OH)D levels at 12 weeks. Secondary outcomes included markers of mineral metabolism, hospitalizations, and one year mortality.

Results: Baseline features and active vitamin D use were similar across the groups. Most subjects were white (62.9%) and male (78.1%). The mean age was 57 ± 17 years. Mean 25(OH)D levels at 12 weeks were significantly higher than placebo (27.3 ng/ml ± 2.3) in the weekly (49.8 ng/ml ± 2.3; p=0.001) and monthly (38.3 ng/ml ± 2.4; p=0.001) treatment arms. 25(OH)D sufficiency (>32 ng/ml) was achieved in 90.9%, 64.5%, and 35.3% of patients on weekly, monthly, and placebo, respectively. There were no differences between groups in serum calcium, phosphorus, or PTH. Overall hospitalizations (p=0.64), hospitalizations for infection (p=0.32) and cardiovascular hospitalizations (p=0.47) did not differ between groups. All-cause mortality at one year was significantly lower in the combined ergocalciferol arms than in the placebo arm (p=0.02; see figure).

Conclusions: Ergocalciferol can safely and effectively increase 25(OH)D levels in incident dialysis patients. Preliminary analysis suggests a lower one-year mortality rate among ergocalciferol-treated patients compared with placebo.

Clinicaltrials.gov NCT99728099, Funded by NIDDK R01DK09143.

Funding: NIDDK Support

SA-PO1083
Prospective Randomized Controlled Trial of Individualized Dialysate Cooling to Provide Brain and Cardiac Protection in Haemodialysis Patients
Chris W. McIntyre, Mohamed Tarek Eldehni, Aghogho Odudu. Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Derby, United Kingdom.

Background: Conventional haemodialysis (HD) results in functionally significant brain and cardiac injury. Dialysate cooling is well tolerated and effectively abrogates these effects. This intervention can be delivered without additional cost and is universally applicable. This study justifies further larger scale testing of dialysis based interventions (directed at iatrogenic HD induced organ injury).

Funding: Government Support - Non-U.S.

SA-PO1084
A Randomized Controlled Multicenter Trial of a Heparin-Grafted Polyacrylonitrile Membrane for No-Heparin Hemodialysis versus Standard-of-Care: Results of the HepZero Study
Maurice Laville,1 Marc Dorval,2 Joan Fort,2 Renaud Fay,2 Frederique Motauv2e,4 Nathalie Loughrabe,4 Patrick Rossignol.4 Nephrology Department, Lyon-Sud Hospital Centre, Lyon University, Lyon, France; 2D-Georges-L-Dumont University Hospital Centre, Moncton, Nouveau-Brunswick, Canada; 3Nephrology Department, University Hospital Vall d’Hebron, Autonomous University of Barcelona, Spain; 4Gambro-Hospital, Meyzieu, France; 5Nancy-University Hospital, Lorraine University & ALTR, Nancy, France.

Background: Heparin is used in most patients on maintenance hemodialysis (MHD), but no-heparin HD (NH-HD) is occasionally needed to decrease bleeding risk. A new dialyzer, (Evodial®; Gambro-Hospital, Meyzieu, France) contains a heparin-grafted polyacrylonitrile membrane (HGPM) and may allow safe and efficient NH-HD.

Methods: The HepZero study NCT01318486 is the first large randomized controlled trial comparing no-heparin strategies. This multicenter international open-label trial was designed to demonstrate non inferiority (ultimately superiority if demonstrated) in two parallel groups comprising 251 MHD patients requiring NH-HD. Patients were randomly allocated for up to three NH-HD sessions, to be treated with either HGPM, or standard-of-care (Controls) including regular saline flushes or on-line predilution. The first NH-HD session was considered successful when there was neither complete occlusion of air traps or dialyzer, nor additional saline flushes, changes of dialyzer or bloodlines, or premature termination.

Results: It is found that current standard-of-care results in high failure rates (50%). Success rate in the HGPM arm was higher than in Controls (68.5% vs. 50.4%, p = 0.003), consistent for all standard-of-care modalities. Absolute HGPM vs Controls arms difference was 18.2%, with a lower bound of the one-tailed 95% confidence interval (O-T, 95% CI) equal to 10%. Hypothesis of the non-inferiority at 15%-level was accepted, although superiority at the 15%-level was not reached.

Conclusions: Hence, HGPM achieves 18% higher successful anticoagulation-free HD session compared to both saline flushes and on-line pre-dilution, and is shown to be firmly non-inferior to standard-of-care.

Funding: Pharmaceutical Company Support - Gambro

SA-PO1085
A Two-Part Trial of Patiromer for the Treatment of Hyperkalemia in Chronic Kidney Disease Subjects on Renin Angiotensin Aldosterone System Inhibition
Matthew R. Wein,1 George L. Bakris,2 Martha Mayo,3 Yuri Stavis,3 Heidi Christ-Schmidt,4 Janet Wittes,4 Lance Berman.3 1University of Maryland; 2University of Chicago Medicine; 3Relypsa; 4Statistics Collaborative.

Background: Hyperkalemia (HK) affects patients with chronic kidney disease (CKD), especially when treated with renin angiotensin aldosterone system inhibitors (RAASi). Patiromer (RLY5016), a novel ion exchange polymer with good gastrointestinal tolerability, lowered serum potassium (K+) with daily administration in clinical trials. This multicenter international study in 243 hyperkalemic subjects with an eGFR 15 to < 60 mL/min/1.73m2 with/diabetes and on RAASi medication, was a two-part Phase 3 study: Part A, the 4-week single-blind treatment study, assessed patiromer for the treatment of HK; Part B, the 8-week placebo-controlled randomized withdrawal study, assessed whether chronic treatment with patiromer prevented recurrent HK.

Methods: Two subgroups were defined by screening serum K+: 5.1 to < 5.5 (n=92) and 5.5 to < 6.5 mEq/L (n=151). The Part A primary outcome was change in serum K+ from Part A Baseline to Part A Week 4 (all subjects). The Part B primary outcome was the between group difference in the change in serum K+ from Part B Baseline to Part B Week 4. Secondary outcomes included the proportion of subjects with a serum K+ in the target range at Part A Week 4 and the proportion of subjects with recurrent HK in Part B. An additional outcome was the proportion of subjects with modified RAASi treatment due to recurring HK.

Results: Underline represents presenting author/disclosure.
SA-01086
Effects of Atorvastatin on Renal Function in Patients with Dyslipidemia and Chronic Kidney Disease: Assessment of Clinical Usefulness in CKD

Patients with Atorvastatin (ASUA) Trial Genjiro Kimura,1 Kenji Ueshima,2 Masato Kasahara,2 Sachiko Tanaka,2 Shintaro Yasuno,3 Akira Fujimoto,2 Tosiya Sato,2 Shinji Kosugi,2 Kazuwa Nakao. 3
1Asahi Rosai Hospital, Owariasahi, Japan; 2Department of EBM Research, Institute of Advancement of Clinical and Translational Science, Kyoto University Hospital, Kyoto, Japan; 3Department of Biostatistics, Kyoto University School of Public Health, Kyoto, Japan; 4Department of Medical Ethics/Medical Genetics, Kyoto University School of Public Health, Kyoto, Japan; 5Medical Innovation Center, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Background: The effects of a strong statin, atorvastatin, on renal function was examined in patients with dyslipidemia and CKD.

Methods: The ASUA trial was a prospective, multi-center, open-labeled, randomized study to compare the renoprotective effects between lipid-lowering agents other than statins (control group, Group C) and atorvastatin (atorvastatin group, Group A) under diet therapy in 349 patients with dyslipidemia (LDL-C ≥100 mg/dL) in subjects taking lipid-lowering agents other than statins or ≥140 mg/dL) and CKD (eGFR <60 mL/min/1.73m²). Target of LDL-C was less than 100 mg/dL. The primary endpoint was the change in eGFR after 2 years of treatment.

Results: The patients were randomly assigned to either Group C or A, and the FAS population consisted of 166 patients in Group C and 168 patients in Group A (mean age: 63.1 vs 63.2 y.o.; mean LDL-C: 145.9 vs 142.2 mg/dL; median urinary albumin/creatinine ratio: 29.1 vs 24.9 mg/gCr, respectively). LDL-C was significantly reduced in Group A compared with Group C. Changes in mean eGFR were -2.6 mL/min/1.73m² (from 54.4 to 51.9) in Group C and -2.3 mL/min/1.73m² (from 56.2 to 53.9) in Group A, showing no difference between the two groups (P=0.85). Similarly, the changes in albuminuria were not different.

Conclusions: The ASUA trial indicates no significant difference between atorvastatin and non-statins in the effect on renal function after 2 years of treatment in patients with dyslipidemia and CKD.

Funding: Pharmaceutical Company Support - Relysa, Inc.

SA-PO1089
Risk and Severity of Hyperkalemia with Combined Angiotensin Antagonism in Diabetic Nephropathy – The VA-NEPHROND Study

Jennifer Seliger,1 Jane Hongyuan Zhang,1 Nicholas Emanuel,1 Paul M. Palevsky,1 Linda F. Fried.2
1Medicine, Baltimore VA, Baltimore, MD; 2Medicine, Pittsburgh VA, Pittsburgh, MD; 3Medicine, Hines VA, Hines, IL; 4Coordinating Ctr, VA Co-Operative Studies, West Haven, CT.

Background: Greater angiotensin antagonism may increase the risk of hyperkalemia in renal disease. Few studies have compared the risk and severity of hyperkalemia with dual angiotensin antagonism in diabetic nephropathy patients.

Methods: We performed a secondary analysis of the VA-NEPHROND study, a randomized clinical trial comparing losartan monotherapy to losartan + lisinopril combination therapy in patients with type 2 diabetes, overt albuminuria, and stage 2-3 CKD. Hyperkalemia was a pre-specified safety outcome defined as a potassium≥6 mEq/L or requiring emergency care or dialysis. Cox survival regression was used to identify factors predictive of hyperkalemia, and to test for interaction between treatment group and clinical factors. Severity and management of hyperkalemia was compared between the groups.

Results: Among 1448 participants, there were 104 with hyperkalemic events over a median 2.2 years. Those randomized to losartan/lisinopril had a 177% greater risk of hyperkalemia (HR=2.77, 95%CI=1.79, 4.28). This excess risk from combination therapy was not modified by race, baseline potassium, heart failure, use of diuretics, albuminuria, eGFR, use of insulin, or HbA1C (p>0.2 for all tests of interaction). Among all participants, other factors associated with hyperkalemia were initial eGFR (per mL/min/1.73m²: HR=0.97, p<.001) and initial potassium concentration (per 1-mEq/L increment, HR=3.78, p<.001). Among hyperkalemic cases, the losartan + lisinopril group had higher peak potassium (6.00±0.50 vs. 6.33±0.56 mEq/L, p<.017), were more likely to be referred for emergency care (69% vs. 50%, p=0.07), to be treated with IV calcium (25% vs. 9.4%, p=0.07) and insulin (34.7% vs. 15.6%, p=.047), and to have study medications permanently discontinued (40.4% vs. 18.8%, p=.033).

Conclusions: Dual angiotensin antagonism in overt diabetic nephropathy markedly increases both the risk and severity of hyperkalemia, and this excess risk is similar regardless of renal function, co-morbidity, initial potassium and concurrent diuretic use.

Funding: Veterans Administration Support

SA-PO1090
A Comparison of Short-Term Exposure of Once-Daily Extended Release Telocromil (Advagraf®) and Twice-Daily Telocromil (Prograf®) on 24 Hour Renal Hemodynamics and Function in Healthy Volunteers

David Cherney,1 Jeffrey S. Zaltzman.1
1University of Toronto.

Background: Calcium inhibitor neon (CNI) nephropathy remains an ongoing concern in organ transplant recipients, however the pathophysiology of this nephropathy is unclear. Previous studies have demonstrated that after administration of Neoral® there is a strong correlation between Ccr and decreases in renal perfusion and GFR, possibly contributing to long-term nephrotoxicity. This response is attenuated with both tacrolimus formulations, the twice-daily Prograf®(P) and the once daily Advagraf®(A), the latter demonstrating similar AUC24, but a different PK profile, with a lower Cmax and no second peak.

Methods: Healthy, normotensive, adult male volunteers (n=19) were randomized to receive once daily A and twice daily P in a prospective, randomized, open label, cross over design. Baseline and drug studies included 24 hr effective renal plasma flow (ERPF), and 24 hr GFR by PAH and inulin clearances. Renal blood flow (RBF), filtration fraction (FF) and renal vascular resistance (RVR) were then calculated and all measurements were repeated over a number of time points throughout the 24 hour period. Tacrolimus dosing was initiated at 0.15 mg/kg/d with TDMs targeted to [C1] of 8-12 ng/ml. All studies were repeated on day 10 and 20 of A/P or P/A.

Funding: Pharmaceutical Company Support - Roche Foundation for Anemia Research (RoFAR), Amgen, Janssen-Cilag, Government Support - Non-U.S.
SA-PO1091

Changes in Cardiac Structure and Function after Revascularization versus Medical Therapy for Renal Artery Stenosis: The ASTRAL HEART Echocardiography Sub-Study

Darren Green,1 Natalie Ives,2 Kelly Handley,3 Philip A. Kalra.1 Salford Royal Hospital, United Kingdom; 2University of Birmingham, United Kingdom.

Background: The ASTRAL trial showed no difference in clinical outcomes between medical therapy and revascularization for atherosclerotic renal vascular disease (ARVD). Here we report a sub-study using echocardiography to assess differences in cardiac structure and function at 12 months.

Methods: ASTRAL patients from 7 participating centres underwent echocardiography at baseline and 12 months after randomization. Changes (mean ± standard deviation) in left ventricular mass, left ventricular ejection fraction (LVEF), left atrial diameter (LAD), aortic root diameter (AoRD), E/A and E deceleration time (EDT) were compared between study arms.

Results: 92 patients were included (50 medical vs 42 revascularization). There were no significant differences in baseline co-morbidities and clinical characteristics between the groups (mean age 71 ± 7 years, eGFR 43 ± 21 mL/min, systolic blood pressure 152 ± 24 mmHg, duration of ARVD 56 ± 41 months). Change in LVEF at 12 months was greater in medical patients: ALVEF medical 0.8 ± 7.8% vs -2.8 ± 6.8% (p = 0.049). In a multivariate model including age, blood pressure, renal function, degree of stenosis, beta blockade and ACE-inhibitor use this was no longer significant. There were no significant differences in ventricular mass, LVEF, aortic root size and AoRD. There was a significant decline in LV E/A and EDT with revascularization (0.5 mg: -0.08 ± 0.3; 2 mg: -0.10 ± 0.4; rhEPO: -0.25 ± 0.4).

Conclusions: This sub-study did not show any significant differences in cardiac structure and function accompanying renal revascularization in ASTRAL. Limitations include sample size, relative insensitivity of echocardiography, as well as clinical heterogeneity of the patient population as described in the main study. This abstract is presented by the authors on behalf of the ASTRAL Heart Collaborators.

SA-PO1092

Four-Week Safety, Efficacy and Pharmacodynamic Study of Hypoxia Inducible Factor (HIF)-Prolyl Hydroxylase Inhibitor GSK1278863 in Anemic Hemodialysis Subjects Switching from Recombinant Human Erythropoietin

Amy M. Meadowcroft,1 Louis Holdstock, Rayma Maier, Delthy Jones, Brendan Johnson, Alexander Ralph Cobitz, John J. Lepore. GlaxoSmithKline, Research Triangle Park, NC.

Background: Hypoxia inducible factor (HIF)-prolyl hydroxylase inhibitors (PHIs), such as GSK1278863, are an emerging class of oral agents for treatment of chronic kidney disease (CKD) anemia. PHIs inhibit HIF-prolyl hydroxylases, resulting in accumulation of HIFα transcription factor, thus stimulating pathways activated during hypoxia, including erythropoiesis and iron mobilization.

Methods: This 4-week, randomized, blinded (with respect to GSK1278863 dose) multicenter study examined the safety and efficacy of GSK1278863 dose and hemoglobin (Hgb) level in 83 hemodialysis-dependent (HDD) subjects with anemia of CKD previously receiving a stable dose of recombinant human erythropoietin (rhEPO). Effects of GSK1278863 on circulating levels of erythropoietin (EPO) and vascular endothelial growth factor (VEGF) were also explored. Subjects with a baseline Hgb of 9.5-12.0 g/dL were randomized to stop rhEPO and receive once daily 0.5, 2 or 5 mg GSK1278863 or to continue on rhEPO.

Results: Baseline Hgb (overall mean 10.9±0.6 g/dL) was similar across treatment groups. Switching from rhEPO to 5 mg GSK1278863 had a similar effect on Hgb as continuing rhEPO, maintaining stable Hgb over 4 weeks (mean change from baseline at Week 4: 5 mg: +0.08±0.6 g/dL; rhEPO: -0.25±0.4 g/dL), whereas switching to 0.5 or 2 mg GSK1278863 resulted in a decline in Hgb (0.5 mg: -1.06±0.6 g/dL; 2 mg: -0.93±0.4 g/dL). The maximum observed circulating EPO levels with GSK1278863 were markedly lower than those in the rhEPO group (0.5 mg: 13.9±U/L; 2 mg: 12.7±U/L; 5 mg: 24.7±U/L; rhEPO: 42.4±9.4 U/L). No significant change in VEGF was observed in any group. GSK1278863 was safe and well tolerated.

Conclusions: These data inform the Hgb dose-response relationship of GSK1278863 in anemic HDD subjects after being switched from a stable dose of rhEPO and demonstrate that GSK1278863 can maintain Hgb with minimal effects on EPO levels and without significantly elevating VEGF.

Funding: Pharmaceutical Company Support - GlaxoSmithKline
SA-PO1095

Universal Prophylaxis for Cytomegalovirus in Pediatric Kidney Transplantation in Developing Country: Medellin, Colombia

Liliana Rubio, Jorge Henao, Joaquin Rodelo Ceballos. Pediatric Nephrology, Hospital Universitario San Vicente Fundacion, Medellin, Antioquia, Colombia.

Background: Cytomegalovirus affects more than 50% of transplant recipients, is one of most common complications, including infection with opportunistic pathogens and allograft rejection.

Objective determine the effectiveness of prophylaxis with ganciclovir and valganciclovir for 3 months in pediatric kidney transplantation in one year of follow-up because data in pediatrics are limited.

Methods: This prospective cohort study included 34 kidney transplant, between December 2005 and April 2013. 82,4% and 100% respectively, received iv ganciclovir, 10mg/kg/day, dose 166 mg/day during 9,5 days followed by valganciclovir, using the following formula: (mg) = 7 x body surface area (m2) x creatinine clearance (mL/min per 1, 73 m2) the dose was 462mg day for 99 days, adjusted for renal function.

Results: (71%) were males, median age was 8 years and 97% were the cadaveric origin. Most kidney transplant recipients received induction therapy with thymoglobulin (n=27) other induction therapy included basiliximab (n=7). Maintenance immunosuppression consisted of tacrolimus, prednisone plus mycophenolate; Regarding CMV antibody status, 25 patients (73,5%) were D+/R+, 4(11,7%) were D-/R+, and 5 (14,8%) were D+/R-. 5,8 % patients with serology D+/R- had CMV disease and 5,8% with serology D-/R+ had CMV disease for an incidence of 11,76 % and the late- onset CMV disease was 8%. The bivariate analysis showed that the highest risk group for CMV disease was D+ R-.(p=0.05).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Disease</th>
<th>No Disease</th>
<th>Chi squared</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor CMV IgG positive</td>
<td>2 (50%)</td>
<td>28 93,3 %</td>
<td>6,38</td>
<td>0.05</td>
</tr>
<tr>
<td>Donor CMV IgG negative</td>
<td>2 (50%)</td>
<td>2 6,7 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient CMV IgG positive</td>
<td>2 (50%)</td>
<td>27 90 %</td>
<td>4,5</td>
<td>0.09</td>
</tr>
<tr>
<td>Recipient CMV IgG negative</td>
<td>2 (50%)</td>
<td>3 10 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There was no mortality or graft loss secundary to infection, either resistance and difference in creatinine in the 1 year.

Conclusions: The main preventive strategy against CMV in pediatric renal transplantation is the universal prophylaxis and extension to 200 days is a benefit to prevent late onset CMV disease.

SA-PO1096

Acute Kidney Injury (AKI) Associated with Combined Angiotensin Antagonism in Patients with Diabetic Nephropathy – A Secondary Analysis of the VA NEPHRON-D Study

Paul M. Palevsky,1 Jane Hongyuan Zhang,2 Stephen L. Seliger,3 Nicholas Emanuele,4 Linda F. Fried.1 1VA Pittsburgh HCS, Pittsburgh, PA; 2CSP Coordinating Center, VA Connecticut HCS, West Haven, CT; 3VA Maryland HCS, Baltimore, MD; 4Hines VAMC, Hines, IL.

Background: Dual blockade of the renin-angiotensin system (RAS) is associated with an increased risk of acute kidney injury (AKI); however the etiology, severity and outcome of AKI have not been carefully evaluated.

Methods: We performed a secondary analysis of the VA NEPHRON-D study, a RCT comparing losartan monotherapy (MT) to losartan/lisinopril combination therapy (CT) in patients with type 2 diabetes, overt albuminuria, and stage 2-3 CKD. Data were collected on etiology, severity and outcomes of episodes of AKI. Cox regression was used to identify predictive factors and test interactions with treatment group.

Results: 295 episodes of AKI occurred in 210 of 1448 (14.1%) study participants; 105 in 80 MT patients (6.7 events/100 person-years) and 190 in 130 CT patients (12.2 events/100 person-years; p<0.001). The maximal serum creatinine was <2x baseline in 54.4% of episodes in MT and 57.6% of episodes in CT (p=0.18); 12 episodes required dialysis in MT and 17 in CT. AKI was attributed to prerenal azotemia in 73.1% and 76.3%, respectively, and to ATN in 24.0% and 24.7% of episodes, respectively, in MT and CT. Predictors of AKI included albuminuria >1 g/g creatinine, lower baseline eGFR, and treatment group. Recovery of kidney function was similar in both arms, although mortality after AKI was higher in MT patients (15.0% vs. 4.7%; p=0.009). Patients who developed AKI were more likely to progress to the primary study endpoint of death, ESRD or CKD progression (HR: 1.78; 95% CI: 1.34-2.36; p<0.001). Among patients with AKI, the hazard for the endpoint was lower with CT than MT (HR: 0.60; 95% CI: 0.37-0.98; p=0.04).

Conclusions: Dual blockade of the RAS increases the risk but not the severity of AKI in patients with overt diabetic nephropathy as compared to monotherapy. Although the hazard for death, ESRD or CKD progression was higher in patients on monotherapy who developed AKI, the higher frequency of AKI in the combination therapy arm may have attenuated its potential benefit on progression of CKD.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Merk (study drug donation)